Hotel del Coronado

San Diego, CA

February 21-26, 2015

North American Neuro-Ophthalmology Society

1975-2015

North American Neuro-Ophthalmology Society

41st Annual Meeting

February 21–26, 2015
Hotel del Coronado • San Diego, CA

SATURDAY, FEBRUARY 21		**LOCATION**
10:00 a.m. – 4:00 p.m.	San Diego Zoo Safari Park Excursion	Depart from Hotel del Coronado Lobby
2:00 p.m. – 8:00 p.m	Registration	Ballroom Foyer
6:00 p.m. – 7:30 p.m.	Opening Reception (all are welcome)	Sun Deck
SUNDAY, FEBRUARY 22		
6:00 a.m. – 6:45 a.m.	Yoga Class	Spreckels Complex
6:30 a.m. – 5:30 p.m.	Registration	Ballroom Foyer
6:30 a.m. – 7:45 a.m.	Breakfast	Crown Room
6:30 a.m. – 3:30 p.m.	Exhibits	Crown Room
7:45 a.m. – 5:00 p.m.	FRANK B. WALSH SESSION [7.25 CME]	Ballroom
11:50 a.m. – 1:10 p.m.	Lunch (Included)	Crown Room
12:15 p.m. – 1:15 p.m.	Carrier Relations Committee Meeting	Garden Room
12:15 p.m. – 1:15 p.m.	Membership Retention and Recruitment Committee Meeting	Executive Room
12:15 p.m. – 1:15 p.m.	Patient Advocacy Groups Liaison Committee Meeting	Tudor Room
5:15 p.m. – 5:45 p.m.	Frank B. Walsh Committee Meeting	Executive Room
5:15 p.m. – 5:45 p.m.	Fellowship Director's Meeting	Hanover Room
5:45 p.m. – 6:15 p.m.	Fellowship Committee Meeting	Hanover Room
5:30 p.m. – 6:30 p.m.	Members-in-Training Program and Reception	Garden Room
Evening	Dinner	On your own
MONDAY, FEBRUARY 23		
6:00 a.m. – 6:45 a.m.	Yoga Class	Spreckels Complex
6:30 a.m. – 12:30 p.m.	Registration	Ballroom Foyer
6:30 a.m. – 7:30 a.m.	Breakfast	Crown Room
6:30 a.m. – 12:15 p.m.	Exhibits	Crown Room
7:00 a.m. – 7:30 a.m.	NOVEL Editorial Board/Curriculum Committee Meeting	Garden Room
7:00 a.m. – 7:30 a.m.	Finance Committee Meeting	Executive Room
7:30 a.m. – 9:30 a.m.	Journal Club [2.0 CME]	Ballroom
9:30 a.m. – 10:00 a.m.	Coffee Break	Crown Room
10:00 a.m. – 12:00 p.m.	Hot Topics: To Boldly Go Where No Neuro-Ophthalmologist has Gone Before [2 CME]	Ballroom
12:15 p.m. – 12:45 p.m.	Archives Committee Meeting	Executive Room
12:15 p.m. – 1:30 p.m.	Women in Neuro-Ophthalmology (WIN) Meeting	Coronet Room
1:30 p.m. – 3:30 p.m.	Optional Symposium: International Neuro-Ophthalmology [2 CME]	Ballroom
2:00 p.m. – 4:30 p.m.	Consortium of Pediatric Neuro-Ophthalmologists Meeting (CPNO)	Garden Room
2:30 p.m. – 4:30 p.m.	Optional Symposium: Hands on Workshop Utilizing the Prism Cover Test and Prism Therapeutics for the Diplopic Patient [2 CME]	Carousel 3
3:00 p.m. – 5:00 p.m.	Young Neuro-Ophthalmologist (YONO) Forum	Hanover Room
5:00 p.m. – 7:00 p.m.	SCIENTIFIC PLATFORM PRESENTATIONS: SESSION I [2 CME]	Ballroom
TUESDAY, FEBRUARY 24		
6:00 a.m. – 6:45 a.m.	Yoga Class	Spreckels Complex
6:30 a.m. – 12:30 p.m.	Registration	Ballroom Foyer
6:30 a.m. – 7:30 a.m.	Breakfast	Crown Room
6:30 a.m. – 12:15 p.m.	Exhibits	Crown Room
6:30 a.m. – 7:30 a.m.	JNO Editorial Board Meeting	Hanover Room
7:00 a.m. – 7:30 a.m.	YONO Committee Meeting	Garden Room
7:00 a.m. – 7:30 a.m.	CME Committee Meeting	Executive Room
7:30 a.m. – 12:00 p.m.	SCIENTIFIC PLATFORM PRESENTATIONS: SESSION II [3.75 CME]	Ballroom
9:15 a.m. – 9:30 a.m.	Update: The Journal of Neuro-Ophthalmology	Ballroom
9:30 a.m. – 10:00 a.m.	Coffee Break	Crown Room
12:15 p.m. – 4:15 p.m.	The USS Midway Tour	Depart from Orange Avenue Lawn
12:15 p.m. – 4:15 p.m.	San Diego Zoo Excursion	Depart from Orange Avenue Lawn
12:15p.m. – 5:15 p.m.	Balboa Park/Museums Excursion	Depart from Orange Avenue Lawn
12:15 p.m. – 5:00 p.m.	NANOS Board Meeting	Windsor Room
6:00 p.m. – 9:30 p.m.	POSTER SESSION	Grand Ballroom
WEDNESDAY, FEBRUARY 25		
6:30 a.m. – 12:30 p.m.	Registration	Ballroom Foyer
6:30 a.m. – 7:30 a.m.	Breakfast	Crown Room
7:00 a.m. – 7:30 a.m.	Annual NANOS Business Meeting (all encouraged to attend)	Ballroom
7:30 a.m. – 9:30 a.m.	Sizzling Hot Topic: The IIHTT: What Have We Learned? [2 CME]	Ballroom
9:30 a.m. – 9:45 a.m.	Coffee Break	Crown Room
9:45 a.m. – 11:00 a.m.	Mechanical Causes of Strabismus [1.25 CME]	Ballroom
11:00 a.m. – 11:10 a.m.	NOVEL Update	Ballroom
11:10 a.m. – 12:00 p.m.	Jacobson Lecture: Neuroendocrine Tumors In Neuro-Ophthalmology [1 CME]	Ballroom
12:15 p.m. – 1:30 p.m.	Research Committee Meeting Luncheon	Garden Room
1:30 p.m. – 3:30 p.m.	Optional Symposium: IIHTT- Weight Loss and Management [2 CME]	Ballroom
2:30 p.m. – 5:30 p.m.	Optional Symposium: Eye Movement and Vestibular Skills Transfer Session [3 CME]	Carousel Room
4:30 p.m. – 5:30 p.m.	Abstract Committee Meeting	Garden Room
4:30 p.m. – 5:30 p.m.	International Relations Committee Meeting	Tudor Room
4:30 p.m. – 5:30 p.m.	Productivity/Compensation Committee Meeting	Hanover Room
5:30 p.m. – 6:30 p.m.	Bylaws Committee Meeting	Garden Room
5:30 p.m. – 6:30 p.m.	Patient Information Committee Meeting	Tudor Room
5:30 p.m. – 6:30 p.m.	Publications Committee Meeting	Hanover Room
6:45 p.m. – 10:00 p.m.	Annual NANOS Reception and Banquet	Windsor Lawn
THURSDAY, FEBRUARY 26		
6:30 a.m. – 12:30 p.m.	Registration	Ballroom Foyer
7:00 a.m.-8:00 a.m.	Breakfast	Crown Room
8:05 a.m. – 12:32 p.m.	Glaucoma: The Other Optic Neuropathy [4 CME]	Ballroom
9:44 a.m. – 10:14 a.m.	Break	Crown Room
2:00 p.m.-5:30 p.m.	AGS/NANOS Afternoon Session	Ballroom

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MISSION STATEMENT

The North American Neuro-Ophthalmology Society (NANOS) is dedicated to the achievement of excellence in patient care through the support and promotion of education, communication, research, and the practice of neuro-ophthalmology.

TARGET AUDIENCE

Neurologists, Ophthalmologists, Neuro-Ophthalmologists, physicians and other health care professionals who have a special interest in neuro-ophthalmology, or have fellowship training in neuro-ophthalmology and are members of the North American Neuro-Ophthalmology Society.

POLICY ON COMMERICAL SUPPORT AND FACULTY DISCLOSURE

The North American Neuro-Ophthalmology Society maintains a policy on the use of commercial support which ensures that all educational activities sponsored by NANOS provide in-depth presentations that are fair, independent, and scientifically rigorous. To this end, all speakers and planners are required to complete a "Disclosure Form". This information is included in this syllabus and/or may be supplemented by announcements by moderators.

DISCLOSURE OF UNLABELED/UNAPPROVED USES

This educational program may include references to the use of products for indications not approved by the FDA. Areas of unapproved uses will be disclosed at each presentation. Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the North American Neuro-Ophthalmology Society or any other manufacturers of pharmaceuticals.

ACCREDITATION

The North American Neuro-Ophthalmology Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION

NANOS designates this live activity for a maximum of 32.25 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation.

NANOS CME MISSION STATEMENT

The North American Neuro-Ophthalmology Society (NANOS) is dedicated to achieving excellence in care of patients with neuro-ophthalmic diseases by the support and promotion of education, research, and the practice of neuro-ophthalmology.

The Society's main CME activity is its annual scientific meeting. The educational meeting includes seminars, workshops, hands-on training, platform presentations, and discussion of cases and best practices in neuro-ophthalmic research, basic science, and patient care.

The expected result of our CME program, and of our annual meeting which is its main CME activity, is that our members will improve their knowledge of neuro-ophthalmology and change their skill in its practice, so that they can apply that knowledge and skill to improve their performance and competence as clinical neuro-ophthalmologists, research neuro-ophthalmologists, and teachers of neuro-ophthalmology.

NANOS uses multiple data sources to measure the impact of its educational activities on learners and on the discipline of neuro-ophthalmology. These measures reflect professionals' need to examine current practices, evaluate the appropriateness of educational activities in order to improve their levels of knowledge of neuro-ophthalmology basic science and clinical practice, competence in diagnosing and treating neuro-ophthalmic disease, and performance in diagnosing and treating neuro-ophthalmic diseases.

Approved by the NANOS CME Subcommittee and NANOS Board of Directors as of July 2014

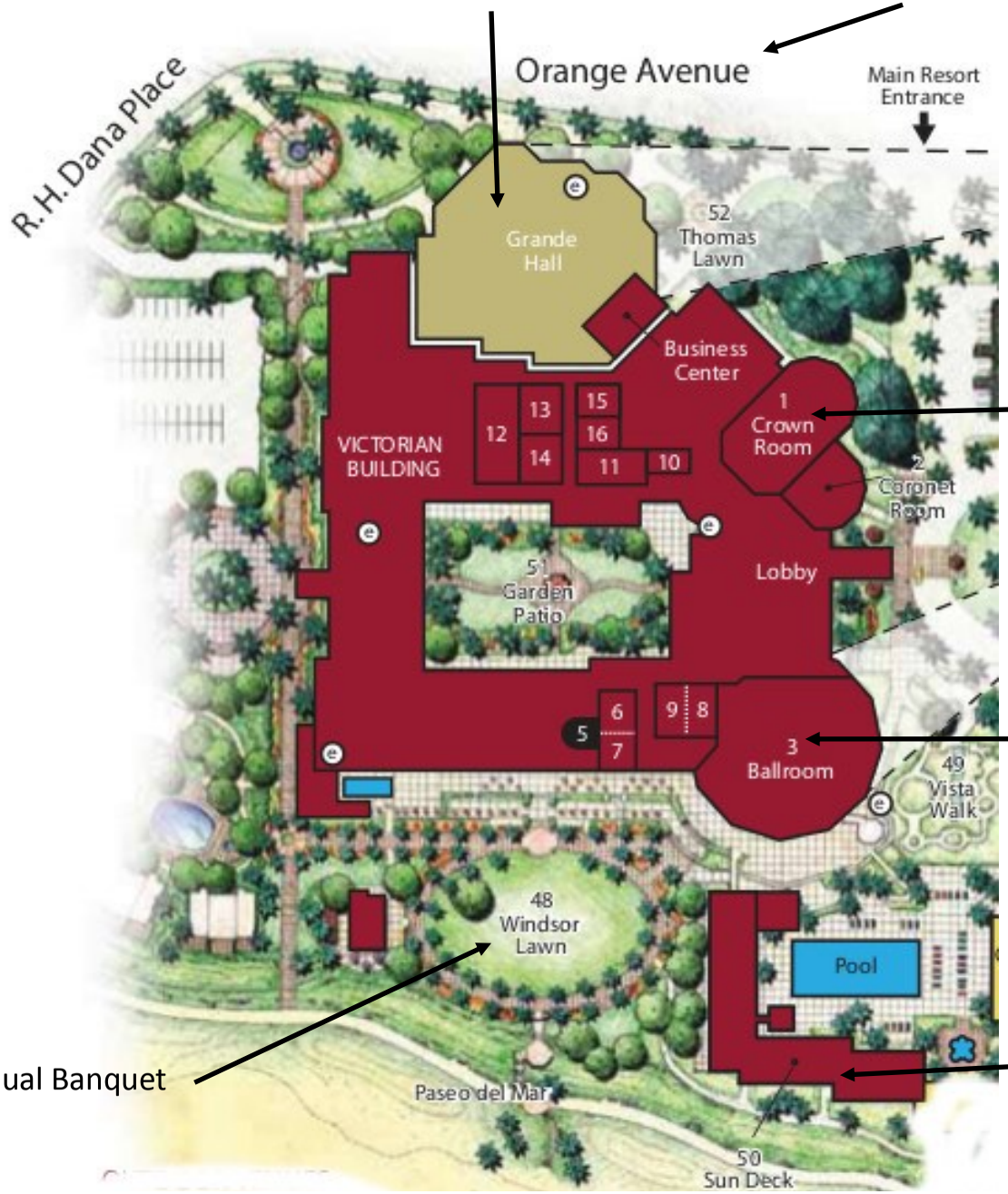
MEETINGS & EVENTS MAP

VICTORIAN BUILDING

1. Crown Room
2. Coronet Room
3. Ballroom
4. Carousel
5. Windsor Complex
6. Windsor
7. Embassy
8. Crystal
9. Continental
10. Executive Room
11. Garden Room
12. Hanover
13. Stuart
14. Tudor
15. Kent
16. York

GRANDE HALL

17. Grande Hall Foyer
18. Empress
19. Regent
20. Viceroy
21. Upper Grande Hall
22. Spreckels Complex
23. Spreckels Salon A
24. Spreckels Salon B
25. Spreckels Salon C
26. Spreckels Salon D
27. Wilder Complex
28. Wilder Salon E
29. Wilder Salon F
30. Wilder Salon G
31. Wilder Salon H
32. Edison Complex
33. Edison Salon I
34. Edison Salon J
35. Edison Salon K
36. Board Room



HOTEL DEL CORONADO FLOOR PLAN

NANOS would like to thank the following individuals for their generous donations:

Silver $10,000 - $19,999
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(as of January 7, 2015)

NANOS would like to thank the following Supporters and Exhibitors for their financial support of these activities

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Merz Neurosciences - $10,000
TEVA Neurosciences - $10,000

2015 Exhibitors:

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CME ACTIVITIES FACULTY AND PLANNER DISCLOSURE STATEMENTS

It is the policy of the North American Neuro-Ophthalmology Society (NANOS) in accordance with the Accreditation Council for Continuing Medical Education (ACCME) to ensure independence, balanced view of therapeutic options, objectivity, scientific rigor, and integrity in all of its continuing education activities.

Anyone engaged in content development, planning, or presenting must disclose any relevant financial relationships. The ACCME defines relevant financial relationships as those in which an individual (including the individual's spouse/partner) in the last 12 months: 1) has had a personal financial relationship in any amount with a commercial interest. A commercial interest is any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients; and who 2) also has the opportunity to affect the content of CME activity about the products or services of that commercial interest.

Disclosure information is reviewed by the NANOS Scientific Program Committee and CME Committee in advance in order to manage and resolve any possible conflicts of interest prior to the activity. Conflict resolution must be resolved through any of the following options: Peer review for evidence-based content by experts, provide faculty with alternate topic, independent review to ensure evidence supports recommendations, and/or attestation to non-commercial content. If a conflict cannot be resolved, the individual is not allowed to participate in any aspect of the program or planning.

Below is the list of relevant financial disclosures for the faculty and planners.
Please note that platform presenter disclosure information is listed in the syllabus at the end of each abstract.

Name	Commercial Interests	Nature/Role
Rudrani Banik, MD (F)	The National Eye Institute	Site Investigator for IIHTT
Valérie Biousse, MD (F)	GenSight, Thieme, Elsevier, Novartis	Consultant, Book Royalty, Book Royalty, Publication of education material
Claude F. Burgoyne, MD (F)	Heidelberg Engineering, Reichart Instruments	instruments, unrestricted research support, occasional travel expenses, no peronal income, consultant, Instruments
Anne L. Coleman, MD, PhD (F)	Allergan	Honorarium,
Helen V. Danesh-Myer, MD, PhD, FRANZCO (F)	Allergan, Optic Nerve Research Fellow	Unrestricted Research Funds
Rod Foroozan, MD (P)	Lundbeck	Speaker
Jeffrey Goldberg, MD, PhD (P)	Allergan	Teaching
Ari J. Green, MD (F)	Apoplied Clinical Intelligence/Biogen Idec, Medimmune, Novartis Pharma, Mylan Pharma	End Point Adjudication Committee, End Point Adjudication, Steering Committee, Expert Witness/Advisory Board
Paul Kaufman, MD (F)	Advanced Genetics Technology Corp, Alcon, Allergan, Bausch and Lomb	Consultant
Daniel Kelly, MD (F)	Mizuho, Inc.	Surgical Instrument Design Royalties
Leonard A. Levin, MD, PhD (F)	Merz, Inotek, Aerie, Allergan	Consultant, Consulting/Research, Consultant, Lectures
Jonathan Myers, MD (F)	Alcon, Allergan, Haag Streit	Speaker, Research Grant, Consultant
Mark L. Moster (F)	Biogen Idec, Speakers Bureau, Research Support	Honorarium, Acorda Therapeutics, Clinical Study
Harry Quigley, MD (F)	Zeiss, Sensimed, AC Immune, Graybug	Consultant, Consultant, Consultant, Science Advisory Board
Alfredo Sadun, MD, PhD (F)	Stealth Peptides, Edison Pharmaceutical	PI Laboratory Science, PI clinical Trial,
Michael Wall, MD (F)	Zeiss Humphrey	Consultant and completing perimetry protocol
Robert N. Weinreb, MD (F)	Alcon, Allergan, Valeant, Zeiss, Heidelberg Engineering, Zeiss, Topcon, Optovue, Tomey, Konan, Lumenis,	Consultant, consulting fees,

Key: P = Planner; F = Faculty
All other faculty and planners have declared that they have no relevant financial disclosures.

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Program Schedule

SATURDAY, FEBRUARY 21, 2015

10:00 a.m. – 4:00 p.m.	**San Diego Zoo Safari Park Excursion**	**Depart from Hotel del Coronado Lobby**
2:00 p.m. – 8:00 p.m.	**Registration**	**Ballroom Foyer**
6:00 p.m. – 7:30 p.m.	**Opening Reception (all are welcome)**	**Sun Deck**

SUNDAY, FEBRUARY 22, 2015

6:00 a.m. – 6:45 a.m.	**Yoga Class**	**Spreckels Complex**
6:30 a.m. – 5:30 p.m.	**Registration**	**Ballroom Foyer**
6:30 a.m. – 7:45 a.m.	**Breakfast**	**Crown Room**
6:30 a.m. – 3:30 p.m.	**Exhibits**	**Crown Room**
7:45 a.m. – 5:00 p.m.	**FRANK B. WALSH SESSION [7.25 CME]** *Co-Chairs: Benjamin M. Frishberg, MD & Howard R. Krauss, MD* *Neuroradiologist*: *John Rhee, MD* *Neuropathologist: Yuki Takasumi, MD* *Additional Experts:* *Neurosurgeon: Daniel Kelly, MD* *Otorhinolaryngology/Head & Neck Surgeon: Chester Griffiths, MD, FACS*	**Ballroom**

This session is designed to present a wide variety of Neuro-Ophthalmic cases to an audience of physicians with varying neuroscience backgrounds who have a common intellectual interest in the broad range of conditions that impact the human visual pathways and ocular motor systems.

The format is a clinicopathologic conference. Clinical cases will be presented by Neuro-Ophthalmologists with comments by a neuroradiologist, neuropathologist and other selected experts. Necropsy, surgical pathology, and neuroimaging will help illuminate clinical points. Cases will be discussed from clinical, anatomic, radiologic and pathologic aspects with emphasis on diagnosis, pathophysiology and management. Audience participation is encouraged.

Upon completion of this course, participants should be able to: 1) Recognize the varied presentations of Neuro-Ophthalmic disease; 2) Correlate the anatomic localization and histopathologic appearance with the clinical presentations; 3) Effectively use radiologic procedures in diagnosis; 4) Recognize both the value and limitations of neuropathology; and 5) Discuss newly described diseases and their connection to Neuro-Ophthalmology.

11:50 a.m. – 1:10 p.m.	**Lunch (Included)**	**Crown Room**
12:15 p.m. – 1:15 p.m.	**Carrier Relations Committee Meeting**	**Garden Room**
12:15 p.m. – 1:15 p.m.	**Membership Retention and Recruitment Meeting**	**Executive Room**

12:15 p.m. – 1:15 p.m.	**Patient Advocacy Groups Liaison Committee Meeting**	**Tudor Room**
5:15 p.m. – 5:45 p.m.	**Frank B. Walsh Committee Meeting**	**Executive Room**
5:15 p.m. – 5:45 p.m.	**Fellowship Director's Meeting**	**Hanover Room**
5:45 p.m. – 6:15 p.m.	**Fellowship Committee Meeting**	**Hanover Room**
5:30 p.m. – 6:30 p.m.	**Members-in-Training Program and Reception** (All Students, Residents and Fellows are encouraged to attend)	**Garden Room**
Evening	**Dinner on your own**	

Frank B. Walsh Session I

Moderators: Laura Bonelli, MD, MDCE & Peter Savino, MD

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8:00 a.m. - 8:20 a.m.	**Some Like It Hot** Ahmara G. Ross, MD, PhD	**17**
8:20 a.m. - 8:40 a.m.	**A Shot in the Dark** Joshua Pasol, MD	**19**
8:40 a.m. - 9:00 a.m.	**Speakeasy** Joseph G. Chacko, MD	**21**
9:00 a.m. - 9:20 a.m.	**Shady Double Crosser** Francine Wein, MD	**23**
9:20 a.m. - 9:40 a.m.	**Under Pressure** Nathan H. Kung, MD	**25**
9:40 a.m. - 10:10 a.m.	***Coffee Break***	

Frank B. Walsh Session II

Moderators: Lynn Gordon, MD, PhD & Guy Jirawuthiworavong, MD, MA

10:10 a.m. - 10:30 a.m.	**Requiem for a Cabinet Maker *(Numb of the Above)*** Jennifer I. Doyle, MD	**27**
10:30 a.m. - 10:50 a.m.	**Three Weeks in Florida** Andrew R. Carey, MD	**29**
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11:10 a.m. - 11:30 a.m.	**Hiding and Out of Sight** Michael L. Morgan, MD, PhD	**33**
11:30 a.m. - 11:50 a.m.	**It's Not Just a FAD**, ***(EHR Fatigue Syndrome)*** Jacqueline A. Leavitt, MD	**35**
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Frank B. Walsh Session III

Moderators: Courtney Francis, MD & Alfredo Sadun, MD, PhD

Frank B. Walsh Session IV

Moderators: Leah Levi, MBBS & Elizabeth Palkovacs, MD, FRCSC

Some Like It Hot

Ahmara G. Ross[1], Islam Zaydan[2,3], Gabrielle Bonhomme[3], Ellen Mitchell[3], Tarek Shazly[1,3], Deborah Parrish[1]

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History & Exam

A 71 year old Caucasian man with a past medical history of hypertension, hyperlipidemia, Type 2 DM, ESRD status post renal transplant, facial melanoma, currently on ASA for a stable left sided putaminal hemorrhage presented with new right sided ptosis and lower extremity weakness. Brain MRI obtained on admission showed small cortical hemorrhages consistent with prior stroke, without evidence of acute pathologic changes. Repeat fine cut MRI of the brain and orbits with and without contrast showed an enhancing lesion in the right parietal bone, clinoid process, and associated abnormal soft tissue changes extending into the right orbital apex, adjacent superior right sphenoid sinus, and the right anterolateral cavernous sinus.

EMG showed no evidence of a neuromuscular disorder. Lung and parietal bone biopsy revealed CD10 positive atypical lymphoid cells. On laboratory evaluation, a CBC revealed a low red blood cell count. A lumbar puncture revealed an opening pressure of 12.5 mmHg with an Epstein Barr Virus load of 115 with normal cell counts otherwise. Lymphoma panel showed no abnormal lymphatic cells. Additional CT of the chest, abdomen, and pelvis revealed multiple well-circumscribed pulmonary nodules suspicious for pan-lobar metastatic disease involving both the right and left lungs in addition to profound mesenteric lymphadenopathy. Bone scan showed evidence of multiple areas of involvement in the skull, right humerus and left tibia.

Vital signs were normal. Visual acuity was 20/60 OD and 20/30 OS, color vision was intact, visual fields were normal and pupils were anisocoric (R 4mm, L 3mm both reactive) with near complete ptosis on the right with severely depressed levator function. His right eye was unable to adduct past the midline while the left eye had normal range of motion. There was an associated right-sided facial droop. Motor testing showed normal bulk and tone with normal reflexes. There were no sensory deficits.

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Some Like It Hot

Answer

Final Diagnosis
Infiltrative Right Cranial Nerve Palsy secondary to Post Transplant Lymphoproliferative Disorder

Summary of Case
Findings were concerning for Myasthenia Gravis, Recurrent Melanoma, Lymphoma, or a Post-transplant Lymphoproliferative Disorder (PTLD). EMG showed findings suggestive of chronic lumbosacral radiculopathies superimposed on a mild sensorimotor polyneuropathy, but a normal functioning neuromuscular junction. Repeat MRI of the brain and orbits showed abnormal enhancement of the right anterior clinoid process with soft tissue extending into the right orbital apex, adjacent superior right sphenoid sinus as well as the anterolateral right cavernous sinus. Bone scan showed increased uptake in the right humeral head extending into the proximal humerus with a focal, circular region of uptake in right posterior parieto-occipital skull.

After non-diagnostic pathologic examination of a lymph node obtained by CT guided lung biopsy, parietal bone biopsy was obtained which showed abnormal B cell predominate cell populations, LMP-positive cells differentiating between Primary Lymphoma and PTLD.

Struggle/Dilemma of the Clinical Presentation Description
PTLD is a common cancer in patients after organ transplants resulting in lymphatic cell proliferation from immunosuppression[1]. The cancer has a propensity to spread to extranodal sites, most commonly the lung and GI tract[2]. Presentation in the orbit and cranial nerves represents a rare manifestation of this disease. Good pathology and a strong clinical suspicion is critical to the diagnosis of this disease and requires a good histology work up with special staining and in-situ hybridization.

Keywords: Diplopia, Ocular Motor Nerve Palsy, Cranial Nerve Palsies, Post-Transplant Lymphoproliferative Disorder

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2. Lim, W.H., G.R. Russ, and P.T. Coates, Review of Epstein-Barr virus and post-transplant lymphoproliferative disorder post-solid organ transplantation. Nephrology (Carlton), 2006. 11(4): p. 355-66.

A Shot in the Dark

Joshua Pasol[1], Ricardo Komotar[2], Feisal Yamani[2]

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History & Exam

A 74 year-old man with a chief complaint of difficulty with night time driving for several years as well as difficulty going from a lighted room to a dark room. PMH of high cholesterol, BPH, hypothyroidism, GERD, glottic squamous cell cancer without recurrence, and a prior history of alcoholism. POHx: cataract extraction right eye and AMD. Medications include
Multivitamin, Aspirin, Synthroid, Tamsulosin, Omeprazole, Crestor. Drinks wine intermittently and stopped drinking after possible DT's. He owns a bar. His initial exam VA: 20/25 OU, normal IHCP, CFVF: OD constricted, OS normal. Pupils with no APD but were sluggish. IOP's 13 mm Hg
OU. Motility showed some slight decreased abduction OU: 5ET primary, 10ET left, 5ET right gazes. SLE: PCIOL OD, NS cataract OS. Optic nerves had 0.7 cups with difficulty in appreciating any pallor. He had a few RPE macular changes OU. The HVF appeared reliable with severe constriction OD>OS (MD -29 and -17 respectively). RNFL OCT showed a mean thickness of 69 and 61 microns respectively. Testing was later done.

Financial Disclosures: The authors had no disclosures.

Grant Support: None

A Shot in the Dark

Answer

Final Diagnosis
Idiopathic Hypertrophic Pachymeningitis mimicking Normal Tension Glaucoma Visual Field loss

Summary of Case
Given his complaints and VF findings, a full field ERG was performed which showed no evidence of rod dysfunction or CAR/MAR. The dx of NTG was made given cupping and VF constriction. However, an MRI was ordered which revealed pachymeningeal thickening with enhancement around both optic nerves and a mass in the foramen magnum. A spinal tap revealed normal pressure, CSF protein of 370 mg/dL, normal glucose, 45 WBC with 95% lymphs. Flow and cytology were negative for malignancy or monoclonality. Numerous lab tests were negative for any inflammatory disease (ACE, ANCA, RPR, SPEP, SSa/SSb, ANA, RF, Beta-2 microglobulin, PSA). A biopsy of the foramen magnum lesion was performed and it revealed: "dense fibrosis with inflammatory cells containing T and B lymphocytes and plasma cells without any evidence of lymphoma". The diagnosis of an inflammatory pachymeningitis was made. He was given oral prednisone with improvement of the visual field.

Struggle/Dilemma of the Clinical Presentation Description
1. Idiopathic pachymeningitis presentation of constricted visual fields mimicking normal tension glaucoma given optic nerve cupping and visual field findings.
2. Initial complaints sounded like a rod dysfunction but proved to be optic nerve related.

Keywords: Optic Neuropathy, Autoimmune Diseases, Cupped Optic Nerve, MRI, Visual Field

Speakeasy

Joseph G. Chacko, Marcus Moody, Harry H. Brown, Sarkis Nazarian

University of Arkansas for Medical Sciences Little Rock, AR, USA

History & Exam
A 64 year-old Caucasian gentleman presented with an unusual complaint. He stated that if he touched the inside of his right cheek with his tongue, he felt a tingly sensation in his R eyebrow. This had started one month ago. He also complained of foreign body sensation and discomfort in the right eye for six months. Additionally, he had recently noted a droopy R eyelid for which his local ophthalmologist had placed a stitch in his R upper lid to lift it. He also complained of recent binocular diagonal double vision. Past medical history included hypertension, hyperlipidemia, emphysema, and coronary artery disease requiring 4 stents (2002 and 2011). Social history was significant for 50 pack-years of smoking, and he drank 6 beers per week. His medication list included simvastatin, prasugrel, fluticasone-salmeterol, tiotropium bromide, aspirin, metoprolol, and hydrochlorothiazide. Exam revealed best-corrected visual acuity of 20/40 and 20/25. BP was 125/70. Pupils were 5.5 mm and 5 mm, with no RAPD. IOP was 19 and 21. Eye movements revealed -1 adduction, -3 supraduction, and -1 abduction in the R eye only. Visual fields were full to confrontation OU. External exam revealed ptosis with an MRD of -2 OD and +2 OS. Facial sensation to cotton tip was WNL bilaterally. Slit lamp revealed a decreased tear film OD and mild corneal scarring OD. There were 2+ nuclear sclerotic cataracts OU. Dilated fundus exam revealed pink, sharp optic discs with normal cups and spontaneous venous pulsation OS. A diagnostic procedure was then performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Speakeasy

Answer

Final Diagnosis
Adenoid cystic carcinoma of right pterygopalatine fossa with perineural spread to the cavernous sinus

Summary of Case
The patient had a right partial 3rd nerve palsy combined with a mild R 6th nerve palsy, as well as right 5th nerve dysfunction. A right cavernous sinus lesion was suspected. An MRI of brain without contrast and CT head had been done six months ago and had been reported as normal to the patient. Review of those studies revealed some asymmetry to the cavernous sinus area on the right. MRI/MRA brain/orbits without and with gadolinium was then performed. A 2 cm enhancing mass was found in the R pterygopalatine fossa with perineural spread to the cavernous sinus with involvement of R 3rd and 5th cranial nerves. CT scan showed bony erosion and lytic changes involving the R pterygoid base and pterygoid portion of the R sphenoid wing. The patient was then promptly referred to ENT for endoscopic biopsy of the mass via a transnasal approach. Pathologic examination was indicative of Adenoid cystic carcinoma (ACC). The tumor cells were reactive to 34betaE12 while nonreactive to chromogranin and synaptophysin. Two months later, the cancer was resected via a combined ENT/Neurosurgery procedure. This was followed by post-operative XRT (30 treatments). 8 months later, MRI with gadolinium revealed no suspicious area of enhancement to suggest tumor recurrence. Neuro-ophthalmic follow-up revealed a decrease in vision OD to 20/80 due to dry eye and corneal scarring. Color vision was normal. Pupils were 4 and 3.5 mm without RAPD. R face had decreased sensation. Motility of R eye was stable. Frequent lubrication of the R eye was encouraged, and smoking cessation was stressed. ACC, a malignant epithelial cancer, mostly arises in the major and minor salivary glands, nasopharynx, and lacrimal glands. The incidence of intracranial invasion is 4-22%, most commonly by perineural invasion. Prognosis is poor with a survival of less than 50% at 5 yrs. (1)

Struggle/Dilemma of the Clinical Presentation Description
First of all, the initial local MRI gave the patient false assurance that he did not have a tumor. But this MRI was done without contrast, and it was done early in the patient's presentation. So the tumor was missed. Secondly, the local ophthalmologist went ahead and tried to fix the patient's ptosis since he thought the MRI was clear. This, however, probably delayed the diagnosis. The ptosis surgery was masking the true droopy eyelid.

Keywords: Cavernous Sinus Tumor, Perineural Invasion, Adenoid Cystic Carcinoma

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Shady Double Crosser

Francine Wein

McGill University Montreal, QC, Canada

History & Exam
A 62-year-old woman presented with a one-month history of severe light sensitivity and headache, and a two week history of diplopia. Her photophobia was severe enough for her to wear sunglasses indoors. Her past medical history was significant for a cholecystectomy and Crohn's disease, for which she had undergone a partial colectomy. Her only medication was ranitidine. Review of systems was unremarkable. Neuro-ophthalmic examination revealed visual acuity of 20/20 OU. She had normal anterior segments, pupillary reactions, and fundi OU. Motility assessment showed an isolated left abduction deficit. The fifth and seventh cranial nerves were intact. There was no ptosis, proptosis, or nystagmus. CT scan of the brain revealed a 3.6 x 2.4 cm lesion centered on the left skull base. It extended to and filled most of the sphenoid sinus. There was bony destruction, with complete destruction of the petrous apex. The mass also broke through the clivus to extend into the premedullary cistern. There were areas of hyperdensity within the mass. MRI showed a large lesion of the left clivus and petrous bone. It was hyperintense on TI and enhanced homogeneously with gadolinium. The mass was shown to extend to the lower aspect of the sella. The patient underwent a metastatic workup. Her blood work was significant for an elevated alkaline phosphatase of 155 and a carcinoembryonic antigen of 61.6. CT of the chest was unremarkable. Abdominal CT showed several hypodense liver lesions, suggesting metastases. A 2.5 x 2.1 cm hypodense mass was present in the pancreatic tail. CA19-9, a serum marker for pancreatic cancer, was less than one. A diagnostic study was performed.

Financial Disclosures: The author had no disclosures.

Grant Support: None

Shady Double Crosser

Answer

Final Diagnosis
Pancreatic adenocarcinoma metastatic to the skull base

Summary of Case
The patient underwent a liver biopsy. Pathology revealed moderately differentiated adenocarcinoma. The immunohistochemical profile of the tumor was CK7+, CK19+,CK20-, CDX2 focally +, TTF1-, consistent with a pancreatico-biliary or upper GI origin. A subsequent biopsy of the clival mass showed identical pathology. Pancreatic cancer is a fatal disease, with a 5 year survival rate of 5%. Patients often present with nodal and/or metastases to liver, lung or bone. Cranial and brain metastases are extremely rare. In a 2003 review of 1229 consecutive patients with pancreatic adenocarcinoma, Park et al found only 4 (0.33%) with cerebral metastases. There have been only 23 reported cases of ante mortem intracranial metastases. Of these, 17 had metastases to the brain parenchyma (usually multiple), 5 presented with carcinomatous meningitis, and one with epidural metastasis. In only 3 of these cases were the intracranial lesions the primary manifestation of pancreatic adenocarcinoma. This woman is the fourth such patient, and is unique in that she presented with a single, large metastatic lesion to the skull base, with symptoms that have never been associated with pancreatic adenocarcinoma: severe photophobia and diplopia from sixth nerve compression at the clivus. The median survival when pancreatic carcinoma metastasizes to the brain is less than 3 months. However, Lemke et al reported 2 unusual patients with brain metastases presenting 11 months and 6 years after their primary tumors had been resected. The brain metastases were microsurgically resected, and these patients survived more than 6 and 10 years, respectively.

Struggle/Dilemma of the Clinical Presentation Description
Did two biopsies need to have been done? Metastatic brain lesions are more common than primary tumors; however the neuroradiologist felt that it was unusual for a single metastatic lesion to grow to such a size without evidence of other metastases. Two different malignancies would be highly unusual, but so is intracranial metastasis as the primary manifestation of pancreatic adenocarcinoma.

Keywords: Photophobia, Diplopia, Metastasis, Skull Base

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Under Pressure

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[1]Department of Neurology, Washington University School of Medicine St Louis, MO, USA, [2]Department of Ophthalmology, Washington University School of Medicine St Louis, MO, USA

History & Exam

A 29-year-old woman was referred to neuro-ophthalmology clinic for 1 year of headaches and papilledema discovered 2 months earlier. She complained of recently blurred vision but no positional headache, pulsatile tinnitus, transient visual obscurations, or other neurologic issues. She used no medications and denied any recent illnesses except for thrombocythemia (591k) on recent blood work, and had no significant past medical history. Her initial examination in 4/2009 revealed normal acuity with 20/20 VA OU, equal pupils without RAPD, and severe grade 4 papilledema OU with several choroidal folds through both maculae. No hemorrhages were noted. All other portions of the examination were normal. Her BMI was 27. Humphrey SITA Standard visual fields were performed and showed slight enlargement of the blind spot OU with a nasal step in the L eye. An MRI of the brain and orbits with and without gadolinium was normal with normal venous flow voids. CSF analysis showed an opening pressure of 26 cm H2O with 1 RBC, 1 WBC, Protein 75, Glucose 69, and no abnormalities on cytology. Although she had atypical features, a preliminary diagnosis of Probable Pseudotumor Cerebri was made and she was initiated on acetazolamide, with improved papilledema over the next several months. Over the next three years, however, she developed worsening vision with multiple additional symptoms.

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Under Pressure

Answer

Final Diagnosis
POEMS syndrome. She fulfilled all major criteria: 1) lambda-restricted plasma cell population, 2) polyneuropathy, 3) sclerotic bone lesion, 4) Castleman disease; and all minor criteria: 1) organomegaly (splenomegaly), extravascular volume overload (body wall anasarca), 3) endocrinopathy (elevated TSH/ACTH/Prolactin), 4) skin changes (hyperpigmented rash), 5) papilledema, and 6) thrombocytosis.

Summary of Case
5/2009: Essential thrombocythemia was considered for her isolated thrombocytosis (591k). However, two bone marrow biopsies showed megakaryocytic hyperplasia without atypia, and JAK-2/BCR-ABL were negative. 2/2011: CIDP was considered when she reported a three year history of distal sensory loss with several months of mild gait ataxia and distal weakness. Outside electrodiagnostics showed a mixed axonal-demyelinating polyneuropathy. Regular IVIG infusions were initiated without benefit. 3/2012: Lupus was considered following several months of fatigue, photosensitive facial rash, distal hand hyperpigmentation, and positive ANA 1:320. Splenomegaly, mild axillary and retroperitoneal lymphadenopathy, and anasarca were noted on CT, but PET revealed no FDG-avid targets. She had no response to prednisone, hydroxychloroquine or methotrexate. 5/2012: Her vision worsened with decreased visual fields. Grade 5 disc edema was seen OU. Repeat Brain/Orbit MRI/MRV were negative. Repeat LP showed an acellular fluid with increasing protein (now 140). Opening pressure was 26. Acetazolamide was uptitrated with repeated prednisone bursts to preserve vision. 9/2012: A second opinion was obtained at our neuromuscular clinic. Electrodiagnostics showed a primary demyelinating polyneuropathy without conduction block or abnormal temporal dispersion, changes consistent with a paraproteinemic neuropathy. Serum and urine immunofixation showed no monoclonal gammopathy. Serum VEGF level was markedly elevated at 6240 pg/ml. 12/2012: Biopsy of a sclerotic T5 vertebral body lesion showed lambda-predominant nucleolated plasma cells suggestive of a plasma cell neoplasm. Biopsy of an enlarged axillary lymph node showed abnormal follicles with involuted germinal centers and increased interfollicular vascular proliferation and plasma cells consistent with Castleman disease. She was diagnosed with POEMS syndrome. She received XRT to T5/9 followed by Lenalidomide/dexamethasone. Her VEGF level became undetectable, but she required L-optic nerve sheath fenestration in 4/2013 to preserve vision. Following a consolidative autologous stem cell transplant in 6/2013, her papilledema resolved and her strength and gait improved significantly. She remains in remission.

Struggle/Dilemma of the Clinical Presentation Description
The primary challenge in this case was determining the unifying diagnosis for her papilledema, mixed axonal-demyelinating polyneuropathy, thrombocytosis, and hypothyroidism. POEMS syndrome was especially difficult to diagnose given the absence of a serum monoclonal paraprotein, a finding present in nearly all cases reported to date.

Keywords: Paraneoplastic Disorders, Polyneuropathy, Papilledema, Optic Nerve Sheath Fenestration

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Requiem for a Cabinet Maker *(Numb of the Above)*

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[1]University of Alabama, Dept. of Ophthalmology Birmingham, AL, USA, [2]University of Alabama, Dept. of Neurology Birmingham, AL, USA, [3]University of Alabama, Dept. of Neurosurgery Birmingham, AL, USA, [4]4University of Alabama, Dept. of Neuropathology Birmingham, AL, USA

History & Exam

A 54-year-old white male presents with 3 weeks of painless horizontal nystagmus and 6 months of left sided forehead numbness. He reports a 20 lbs weight loss. Medical history includes a renal transplant 30 years prior. He takes prednisone 30 mg QOD and azathioprine. Visual acuity is 20/20 OU, color vision is 8 of 8 OU and confrontational fields are full OU. Pupils are equal and reactive without an R APD. Ductions are full but with end gaze nystagmus. There is no proptosis or ptosis but there is decreased V1 sensation on the left. Fundus examination is normal. A contrasted cranial and orbital MRI showed an enhancing mass in left superior orbit. He was treated with a Medrol dose pack and had mild improvement in symptoms. Left orbital biopsy was read as orbital fibrotic histiocytoma. One month later his examination showed NLP vision OS associated with an amaurotic pupil. He had decreased abduction OS. He had 4 mm of proptosis OS. Left V1 sensation was still diminished and fundus remained normal OU. He was admitted to the hospital and prescribed IV methylprednisone. Repeat MRI showed increased in size of left orbital mass, now involving the optic nerve. CT orbits showed adjacent bone demineralization. He underwent left orbital radiation. Five months later, patient presents to ED with shortness of breath and transient visual loss OD. Vision remained 20/20 OD and NLP OS. Ductions now show limited superior gaze OD and limited all directions OS. Decreased left sided V1 and V2. No optic disc edema OD and mild optic nerve edema OS. MRI shows enlarging left sided orbital mass with a new right-sided retro-orbital mass. Further work up reveals new bilateral pulmonary nodules and metastatic appearing hepatic lesion. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Requiem for a Cabinet Maker *(Numb of the Above)*

Answer

Final Diagnosis
Poorly differentiated carcinoma with sarcomatoid features of the orbit, liver, and pleura

Summary of Case
54 year-old white male with visual acuity of 20/20 OU presents with nystagmus and decreased sensation along left V1 distribution and subsequently goes to NLP OS. Left orbital mass biopsy prior to vision loss and subsequent to visual loss OS indicated orbital pseudotumor and patient was treated with steroids and orbital radiation. MRI shows enlargement of left orbital mass and new right orbital mass. Systemic work up reveals pulmonary nodules, pleural effusion, and liver lesion. Second orbital biopsy, pleural biopsy, and liver biopsy all showed poorly differentiated carcinoma with sarcomatoid features. Patient continued to have visual loss OD. He remained on oral steroids in an attempt to retain vision as long as possible. He was placed on hospice and passed away two weeks later. Sarcomatoid carcinoma (Carcinosarcomas) is defined by the World Health Organization as a biphasic tumor consisting of malignant epithelial and mesenchymal elements (1). There have only been three cases of sarcomatoid carcinoma of the orbit not associated with paranasal sinus malignancy (2,3). These types of cancers in the orbit and elsewhere are very aggressive and with poor prognosis.

Struggle/Dilemma of the Clinical Presentation Description
With initial presentation and biopsy result, orbital pseudotumor seemed likely, yet due to aggressive nature of lesion with minimal response to steroids and radiation, an alternate diagnosis was suspected. The struggle was trying to preserve vision and ultimately life in the setting of an original biopsy interpreted as a benign process.

Keywords: Transient Monocular Visual Loss, Orbital Tumor, Facial Numbness, MRI, Pathology special staining

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Three Weeks in Florida

Andrew R. Carey[1], J. Antonio Bermudez-Magner[1], Sander R. Dubovy[1], Norman J. Schatz[1], Linda L. Sternau[2], Byron L. Lam[1]

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History & Exam

A 36 year-old man presented with severe headaches, bilateral leg numbness, and bilateral decreased vision. He was born in Ecuador where he received BCG vaccination and immigrated to US at age 19. In 2005 he enrolled in nursing school and volunteered in homeless shelters. PPD was positive with a negative chest x-ray. In August 2011 he developed pleuritic chest pain; chest x-ray showed a 2 cm cavitary lesion in the right upper lobe. He was diagnosed with active TB and completed treatment in August 2013. In December 2013 he developed headaches associated with neck stiffness and intermittent blurry vision which progressed over 6 months. In May 2014, while on vacation in Ecuador, he had a prolonged seizure requiring intubation. Upon recovery he returned to Florida and presented to the emergency department with visual loss and drowsiness, but arousable to verbal stimuli. Vision was light perception OU with sluggish pupils. Extraocular movements were full but demonstrated exotropia. Fundus examination showed papilledema. Strength was reduced in all four limbs with apraxia in the upper right. Sensation was decreased from groin to foot, left worse than right. Serum white count was elevated to 25,300. Brain MRI demonstrated hydrocephalus and diffuse leptomeningeal enhancement including bilateral intracranial optic nerves and chiasm. CSF analysis showed 110 leukocytes with 66% monocytes. Lumbar spine MRI was negative. The patient was diagnosed with recurrent TB with meningitis and was restarted on TB medications. CSF smears, cultures, and PCR were negative for infection including TB. Lumbar drain was placed and ICP was 40 cm water. Repeat brain MRI showed progressive leptomeningeal enhancement and hydrocephalus. Repeat CSF analysis demonstrated cellular atypia with equivocal immuno-histochemical staining. Flow cytometry revealed a mixture of immune cells but no B lymphocytes. A diagnostic procedure was performed.

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Three Weeks in Florida

Answer

Final Diagnosis
Primary Leptomeningeal Melanomatosis

Summary of Case
The patient underwent leptomeningeal biopsy. During surgery, the meninges were noted to have diffuse pigmentation. Histopathologic evaluation demonstrated proliferation of heavily pigmented cells with prominent nucleoli. Immunostains were diffusely positive for S-100 as well as melanocytic markers HMB-45, MART-1 and tyrosinase while negative for keratinocyte markers AE1/AE3, and PCK26. The Ki-67 staining showed foci of elevated labeling > 10%. Genetic testing was negative for BRAF p.V600E and BRAF p.V600K mutations. Full body dermatologic examination was negative for pigmented skin lesions. CT of the chest, abdomen, and pelvis were negative for tumors. PET scan was unattainable while inpatient. Ophthalmic examination demonstrated the patient was awake but confused and only partially aware of his surroundings. Visual acuity was 20/400 in each eye, visual fields were constricted to confrontation by finger counting. His extraocular movements appeared to be full with some exotropia. His pupils were noted to be sluggish and mid-dilated but no afferent defects were present. His anterior segment was unremarkable without scleral pigmentation; fundus examination was significant for grade 3 papilledema without any tumors present. He then underwent ventriculo-peritoneal shunt placement for persistent hydrocephalus. He was started on ipilimumab, a monoclonal antibody to increase immune response to melanoma cells. The patient was discharged to rehab where he self-extubated his tracheostomy and could not be re-intubated subsequently expiring. Autopsy was not feasible as death notification occurred over 36 hours.

Struggle/Dilemma of the Clinical Presentation Description
This patient presented with chronic headache and progressive vision loss with a history of TB and elevated white count in both serum and CSF indicating infection, likely recurrent TB. Additionally, when CSF showed possible malignancy, this was unexpected given his young age and lack of prior cancer.

Keywords: Papilledema, Leptomeningeal Melanomatosis, Vision Loss, Headache, Magnetic Resonance Imaging

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Growing Suspicion

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History & Exam

A 44 year-old man presented to the emergency department in July 2011 for progressive painless vision loss in the right eye for 3 months. On presentation, vision was 4/200 in the right and 20/20 in the left with an afferent pupillary defect on the right. His visual field was full to confrontation but automated perimetry revealed a central scotoma. The remainder of the exam was normal with the exception of slight elevation of the optic nerve head along with mild perivascular sheathing. He received IV solumedrol for 3 days followed by an oral steroid taper. Fat saturated MRI did not show enhancement of the optic nerve nor any brain abnormalities or mass lesions. He had a normal lab workup including CBC, BMP, quantiferon gold, B12, RPR, and ACE and a normal CXR. On follow up one month later, he experienced no vision improvement. At this point, testing for Leber's hereditary optic neuropathy (LHON) was performed and was negative. He returned 6 months later with subjective worsening of vision in the right eye, however acuity was stable at 4/200. He was started on IVIg therapy and autoimmune and NMO antibodies were drawn. Antibody testing was negative and on follow up one month later, his acuity remained unchanged and his scotoma was larger and denser. He was again lost to follow up for 3 years until he began losing vision in the left eye. Exam revealed counting fingers vision in the right eye and 20/40 with a temporal visual field defect in the left eye. MRI showed an enhancing mass extending from the planum tuberculum and suprasellar area to the right temporal lobe and into both orbits. A procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Growing Suspicion

Answer

Final Diagnosis
Meningeal sarcoidosis masquerading as en plaque meningioma with intraseptal cardiac involvement

Summary of Case
The patient underwent repeat MRI in May 2014 in preparation for surgical resection of the mass. This showed complete enhancement of the skull base with the appearance of meningioma creeping down both intracranial optic canals and considerable tumor in the right orbit along the optic nerve and some tumor along the left optic nerve near the apex. He underwent right frontal skull base craniotomy with microscopic removal of suprasellar, right sphenoid wing, and skull based tumor. Intraoperatively, the tumor was found to be molded to the entire skull base as though carpeting had been laid over the structures including a heavy coating over the arteries. Pieces were removed and sent to pathology intraoperatively for examination. The preliminary description was highly atypical for meningioma and more likely to represent an inflammatory process. As the mass wrapped itself around the optic nerves and chiasm, it was not dissected off for fear of stripping the patient's own blood supply and the area was decompressed. Pathology showed marked granulomatous inflammation with multinucleated giant cells and central necrosis. No organisms were noted and AFB and GMS stains. This was felt to be consistent with meningeal sarcoidosis and the patient was referred to rheumatology for further management. He was placed on oral steroids as well as methotrexate with consideration of use of Remicade for long-term control. However, 3 months post-operatively he became short of breath and sustained a cardiac arrest, requiring defibrillation. Evaluation revealed popliteal DVT and bilateral PE's as well as radiographic evidence of intraseptal sarcoidosis. He underwent placement of an AICD and is currently on amiodarone and anticoagulation for nonsustained ventricular tachycardia. On ophthalmic follow up, his right eye remains counting fingers in the superotemporal quadrant and the left eye vision has returned to 20/20 with near-complete resolution of the visual field defect.

Struggle/Dilemma of the Clinical Presentation Description
This case highlights the importance of re-imaging in patients with steroid and especially IVIg-resistant optic neuritis. The patient initially presented with no diagnostic signs on neuroimaging as an indolent optic neuritis, then showed evidence of radiologic progression of a compressing and infiltrating mass. Furthermore, this case also reiterates the importance of a multi-disciplinary approach to these patients as they often have pulmonary involvement and in this case, cardiac inflammatory changes as well.

Keywords: Optic neuritis, Sarcoidosis, Meningioma, Steroid-resistant

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Hiding and Out of Sight

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History & Exam
A 75-year-old white woman presented with a history of biopsy-proven giant cell arteritis (GCA) presented with recurrence of severe left sided headaches and left global ophthalmoparesis for 4 days. GCA had been diagnosed 4 months prior by biopsy. Left eye vision loss occurred when an outside physician tapered corticosteroid therapy 5 weeks into her illness. MRI 5 weeks into her illness showed enhancement of the left orbital apex, adjacent temporal dura and neighboring cavernous sinus. Dural biopsy at that time was normal, and a second temporal artery biopsy performed then confirmed GCA. Examination was remarkable for left eye vision loss to no light perception with an amaurotic pupil and global left ophthalmoparesis including ptosis and pupil involvement with a normal fundus. Repeat MRI showed progression of the prior lesions. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Hiding and Out of Sight

Answer

Final Diagnosis
Orbital aspergillosis

Summary of Case
Repeat MRI showed progression of the left-sided lesion involving the orbital apex as well as the cavernous sinus, adjacent dura mater, and neighboring ethmoid sinus. Lumbar puncture was non-diagnostic. Left orbitotomy revealed a purulent collection. Microscopic examination and culture showed Aspergillus fumigatus (Wiggin 1995, Hutnik et al 1997). Anti-fungal treatment with systemic voriconazole and local amphotericin B was initiated.

Struggle/Dilemma of the Clinical Presentation Description
The patient presented with GCA confirmed by temporal artery biopsy. Second temporal artery biopsy confirmed the diagnosis, and dural biopsy was normal. Only a third biopsy led to diagnosis.

Keywords: Giant Cell Arteritis, Infection, Temporal Artery Biopsy

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It's Not Just a FAD *(EHR Fatigue Syndrome)*

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History & Exam

A 29 year-old female nurse, nine months postpartum, presented with an inability to see her computer well for the past two months. She denied eye pain, diplopia, numbness, tingling or weakness. There were no changes in vision in bright vs. dim lighting. She also had a headache at the back of her head for two months that was relieved with OTC medications. She denied any events immediately preceding the blurred vision. She also complained of shortness of breath, unexplained weight loss and extreme fatigue, sleeping 10 hours per night and taking naps over her lunch break at work. Workup by her primary care doctor revealed a normal CXR, ECG with sinus bradycardia and anemia (Hgb 9.6, Hct 28.7). Towards the end of her recent pregnancy she was evaluated for polydipsia (drinking up to 9 L /d) and nocturia (6-7 x /night). Water deprivation testing during pregnancy was not possible but sodium of 133 made the diagnosis of diabetes insipidus (DI) unlikely. Symptoms improved after delivery and therefore the polyuria and polydipsia was attributed to pregnancy. Postpartum she also developed fairly severe anxiety and depression that was managed with sertraline and clonazepam. On examination, best corrected visual acuity was 20/30 OU, Ishihara color plates were 11/13 OD, 13/13 OS. Pupils reacted briskly without an RAPD. Visual fields were full to confrontation. Slit lamp and dilated fundus examination was unremarkable, including absence of macular abnormalities or optic disc pallor. Goldmann fields showed a suggestion of a homonymous field defect, but had variable responses and the perimetrist noted that she was often falling asleep during the test. Optical coherence tomography showed a normal average retinal nerve fiber layer thickness OU. Lab workup showed an elevated ESR of 70 and an elevated ACE of 62.Tests were performed.

Financial Disclosures: The authors had no disclosures.

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It's Not Just a FAD *(EHR Fatigue Syndrome)*

Answer

Final Diagnosis
Langherhans cell histiocytosis involving the chiasm, hypothalamus and sacrum

Summary of Case
MRI brain: enhancing chiasmal and hypothalamic lesion with surrounding vasogenic edema extending into the tracts, without leptomeningeal spread, most likely pilocytic astrocytoma. Endocrinology consult: hypopituitarism [AM cortisol 5.9, free thyroxine 0.7, and ACTH 83, LH and FSH low but on birth control pills, prolactin 120 (high)]. She was started on hydrocortisone and levothyroxine with increased energy. She had been a marathon runner but was no longer running because of right lower back pain. MRI pelvis: indeterminate lesions right hemi-sacrum. Sacral biopsy: marked histiocytic infiltrate with cells positive for Langerin, S100 and CD1a immunostains, consistent with Langerhans cell histiocytosis (LCH). Other negative tests: bone marrow biopsy, CT chest and PET scan (only uptake in known pelvic/ intracranial lesions).LCH is characterized by proliferation of CD1a+ dendritic cells. LCH encompasses a range of clinical presentations and includes diseases previously designated as eosinophilic granuloma, Letterer-Siwe disease and Hand-Schuller-Christian syndrome, which were initially separated on the basis of organ involvement and disease severity. (1-3) LCH can affect bone, lung, hypothalamus, pituitary gland, skin, lymph nodes, liver and other organs (1-3). This disease predominantly affects children; adult onset occurs in only ~ 10%.CNS involvement in LCH most commonly involves the hypothalamic-pituitary system causing DI, but any part of the CNS can be involved (4). LCH with CNS disease is more likely to be multi-systemic and have skull lesions (5). While visual compromise in LCH is common from orbital lesions, only a few cases have been reported of intracranial visual pathway involvement (6).Chemotherapy with cladribine was started with improvement in her symptoms (7-9). MRI 3 months after treatment: hypothalamic lesion significantly reduced; PET: markedly reduced activity in the pelvic lesions. Visual acuity 20/20- and color normal OU. Visual fields: normal foveal threshold, inferior bitemporal defects.

Struggle/Dilemma of the Clinical Presentation Description
Polydipsia and polyuria during pregnancy resolved after delivery and was assumed to be pregnancy related. She had a history of anxiety and depression. The extreme fatigue led to unreliable responses on manual visual fields, raising the possibility of nonorganic vision loss. The ESR and ACE were elevated suggesting the possibility of an inflammatory etiology such as neurosarcoidosis. The initial MRI was read by neuro-radiology as a pilocytic astrocytoma. LCH occurs in adults only ~ 10%.

Keywords: Vision loss, Field loss, Fatigue, Intracranial Tumor

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Now you see it. Now you don't.

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History & Exam

A 70 yo RH African American female presented to our institution with sequential, severe vision loss in the preceding 4 months. Her past medical history included well-controlled hypertension and hyperlipidemia, CAD s/p coronary stent placement x 2 after MI, and stroke. She had no prior history of visual loss or eye surgeries. She was well until January 2014 when she was hospitalized for severe cholangitis complicated by septic shock requiring vasopressor support in the ICU. She does not recall exactly when she lost vision in her left eye but suspects it was during the hospitalization. In mid-April 2014 she was noted with Va 20/70 OD and NLP OS, had a left RAPD, and possible left optic disc pallor. Decreased vision OD was consistent with cataract, and uncomplicated surgery was performed on 5/2/14. She noted poor vision postop, and on 5/5/14 was HM OD and NLP OS with possible pallor of the right optic disc. ESR reported 3 days later was 102, and she was prescribed prednisone 60 mg po qd. Bilateral temporal artery biopsies were performed and were read as negative. Prednisone was tapered over the next month to 10 mg daily with some vision improvement OD. She then presented to our institution on 7/10/14 with Va 20/400 OD and NLP OS. The left pupil was amaurotic. Fundus exam showed mild pallor of both optic discs. OCT of the RNFL and macular GCC demonstrated diffuse loss. She remained on 10 mg prednisone daily at that time and felt her vision was slowly improving. A diagnostic procedure was performed.

Financial Disclosures: The author had no disclosures.

Grant Support: None

Now you see it. Now you don't.

Answer

Final Diagnosis
Neuromyelitis optica

Summary of Case
MRI brain/orbits was ordered and showed asymmetric enlargement and enhancement of the left optic nerve from its cisternal segment to the orbital apex, as well as scattered white matter lesions of the pons. Optic neuritis rather than ischemic optic neuropathy was suspected; a paraneoplastic antibody screen as well as inflammatory markers including NMO-IgG were ordered. NMO-IgG seropositivity was found (Mayo cell-based assay), and studies for syphilis, Lyme, TB, and sarcoidosis were negative or normal. About 5 weeks after presentation, the patient developed right sided facial, body, and extremity numbness, facial pain, and difficulty walking. She was admitted to the hospital, and MRI c-spine showed longitudinally extensive demyelinating lesion, giving her a definitive diagnosis of NMO. Plasmapheresis was performed and systemic symptoms improved. Rituximab infusions were initiated for long-term disease control. Vision has remained stable, and repeat imaging 2 months later showed reduced left optic nerve enhancement but persistent pontine lesions.

Struggle/Dilemma of the Clinical Presentation Description
This patient had a classic history for sequential ischemic optic neuropathy with multiple risk factors for PION or AAION. However, her TA biopsies were negative, and she had definite visual improvement in the right eye over 2 months. Pallor of the optic discs much less than expected for the severity of the vision loss. Therefore, alternative diagnoses needed to be considered, and therapy was markedly altered.

Keywords: Vision Loss, Optic Neuropathy, Facial Pain, Transverse Myelitis, Neuromyelitis Optica

References: None

A Weak Presentation

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History & Exam

An 82-year-old right-handed man with myasthenia gravis presented in May 2014 with double vision and right facial numbness and weakness. He was first seen in 1998 with horizontal diplopia. He had an abduction deficit of the right eye, and right nasolabial fold flattening. He was diagnosed with myasthenia based on a positive acetylcholine receptor blocking antibody. His chest CT scan was negative for thymoma. His diplopia and facial weakness resolved with azathioprine and prednisone. He had central retinal vein occlusion (CRVO) in the right in 2002, with resultant optic neuropathy and central vision loss. He had removal of innumerable squamous and basal cell carcinomas, coronary artery disease, prostate cancer with prostatectomy and laryngoplasty. In 2009, he first noticed right brow numbness. He had surgery for ectropion OD in April 2013. In May 2013, he developed dysesthesia of his right brow. A basal cell carcinoma was removed without benefit. In July 2013, his myasthenia was stable, but his azathioprine was decreased due to reduced platelets and hematocrit. In September 2013, he developed stabbing pain of his right cheek, with right cheek sensory loss and right facial weakness. A MRI in November 2013 showed a small enhancing intraconal mass, not in an MRI from 2006. In April 2014, he had Mohs excision of a poorly differentiated scalp squamous cell carcinoma. In May 2014, his afferent examination was stable. Eye movements showed new -2 limitation of abduction OD. He had sensory loss of his right cheek, and right facial weakness. Increasing his prednisone dose did not improve his eye movements. Repeat brain MRI in May 2014 showed increase in size of the orbital mass. The third, fourth, fifth, sixth, and seventh cranial nerves appeared normal. A diagnostic procedure was performed.

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Grant Support: None

A Weak Presentation

Answer

Final Diagnosis
The final diagnosis is squamous cell carcinoma (SCCA) of the orbit with perineural invasion.

Summary of Case
Brain imaging from 2006 to 2014 were re-reviewed to look for cranial nerve enhancement, skull base lesions or leptomeningeal enhancement. All were negative with the exception of an enhancing right intraconal orbital mass. Biopsy of the right intraconal mass was performed. Pathology showed metastatic poorly differentiated squamous cell carcinoma. The final diagnosis is squamous cell carcinoma (SCCA) of the orbit with perineural invasion. Isolated orbital SCCA is rare, as the orbit does not normally contain squamous epithelial elements. More commonly, orbital SCCA arises via hematogenous spread from distant lesions or direct extension from paranasal sinuses, however this orbital tumor would not explain his other neurologic findings. Perineural spread is a well-recognized phenomenon in head and neck cancers, and SCCA is the most frequent neoplasm involved. Various mechanisms of perineural invasion have been postulated, including presence of nerve cell adhesion molecules and toll-like receptor 3 (TLR-3), however their role in perineural invasion associated with SCCA are not well defined. The reported incidence of perineural spread with squamous cell carcinoma of the head and neck is between 2-5%, with increasing risk associated with male gender, recurrent tumors > 2 cm, forehead location, and previous treatment. Because of their extensive subcutaneous distribution, the trigeminal and facial nerves are most commonly affected. Perineural spread most commonly presents with paresthesias, face pain, ptosis, diplopia, facial weakness, and ophthalmoplegia. The sensitivity of MRI in detecting perineural spread has been reported to be 95%. Nevertheless, perineural invasion can be missed without a high index of suspicion. Treatment guidelines for patients with perineural spread have not been established. Patients typically undergo surgery followed by radiation therapy. In the presence of perineural invasion, the five-year survival rate is thought to decrease by about 30%.

Struggle/Dilemma of the Clinical Presentation Description
The intraconal mass did not explain all of his deficits, and was not accompanied by worsened optic nerve function. Biopsy was considered, but delayed due to risk to his vision, and to concern that it was an incidental finding. When it enlarged on serial imaging, biopsy was deemed necessary. Pre-existing neuro-ophthalmic diagnoses clouded the picture with regard to diagnosis.

Keywords: Squamous Cell Carcinoma, Intraconal Orbital Mass, Intraconal Biopsy, Perineural Invasion

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The Man with No Face *(About Face)*

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History & Exam

A 61-year-old man presented with one week history of decreased vision OS. Past medical history includes asthma and amblyopia OD, but with complete visual loss OD 18 years prior. He takes no medications. He is retired but worked for 21 years in social science research. The remarkable thing upon meeting this articulate intelligent individual is he had no face. On exam his visual acuity was NLP OD and HM OS. There was no view of the pupil OD and a poor view OS but there is minimal reactivity. Color vision was non-recordable. Confrontational visual field showed marked constriction OS. Extraocular muscle exam showed complete restriction OD and a small amount of movement in all cardinal directions OS. External exam OD revealed absence of eyelids, exposed globe, and dense corneal scar with no view into the anterior chamber. External exam OS showed thick, keratinized upper and lower lids temporally and absence of lids medially, and 360 degrees of conjunctival chemosis, diffuse corneal edema with white lesion inferonasally, and a formed AC with poor view. Intraocular pressure was non-measurable OD and 40 mm Hg OS. No view of the fundus OU. Cranial and orbital CT and MRI revealed extensive destruction of soft tissue of the face that abuts and likely invades the dura. The right globe was involved, the left globe appeared intact. The intracranial and prechiasmatic portion of the optic nerves appeared normal. There was no definite evidence of involvement of the cavernous sinuses. However, there was disease surrounding several intracranial nerve roots, which likely represents perineural invasion of these structures. A biopsy was obtained.

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The Man with No Face *(About Face)*

Answer

Final Diagnosis
Invasive basal cell carcinoma of the face

Summary of Case
A 61 year-old man presented with visual loss OS. On exam he had extensive facial soft tissue destruction involving both orbits. Imaging revealed perineural invasion of the intracranial nerve roots and involvement of dura. Patient had been wrapping his face since 1997 and did not seek medical treatment due to his phobia of doctors. Biopsy revealed nodular basal cell carcinoma. Basal cell is the most common periorbital skin cancer and complete excision is essential due to its close proximity to vital structures. Lesions that are detected early have a >95% cure rate but left untreated can become very extensive and locally invasive. Typically it is considered a slow growing tumor but recent studies have showed that periorbital basal cell lesions increase in size by about 0.75mm per month. Our patient went untreated for around 17 years and caused extensive tissue damage that will require a multidisciplinary team approach including palliative care.

Struggle/Dilemma of the Clinical Presentation Description
With modern medicine, this patient had a >95% chance of a full recovery of the basal cell carcinoma. Because of his fear of doctors, he did not seek treatment until his vision became involved. At this point, due to the advanced stage and extensive invasion, the decision on how to treat was very difficult. Multiple services were involved including palliative care.

Keywords: Basal Cell, Visual Loss, Destructive Process, Head and Neck, Carcinoma

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Who Deserves a Second Chance?

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History & Exam

An 81-year-old woman presents with a one-month history of blurred vision OS, acutely worse in the past 5 days. She reports pain with left gaze, left sided forehead tenderness and some weight loss. Medical history includes hypertension, borderline diabetes, cerebral vascular accident and basal cell carcinoma of the face. Her medications include rivaroxaban, metoprolol, atorvastatin and omeprazole. Visual acuity is 20/20 OD and light perception OS. Color vision is 11/11 OD and 0/11 OS. Confrontational fields are full in the right eye and non-recordable in the left eye. Pupils are reactive and equal OU, with a greater than 1.2 log unit APD OS. Anterior segment exam reveals bilateral intraocular lenses. Dilated exam: OD is unremarkable, and OS is noted to have pallid disc edema with several hemorrhages. Initial blood work reveals an ESR 36mm/hr and CRP 5.4 mg/L (normal <3.0). MRI head obtained at outside facility showed abnormal enhancement along the orbital portion of the left optic nerve. Prednisone 60mg/day is initiated for presumed GCA and temporal artery biopsy scheduled. Contact is also made with the patient's primary care physician to stop rivaroxaban. A left temporal artery biopsy showed calcific atherosclerosis, without evidence of active or treated arteritis. Vision in left eye progressed to no light perception. Dedicated orbital MRI study with and without gadolinium showed mild enlargement and enhancement of the left optic nerve, possibly worse than prior. Patient admitted to hospital for workup. CT Chest – no evidence of sarcoidosis. LP – glucose 113 (serum 276), protein 31, WBC <1, cytology negative for malignant cells. Repeat dilated exam showed increased vitreous cells and debris in the left eye. A procedure was performed…

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Who Deserves a Second Chance?

Answer

Final Diagnosis
Left optic nerve diffuse astrocytoma, WHO grade II

Summary of Case
An 81-year-old woman presented with visual loss OS, down to light perception, associated with pain on left gaze and scalp tenderness. Funduscopic exam showed pallid disc edema in the left eye. Initial concern was for GCA. ESR normal for age, CRP mildly elevated, but TA biopsy was negative for evidence of arteritis. Vision progressed to no light perception. MRI revealed enlargement and enhancement of the left optic nerve. CT chest, lumbar puncture with CSF analysis including cytology were unrevealing. Re-examination reveals vitreous cells in left eye. A vitreous biopsy evaluating for an infiltrative process was negative for monoclonal lymphoid population. Ultimately the patient was sent for an optic nerve biopsy which revealed a diffuse astrocytoma, WHO Grade II. Gliomas of the optic nerve are rare, and account for 1.5-3.5% of all orbital tumors. While more cases are seen in children, those found in adults are overwhelmingly classified as grade I or IV (1, 2). The literature only reports two cases of histologically proven WHO Grade II optic nerve gliomas (3,4). Pathology in our case was positive for IDH1 (R132H mutant) and p53 immunohistochemistry markers, which further supports the histological diagnosis of WHO grade II astrocytoma. 80% of WHO grade II tumors show IDH mutations and <1% of WHO grade I tumors are positive for p53 mutations. To our knowledge, this is the third reported case of optic nerve histologically proven WHO grade II optic nerve glioma.

Struggle/Dilemma of the Clinical Presentation Description
Given initial presentation of profound visual loss, combined with patient's age and presence of pallid disc edema, the primary consideration was GCA. MRI showed enhancement of the left optic nerve. On repeat exam, vitreous cells were present, concerning for a process such as lymphoma. TA biopsy was negative, vitreous biopsy was unrevealing, and additional testing such as CT chest, lumbar puncture with CSF analysis showed no abnormality. This prompted proceeding with optic nerve biopsy.

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Lights Out

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History & Exam
A 78 year-old man presented with a one-month history of progressive painless binocular vision loss. He had sustained head trauma without loss of consciousness three days prior to the onset of vision loss. On the morning of his presentation to us, he had awoken with complete binocular vision loss and had been started on oral prednisone (70 mg daily) by his local eye care provider. He denied symptoms of giant cell arteritis. His past medical history was remarkable for hypertension, diabetes, and a distant history of prostate cancer that was thought to be in remission. Neurologic review of systems was unremarkable. Examination revealed no light perception OU. The pupils were dilated and minimally reactive to light. There was no RAPD. Intraocular pressures were within normal limits OU. Extraocular movements were full OU. Anterior segment examination revealed pseudophakia OU. Dilated funduscopic examination revealed diffuse optic atrophy OU. Neurologic examination was unremarkable.

There were no choroidal filling defects or perfusion abnormalities on fundus fluorescein angiography. ESR, CRP, and PSA were all within normal limits. MRI brain revealed enlargement and heterogeneous enhancement of the optic chiasm. An enhancing lesion was seen adjacent to the anterior horn of the right lateral ventricle. CSF examination revealed markedly elevated protein and glucose levels, with negative cultures, cytology, and flow cytometry. Bone scan was negative for bony metastases. In an attempt to improve his vision, intravenous methylprednisolone was given for five days, followed by a taper of oral prednisone over seven days. The right frontal lesion decreased in size dramatically with the steroid treatment, making biopsy difficult, but his vision did not improve. Repeat MRI brain obtained two weeks after completion of the steroids revealed interval growth of the right frontal lesion, with surrounding vasogenic edema, and growth of the chiasmal lesion. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Lights Out

Answer

Final Diagnosis
Multicentric glioblastoma multiforme involving the optic chiasm

Summary of Case
Right frontal brain biopsy was performed to obtain tissue from the right frontal mass. Histopathologic examination revealed hypercellular brain parenchyma infiltrated by a proliferation of atypical cells that had hyperchromatic, angular nuclei. Vascular proliferation and large areas of necrosis were noted. The pathology was felt to be consistent with glioblastoma multiforme (WHO grade 4). The chiasmal lesion was presumed to represent the same malignant process and a diagnosis of multicentric glioblastoma multiforme was made. Diffusely infiltrating high-grade astrocytoma with multiple foci of progression to glioblastoma multiforme could not be excluded, however. Palliative radiation and chemotherapy were offered, but the patient and his family declined further treatment. The patient died one month later. An autopsy was not performed.

Struggle/Dilemma of the Clinical Presentation Description
The initial differential diagnosis was expansive, including entities such as leptomeningeal carcinomatosis and metastatic disease, CNS lymphoma, and intrinsic CNS malignancy. CNS lymphoma was considered the likely diagnosis, given the periventricular location of the frontal lesion and dramatic reduction in the size of this lesion with steroid treatment. The reduction in the size of the frontal lesion prevented the neurosurgeon from obtaining a biopsy for several weeks, delaying diagnosis and definitive treatment.

Keywords: Binocular Vision Loss, Optic Atrophy, Optic Neuropathy, Intracranial Tumors

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Star Spangled Banner

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History & Exam

A 12-year-old girl with a history of bilateral optic nerve enlargement, enterovirus meningitis, seizures, and bilateral hygromas, presented with acute onset chronic vision loss in her left eye. Two years prior, she presented to an outside hospital with headaches, intermittent speech arrest and right-sided weakness, and was diagnosed with enterovirus meningitis and seizures. Incidentally, she was noted to have bilateral optic nerve enlargement. She had no visual symptoms until four months prior to presentation when she was again admitted with headaches and transient neurologic deficits. Neuroimaging was notable for new bilateral hygromas, further enlargement of the optic nerves, and septations of the subarachnoid space thought to be related to prior meningitis. Lumbar puncture was unremarkable, and PET scan revealed a paraspinal mass near the left L4-L5 nerve root. Biopsy was consistent with neuroblastic tumor, thought to be isolated, and managed with partial resection. Additionally, extensive dural ectasia of the spine was observed. An attempt to drain the hygromas revealed high CSF output that required subgaleal-peritoneal shunt placement, later removed due to infection. During her admission, she reported blurred vision. Initial ophthalmological evaluation revealed subnormal acuities in the left more than right eye and dyschromatopsia in both eyes, with normal pupils and optic discs. The etiology of vision loss was postulated to be optic neuropathy secondary to high intracranial pressure from her hygromas. After discharge she remained stable for another three months until she noted complete vision loss in her left eye and was referred to our facility for neuro-ophthalmological consultation. Her examination was significant for visual acuity of 20/60 in the right eye and light perception in the left eye, a left afferent pupillary defect, and bilateral optic disc temporal pallor with nasal edema in the right eye. There were no Lisch nodules.

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Grant Support: None

Star Spangled Banner

Answer

Final Diagnosis
Neuroblastoma metastatic to pre-existing benign neoplasm of the optic nerves

Summary of Case
Repeat contrast-enhanced MRI brain and orbits revealed new extra-axial enhancing, diffusion positive masses along the convexities of the skull. Optic nerves and chiasm showed further enlargement with new diffusion restriction and peripheral contrast enhancement. MRI spine revealed growth of the paraspinal lesion with leptomeningeal enhancement and new retroperitoneal lymphadenopathy. She was admitted to the hospital for three days of high dose intravenous steroids followed by an oral steroid taper. Repeat biopsy of her paraspinal lesion and biopsy of a subarachnoid brain mass both demonstrated malignant neuroblastoma. The follow-up neuro-ophthalmologic examination revealed visual acuity of 20/30 in the right eye and hand motion in left eye, with partial improvement in optic disc edema in the right eye. We present a case of neuroblastoma metastatic to previously enlarged optic nerves. Since the initial enlargement proceeded the spread of neuroblastoma by two years, we postulate that there were pre-existing optic nerve gliomas. The patient's overall clinical picture of widespread dural ectasia, optic nerve gliomas, and neuroblastoma raises concern for neurofibromatosis type I (NF1), although a complete evaluation revealed no cutaneous manifestations. A mosaic form of NF1 is suspected. Neuroblastomata are known to cause optic nerve dysfunction from compression related to bony metastases invading the orbit [1] [2], or skull base [3]. More rarely, there have been documented cases of leptomeningeal involvement [4] or direct invasion of the optic nerve [1] [5]. This may be the first case reported of direct neuroblastoma metastasis to optic nerve glioma.

Struggle/Dilemma of the Clinical Presentation Description
Initially, the enlargement of the optic nerves was felt to reflect optic nerve gliomas only, in this patient with dural ectasia suggestive of an NF1 phenotype. However, the speed of enlargement and the development of diffuse metastatic disease, suggested that the recent enlargement was instead due to metastatic neuroblastoma. The initial enlargement seen two years prior to presentation, likely reflected a pre-existing benign neoplasm such as optic nerve glioma.

Keywords: Neuroblastoma, Optic Nerve Glioma

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Joe & Jerry Flew the Coop

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History & Exam

A previously healthy 13-year-old girl presented to a local hospital with fever and myalgia, followed one day later by lethargy and vision loss. Past medical history was significant only for acne, for which she had been treated with doxycycline 40 mg/day intermittently starting 2 months prior to symptom onset. In the emergency department, the patient was difficult to arouse. Within 24 hours of onset, arousal level spontaneously returned to normal, but vision was light perception in both eyes. Based on fundus examination, she was given a presumptive diagnosis of neuroretinitis and transferred to our hospital. On our examination, visual acuity was light perception only in both eyes. Pupils measured 7mm in dim illumination and constricted moderately to direct light. Ophthalmoscopy in both eyes revealed nearly confluent, sharp-bordered ischemic retinal white patches in the posterior pole. Optical coherence tomography (OCT) showed inner retinal thickening and hyperreflectivity. Fluorescein angiography (FA) revealed occlusion of multiple small arterioles in the areas of retinal whitening. A wide-field FA confirmed multifocal arteriolar occlusions posteriorly with minimal late leakage and no retinal vascular abnormalities in the periphery. Brain MRI demonstrated symmetric T2 hyperintensities on FLAIR images in the region in both LGBs, and in the cerebellar vermis and dorsal midbrain. T2-weighted gradient echo images showed hypointensities with blooming in the LGBs, indicative of hemorrhage. These lesions showed restricted diffusion. ESR was 46, CRP was 0.1 and the following labs were negative: cardiolipin antibody, anti-DsDNA, anti-SSb/anti-La, anti-Sm, anti-RNP, anti-scleroderma, anti-Jol, chromatin, ribosomal protein and centromere B. An additional test was performed.

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Grant Support: None

Joe & Jerry Flew the Coop

Answer

Final Diagnosis
H1N1 influenza associated encephalopathy with bilateral retinal and LGB infarction

Summary of Case
The test was a PCR on blood, which was positive for influenza A H1N1.This extent of retinal infarction and LGB infarction has not been previously reported in H1N1 disease or in any other condition. A previous case[1] of non-confluent cotton wool spots in H1N1 may have represented a milder version of ischemic retinopathy. Isolated lateral geniculate body (LGB) infarction has not been described in H1N1 influenza, but bilateral pan-thalamic lesions have been reported.[2-4] However, in none of those cases was the LGB infarcted without involving the rest of the thalamus, and in no case was vision loss or retinal infarction described. Why should the retina and LGB have been selectively targeted for infarction? In acute necrotizing encephalopathy (ANE),[4] an influenza-related condition in which hemorrhages can be seen in the deep gray matter, the pathogenesis is based on breakdown of the blood-brain barrier through cytokine storm in response to virus exposure,[5] akin to a mechanism proposed for Purtscher retinopathy. The patient was treated with oseltamivir, intravenous methylprednisolone, intravenous immunoglobulin (IVIG) and plasmapheresis for presumed influenza-related encephalitis. On examination 60 days after onset, visual acuity had improved to finger counting. The optic discs were pale and the retinal whitening had disappeared. Repeat MRI 75 days from symptom onset showed resolution of FLAIR signal changes and maturation of the LGB hemorrhages.

Struggle/Dilemma of the Clinical Presentation Description
The Purtscher-like retinopathy was so dramatic that it was initially thought to explain the vision loss. However, the relatively intact pupillary reactions were not consistent with the profound vision loss, prompting neuroimaging that revealed bilateral LGB hemorrhagic infarction. H1N1 has been reported to cause cotton wool spots, but not Purtscher-like retinopathy. H1N1 causes thalamic infarction, but never localized to the LGB. The combination of Purtscher-like retinopathy and LGB infarction has not been previously reported.

Keywords: Bilateral Vision Loss, Retina, Lateral Geniculate, Magnetic Resonance Imaging, Encephalitis

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Using Muscle

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History & Exam
A 30- year-old Saudi female student with no past medical history presented an eight month history of progressive blurred vision primarily at near, anisocoria OS, and periocular discomfort with eye movements. Neuro-Ophthalmologic examination revealed best corrected visual acuity of OD 20/20 and OS 20/30. Color vision was OD 12/12 and OS 12/12. Automated threshold perimetry was normal. The pupils were 4 mm and normally reactive OD and 5 mm and minimally reactive OS. There was no relative afferent pupil defect (RAPD). The pupil was characteristic of absent sympathetic and parasympathetic input as may be seen in cavernous sinus lesions. The eyes were quiet. IOP was normal. Ocular motility examination was normal at initial evaluation but over the next 3 months she developed limited adduction and mild proptosis; other eye movements were normal throughout her 10 month course. Funduscopy was normal. Magnetic resonance imaging (MRI) of the brain and orbit with contrast revealed an enlarged left medial rectus and a linear enhancing structure running from the medial rectus muscle back to the superior orbital fissure and superior lateral wall of the cavernous sinus, believed to be an enlarged, enhancing third nerve. The following laboratory studies were performed and were negative or normal: Angiotensin-converting enzyme, lysozyme, T4, T3, TSH, thyroid stimulating immunoglobulin, thyrotropin binding inhibitory immunoglobulins, thyroid peroxidase antibody, serum protein electropheresis, cysticercosis antibodies, trichinella immunoglobulin G, and IgG4 immunoglobulin. A Quantiferon Gold test was sent three times before receiving a report that it was positive after all the above evaluation and the diagnostic procedure were complete. A diagnostic procedure was done

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Using Muscle

Answer

Final Diagnosis
Orbital Amyloidosis Presenting as Extraocular Muscle Mass and Enhancing, Thickened Third Nerve

Summary of Case
A biopsy of the left medial rectus was performed and tissue cultures were sent. Initial histopathology was inconclusive at our institution. Consultation with Dr. Chevz-Barrios at Houston Methodist Hospital established a diagnosis of amyloidosis. The figure includes the following: a. Routine stain showing entrapped striated muscle fibers in an amorphous amphophilic material suggestive of amyloid (H&E, 20X original magnification). b. Adjacent field shows amorphous material in the wall of a vessel. This field is the same as c-e. (H&E, 10X original magnification). c. Congo red stain for amyloid shows positive red staining of the amorphous material (Congo red stain, 10X original magnification). d and e. Congo red under polarization demonstrating the dichroisms of orange to apple green (Congo red stain under polarization, 10X original magnification). Pulmonary function testing was normal. A CT of chest, abdomen and pelvis was performed and was normal. Cardiology and Hematology-oncology consultations were unrevealing with a normal echocardiogram and normal bone marrow biopsy. Amyloidosis is a rare disorder that can be associated with chronic inflammation such as tuberculosis or that may be primary. The quantiferon gold test was positive but there was no cultural or pathologic evidence of tuberculosis in the biopsy specimen and imaging of the entire body did not reveal any suspicious areas in the lungs or elsewhere.

Struggle/Dilemma of the Clinical Presentation Description
There was enhancing enlargement of the medial rectus and third nerve into the cavernous sinus. What inflammatory pathologic process would involve the ocular muscle and its corresponding nerve back to the cavernous sinus? This does not appear to be a tuberculous infection at the site of the pathology; is this primary amyloidosis? How should this be addressed and how should the positive quantiferon gold be addressed?

Keywords: Anisocoria, Ocular Pain, MRI, Special Staining, Amyloidosis

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I Can't See Straight

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History & Exam
In May of 2014 this 30 year old right handed patient was referred for consultation regarding diplopia and dizziness. The patient relates that she had been told that she had "tired eyes" as a child. Two and a half years ago she began to have intermittent exodeviation. She was seen locally and diagnosed as having a IV nerve palsy and treated with 2 diopters of base in prism and 2 diopters of base up prism. Six months before her referral she began to complain of double vision. The patient attributed the onset of double vision to a car accident in 2007. On examination visual acuity was correctable to 20/20 and 20/25. Color was intact. Visual fields demonstrated an inferior Seidel scotoma on the right side. There was no afferent pupillary defect. Motility examination revealed severe limitation in up gaze OD > OS with 45 diopters of right exotropia and 12 diopters of right hypotropia. Counter clockwise torsional nystagmus was noted. Slit lamp examination and applanation tensions were within normal limits. Funduscopic examination revealed no evidence of disc edema or optic atrophy. OCT revealed some epiretinal surface changes, but no obvious epiretinal membrane. Imaging studies were obtained.

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Grant Support: None

I Can't See Straight

Answer

Final Diagnosis

Giant tumefactive mesencephalic spaces of Virchow-Robin. MRI scan demonstrated "multiple large clusters of expanded fluid filled perivascular spaces with CSF characteristics involving the entire central left midbrain and left thalamus involving the left optic tract, hypothalamus, interpeducular cistern, left ambient cistern, collicular plates, and pons."

Summary of Case

Perivascular spaces, otherwise known as Virchow-Robin spaces are normal anatomic structures typically less than 5mm in diameter. Small enlargements of the spaces are not at all infrequent, being detectable on MRI in up to 60% of healthy individuals. They are in direct communication with the subpial space, separated from the subarachnoid space by a single layer of pia mater. There has been postulated to be a communication with the lymphatic system, draining the head and neck. The teleologic purpose of the Virchow-Robin spaces has been debated, including suggestion of involvement in immune modulation, providing an entry route for macrophages. Pathologically they may be a potential route of dissemination for intracranial pyogenic infection. Characteristically on MRI scan they are iso-intense to CSF without enhancement, and the small typical ones follow the path of penetrating cerebral arteries, particularly in the area of the basal ganglion. When grossly dilated they tend to most frequently involve the mesencephalon, as in our patient. They most commonly follow the paramedian mesocephalo-thalamic artery. While the majority of these are asymptomatic, when they enlarge sufficiently, they may produce mass effect. Most of the surgical approaches to these depend on relieving that mass effect. The recent introduction of endoscopic surgery can easily decompress some of the cystic spaces if they appear to be producing compression. In this particular case, it was unclear that any surgical intervention was likely to improve the patient's findings.

Struggle/Dilemma of the Clinical Presentation Description

These lesions have been confused with cystic neoplasia and atypical infection. Their CSF characteristics usually make them easily diagnosed by a neuroradiologist familiar with their occurrence. Their typical features should be recognized even with grossly enlarged or progressive.

Keywords: MRI imaging, Cystic Intracranial Lesions, Virchow-Robin Spaces

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Nobody's Perfect

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History & Exam

In June of 2006 an 8 year old patient was referred for evaluation. Apparently at age 1 ½ she had developed headaches and was found to have a posterior fossa tumor. In El Salvador she was treated with shunting and chemotherapy plus radiation therapy for presumed medulloblastoma. She underwent a shunt revision at age 2 ½. Near vision was 20/20 OU with arcuate visual field defects, no afferent pupillary defect, normal motility, and normal discs including OCT. She did have an MRI which showed some likely post radiation changes, but a negative spinal MRI. On June 19, 2007 a repeat MRI scan, however, demonstrated a lesion at the L1 level. In March of 2006, a 29 year old patient was referred for a 6 month history of problems with his vision, and two weeks of headaches characterized as steady, and unassociated with nausea or vomiting. Visual acuity was correctible to 20/20 and 20/25. Visual fields demonstrated a bitemporal superior visual field defect. He had evidence of a 0.6 log unit left afferent pupillary defect. There were full ductions and versions and 100 seconds of stereopsis. His past medical history was remarkable for an incomplete form of osteogenesis imperfecta. MRI scan showed evidence of a sellar and suprasellar enhancing mass. A meningioma was suspected. A spinal MRI scan, however, demonstrated evidence of lumbar enhancement. CSF analysis was unremarkable.

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Nobody's Perfect

Answer

Final Diagnosis
Leptomeningeal spread of pilocytic astrocytoma.

Summary of Case
In the first case T11-L1 laminectomy revealed a neoplasm with piloid, microcystic and oligodendroglioma-like areas, Rosenthal fibers and glomeruloid-like microvascular proliferation with rare mitotic figures. GFAP and vimentin were positive (KI-67 <5% and weak p53). In the second patient, transphenoidal resection demonstrated a neoplasm consisting of piloid, small, bland cells without cytologic atypia; some oligodendrglial-like cells; and prominent glomeruloid vascular proliferation. GFAP and vimentin were positive (KI-67 moderately elevated, P53 negative). Both patients were treated with chemotherapy. In the second patient, a three year follow-up MRI showed an increase in a mass along the left dorsolateral medulla (I and J). She underwent an occipital craniotomy. Pathology demonstrated dense fibrillary stroma, enlarged gemistocytic-like cells and numerous Rosenthal fibers. Compared to the lumbar specimen, this sample contained more atypia, larger gemistocytic tumor cells and a higher KI-67 index. Gliomas range from indolent low-grade lesions (pilocytic astrocytomas [PA]) to high-grade glioblastoma. PA's account for 30% of primary brain tumors in children and commonly involve the visual pathways. As in our first case, midline PA's may be mistaken for the more common, malignant medulloblastoma. Leptomeningeal dissemination in PA is a rare phenomenon, with only 30 cases having been reported prior to 2003. Leptomeningeal dissemination may occur late in the course of the disease, as in our first case, but may also be present at the time of initial diagnosis, as in our second. This has been estimated to occur in 4% to 12% of grade I gliomas. The *EGFR* gene is speculated to play a role in mediating leptomeningeal spread, but this mechanism remains unclear. Leptomeningeal spread has been reported to occur for up to two decades following the initial treatment and recent studies suggest a higher incidence of spread in hypothalamic chiasmatic lesions, such as in our second case.

Struggle/Dilemma of the Clinical Presentation Description
In El Salvador, our first patient was treated with shunting and radiation for a presumed medulloblastoma. Finding of a leptomeningeal lesion suggested the presence of metastasis, which is common in medulloblastoma but biopsy revealed PA. Our second case presented with evidence of a suprasellar lesion (and chiasmal syndrome) thought to be a meningioma but with evidence of lumbar enhancement. Transphenoidal biopsy demonstrated a PA. CSF was negative and he was treated empirically with chemotherapy.

Keywords: Pilocytic Astrocytoma, Leptomeningeal Meningioma, Childhood Brain Tumor

References
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North American Neuro-Ophthalmology Society

41st Annual Meeting

February 21-26, 2015
Hotel del Coronado • San Diego, California

Program Schedule

MONDAY, FEBRUARY 23, 2015

6:00 a.m. – 6:45 a.m.	**Yoga Class**	**Spreckels Complex**
6:30 a.m. – 12:30 p.m.	**Registration**	**Ballroom Foyer**
6:30 a.m. – 7:30 a.m.	**Breakfast**	**Crown Room**
6:30 a.m. – 12:15 p.m.	**Exhibits**	**Crown Room**
7:00 a.m. – 7:30 a.m.	**NOVEL Editorial Board/Curriculum Committee Meeting**	**Garden Room**
7:00 a.m. – 7:30 a.m.	**Finance Committee Meeting**	**Executive Room**
7:30 a.m. – 9:30 a.m.	**Journal Club [2.0 CME]** *Moderators: Rudrani Banik, MD & Christian Lueck, PhD, FRACP, FRCP(UK)*	**Ballroom**

Clinicians are obliged to keep themselves up to date with what is happening in their various fields of practice. Granted the enormous progress being made in all areas of medicine, keeping abreast of relevant clinical trials and other new developments can be very challenging. This symposium is designed to assist practicing Neuro-Ophthalmologists by providing reviews of recent developments in four different areas: new therapies for multiple sclerosis, the relationship between phosphodiesterase-5 (PDE-5) inhibitors and non-arteritic anterior ischemic optic neuropathy (NAION), the neuro-ophthalmological relevance of bariatric surgery, and obstructive sleep apnea (OSA). Each expert will present a critical review followed by a summary of take-home points, leaving time available for audience comments, questions and discussion.

Upon completion of this course, attendees will have the evidence base to allow them to define: 1) The roles and relative positioning of the many new agents which have appeared (and some which are soon to appear) to treat multiple sclerosis; 2) The relationship between PDE-5 inhibitors and NAION; 3) Who should be referred for bariatric surgery and what complications may arise; and 4) The potential relevance of obstructive sleep apnea to Neuro-Ophthalmic conditions including idiopathic intracranial hypertension and NAION, how to detect OSA, and what to do if it is suspected.

The course is designed to address the following desirable physician attributes: Medical knowledge, practice-based learning and improvement, and patient care.

		PAGE
7:30 a.m. – 7:50 a.m.	**New Therapies for Multiple Sclerosis, Beyond the ABCs** *Ari J. Green, MD*	**61**
7:50 a.m. – 8:00 a.m.	***Q & A***	
8:00 a.m. – 8:20 a.m.	**The Relationship Between PDE-5 Inhibitors and NAION** *Howard D. Pomeranz, MD, PhD*	**69**
8:20 a.m. – 8:30 a.m.	**Q & A**	
8:30 a.m. – 8:50 a.m.	**Bariatric Surgery and the Neuro-Ophthalmologist** *Heather Moss, MD, PhD*	**77**
8:50 a.m. – 9:00 a.m.	**Q & A**	
9.00 a.m. – 9:20 a.m.	**Obstructive Sleep Apnea and Neuro-Ophthalmic Conditions** *Clare Fraser, MD*	**85**

9.20 a.m. – 9:30 a.m. **Q & A**

9:30 a.m. – 10:00 a.m. **Coffee Break** **Crown Room**

10:00 a.m. – 12:00 p.m. **Hot Topics: To Boldly Go Where No Neuro-Ophthalmologist has Gone Before [2 CME]** **Ballroom**

Moderators: Marc Dinkin, MD & Rod Foroozan, MD

With every new observation and new technology comes the question: Should Neuro-Ophthalmologists change their understanding of a disease or their practice patterns or stick with the tried and true teachings of old? The purpose of this Hot Topics session is to address some of the more controversial questions of Neuro-Ophthalmology practice: Is there really a distinct syndrome of chronic relapsing inflammatory optic neuropathy? Is ocular fundus photography the wave of the future or are Neuro-Ophthalmologists better off teaching emergency room physicians old-fashioned direct ophthalmoscopy? Can Neuro-Ophthalmologists use the results of pharmacologic testing and examination findings to focus their imaging protocol for patients with Horner syndrome or should they maximize sensitivity with a "kitchen sink" approach? And finally, does the discovery of optic disc edema in astronauts undergoing long-duration space flight reflect a localized increase in retrolaminar pressure due to microgravity, and if so, can this knowledge inform the management of earth-bound patients with papilledema?

Upon completion of this course, participants should be able to: 1) Approach the diagnosis and treatment of the clinical entity of chronic relapsing inflammatory optic neuropathy (CRION); 2) Describe the data supporting the use of ocular fundus photography in the diagnosis and management of neuro-ophthalmological disorders in the emergency room and other clinical settings; 3) Outline an approach to imaging of patients with Horner syndrome; and 4) Recognize the changes affecting the optic nerve in the settings of high altitude and long-duration space flight.

This course is designed to procure the following desirable physician attributes: Employ evidence-based practice, work in interdisciplinary teams, and medical knowledge.

12:15 p.m. – 12:45 p.m. **Archives Committee Meeting** **Executive Room**

12:15 p.m. – 1:30 p.m. **Women in Neuro-Ophthalmology (WIN) Meeting** **Coronet Room**
An optional lunch selection will be available for purchase. All are welcome to attend even without the purchase of a lunch.

1:30 p.m. – 3:30 p.m. **Optional Symposium: International Neuro-Ophthalmology [2 CME]** **Ballroom**
Moderators: Christian Lueck, PhD, FRACP, FRCP(UK) and Klara Landau, MD, FEBO

In recent years, about 20% of the attendees at NANOS meetings live and practise in parts of the world outside North America. "International" neuro-ophthalmology differs from "North American" neuro-ophthalmology in several ways. For example, the patterns and prevalence of the various diseases vary with geographic location, and there is enormous variability in local facilities for clinical service delivery and research.

This symposium is designed to showcase international aspects of neuro-ophthalmology. It will focus on several different areas including the different profiles of neuro-ophthalmic disease in other parts of the world and the variable levels of service provision and education, particularly in the developing world. The symposium will provide the opportunity to foster international collaboration and increase the involvement of NANOS members at an international level.

Upon completion of this course, participants should be able to: 1) Recognize differences in prevalence of neuro-ophthalmic diseases between different countries; 2) Describe differences in service provision in different regions of the world; and 3) Determine how to foster international neuro-ophthalmologic collaboration.

1:30 p.m. – 2:00 p.m. **Neuro-Ophthalmology in South East Asia**
John Crompton, MBBS, FRANZCO, FRACS

2:00 p.m. – 2:12 p.m. **Neuro-Ophthalmology in Europe (France)**
Caroline Tilikete, MD, PhD

2:12 p.m. – 2:24 p.m. **Neuro-Ophthalmology in Africa (East Africa**)
Mike Burdon MB, BS, FRCOPH, MRCP

2:24 p.m. – 2:36 p.m. **Neuro-Ophthalmology in the Middle East (Israel)**
Ruth Huna-Baron, MD

2:36 p.m. – 2:48 p.m. **Neuro-Ophthalmology in South America (Brazil)**
Mário Monteiro MD, PhD

2:48 p.m. – 3:00 p.m. **Neuro-Ophthalmology in Asia (Japan)**
Satoshi Kashii, MD, PhD

3:00 p.m. – 3:10 p.m. **The History of the International Neuro-Ophthalmology Society**
Klara Landau, MD

3:10 p.m. – 3:30 p.m. ***Q & A***

2:00 p.m. – 4:30 p.m. **Consortium of Pediatric Neuro-Ophthalmologists Meeting (CPNO)** **Garden Room**
Facilitator: Grant Liu, MD

The Consortium of Pediatric Neuro-Ophthalmologists (CPNO) was created to promote and advance pediatric neuro-ophthalmology by performing multi-center studies, providing a forum for research and clinical topics, and creating a sense of community to those specializing in pediatric neuro-ophthalmology. The meeting is open to anyone interested in children with neuro-ophthalmic problems. During this session multi-center research studies will be discussed, and cases relevant to these projects will be presented.

2:30 p.m. – 4:30 p.m. **Optional Symposium: Hands on Workshop Utilizing the Prism Cover Test and Prism Therapeutics for the Diplopic Patient [2 CME]** **Carousel 3**
Moderator: Mitchell B. Strominger, MD

Evaluation and treatment of the diplopic patient is time consuming and demanding. Understanding how to perform the prism cover test, determining fusional amplitudes, differentiating phoria from tropia, use of the prism adaptation test, placing press on prisms, and prescribing prisms is an art. Unfortunately, many Neuro-Ophthalmologists have limited training in this area. During this workshop, short cases of patients with diplopia will be presented. Afterwards, the audience will divide up into stations run by strabismologists and orthoptists demonstrating the prism cover test, alternate prism cover test, manipulation of basic and complex prisms, prism adaptation testing, prescribing and placement of press on or ground in prisms, and indications for strabismus surgery as it pertains to each case.

Upon completion of this course, participants should be able to: 1) Explain the evaluation of diplopic patients where prisms are useful in diagnosis and treatment; 2) Compare the different types of prisms available and their utility in examining and treating patients with diplopia; and 3) Describe the different prism cover tests and their use in differentiating phoria from tropia.

2:30 p.m. – 2:35 p.m. **Introduction of the Faculty and Review of Symposia Learning Objectives**
Mitchell B. Strominger, MD

2:35 p.m. – 2:45 p.m. **The Prism Cover Test**
Shelley Klein, CO

2:45 p.m. – 2:55 p.m. **Prescribing incorporated or Fresnel Prisms**
Mitchell B. Strominger, MD

2:55 p.m. – 3:00 p.m. **Brief Case Presentations: Divergence Insufficiency, Convergence Insufficiency, 4th Nerve Palsy, 6th Nerve Palsy, Thyroid Orbitopathy, and Post Cataract Extraction Vertical Diplopia**
Mitchell B. Strominger, MD

3:00 p.m. – 4:30 p.m. **Break-Out Stations with Hands-On Case Demonstrations**
Mitchell B. Strominger, MD, Shelley Klein, CO, Paul H. Phillips, MD
David Granet, MD, Shira L. Robbins, MD, and Erika Castro, CO

3:00 p.m. – 5:00 p.m. **Young Neuro-Ophthalmologist (YONO) Forum** **Hanover Room**

While all are welcome to attend, this forum is specifically designed for residents, fellows and Neuro-Ophthalmologists in the early years of their career. The YONO Committee has incorporated last year's positive, constructive feedback and present a re-vamped format. The revised forum will have multiple rotating roundtable discussions in small groups facilitated by YONOs, who have just walked in your footsteps, to mid-career folks, who can shed light on the next steps ahead.

3:00 p.m. – 4:00 p.m. **All you ever wanted to know about becoming a Neuro-Ophthalmologist: For Trainees, Residents, and Fellows**

Table 1: Finding A Job/Negotiating Contracts (Neuro Based)
Janet Rucker, MD
Table 2: Expertise On Private Practice And Academic Models
Madhu Agarwal, MD
Table 3: Ophthalmology Perspective On N-O
Julie Falardeau, MD
Table 4: Neurology Perspective On N-O
Greg Van Stavern, MD

4:00 p.m. – 5:00 p.m. **So now I have a job, where do I go from here? For junior attendees in private practice or academics in their first 5 years out of training**

Tables 1 & 2: Academic Advancement/Career Navigation
Kathleen B. Digre, MD & Mark L. Moster, MD
Table 3: Navigating Your Practice, Keeping Up On Your Academics/Administrative Skills
Preston C. Calvert, MD
Table 4: Dollars And Sense: Billing And Coding For Neuro-Ophthalmology
Matthew Kay, MD
Table 5: Private Practice/Academic Neuro-Ophthalmology Perspective JNO/Publishing Advice
Lanning Kline, MD

5:00 p.m. – 7:00 p.m. **SCIENTIFIC PLATFORM PRESENTATIONS: SESSION I [2 CME]** **Ballroom**

NEW THERAPIES FOR MULTIPLE SCLEROSIS: BEYOND THE ABCs

Ari J. Green, MD

University of California
San Francisco

LEARNING OBJECTIVES

1. Understand new therapies available for the treatment of MS and the optimal timing for initiation of these treatments
2. Understand the risks of these new therapies with particular reference to possible neuro-ophthalmologic complications
3. Understand that existing therapies for MS all address the immune dysregulation that defines early disease and understand the immunological features of the disease that these specific therapies address
4. Recognize the relative risks and benefits of each therapy including available data on relative efficacy

CME QUESTIONS

1. Which of the following therapies has/have NOT been shown to have superior clinical efficacy to an Interferon beta product in a double blind placebo controlled trial?

    a. Fingolimod
    b. Daclizumab
    c. Dimethyl Fumarate
    d. Alemtuzamab
    e. Natalizumab
    f. Leflunomide

2. Which of the following medicines is/are not a monoclonal antibody(s)?

    a. Ocreluzimab
    b. Campath
    c. Fingolimod
    d. Natalizumab
    e. Dimethyl Fumarate

3. Which of the following is/are NOT a side effect(s) associated with the use of Fingolimod?

    a. Heart rate reduction with first dose
    b. Flushing
    c. Macular Edema
    d. Herpes Virus Reactivation
    e. Mildly elevated blood pressure
    f. Elevated liver enzyme levels

4. Which of the following is the most significant risk factor for developing PML while on Tysabri?

    a. Prior exposure to interferon
    b. JCV serological status
    c. Length of exposure to Natalizumab
    d. Patient weight
    e. MS disease subtype

5. Which of the following medicines is potentially useful for the treatment of acquired pendular nystagmus?

    a. Donepizil
    b. Paroxetine
    c. Carbamazepine
    d. Memantine

KEYWORDS

1. Multiple Sclerosis
2. Monoclonal Antibodies
3. Immunotherapy/Immune modulators
4. Injectable Therapies
5. Oral Agents

INTRODUCTION

As of 2015, multiple sclerosis (MS) is the only treatable neurodegenerative disease. It has frequent visual manifestations, most of which are in the clinical purview of neuro-ophthalmologists. This syllabus is intended to update neuro-ophthalmologists about new data surrounding, the new and emerging disease modifying therapies, and the use of targeted symptomatic therapies available for treatment of common neuro-ophthalmologic complaints experienced by patients living with MS.

1. Early treatment of MS generally appears to be more effective at controlling inflammatory episodes and immune-mediated injury than delayed treatment and there is some evidence suggesting beneficial effects on long-term outcomes.
2. Neuro-ophthalmologists frequently encounter patients early in the course of MS as ⅓ – ½ have neuro-

ophthalmologic manifestations at onset. Optic neuritis (ON) is the most common (or, in some series, the second most common) presentation at symptom onset. ON has been reported in 17% - 29% of cohorts. Visual motor dysfunction (e.g diplopia or oscillopsia,), is also common, diplopia at onset being noted by 8% - 20% of patients, depending on the series.[1]

3. Therapies for MS can have specific ophthalmologic complications, e.g. cotton wool spots in patients treated with interferon, macular edema in patients treated with fingolimod, and herpes zoster ophthalmicus in patients treated with natalizumab.

4. Neurologists specializing in MS are increasingly interested in monitoring disease progression using neuro-ophthalmologic tools.

5. Newer therapies have greater efficacy but more potential risks than older, less efficacious, therapies.

Multiple Sclerosis is a debilitating neurodegenerative disease of the central nervous system in which the immune system targets and destroys myelin. Ultimately, long term injury to neurons and axons leaves patients permanently disabled. Before the modern therapeutic era, nearly 50% of patients had significant disability (i.e. at least Expanded Disability Status Scale (EDSS 4) by 6-12 years from disease onset and, similarly, half required assistance with walking by 15-20 years after disease onset.[2-4] Today, nearly a dozen FDA-approved therapies exist to help reduce the inflammation that contributes to immune-mediated injury or to prevent the influx of immune cells from peripheral circulation into the CNS. The first 'disease-modifying' therapy for MS (interferon β1b) was approved in 1992; this and the next three therapies to be approved all required subcutaneous or intramuscular injection. More recently, oral small molecules and infusible monoclonal antibodies have been developed that have enhanced biological activity and provided a broader array of options for treatment. However, these treatments possess a more complex risk/benefit profile. Recently, long-term follow up from early clinical trials and efforts to study patients outside of clinical trials using propensity score analyses have suggested that these anti-inflammatory agents delay, but do not eliminate, long-term disability. [5-7]

Data from clinical trials of patients with initial symptoms of MS (clinically-isolated syndromes, CIS) have shown a greater effect on relapse rate than earlier trials that included patients with longer disease duration. Although many factors may have contributed to these apparent changes, one likely contributory factor is that earlier initiation of therapy is more effective at lowering relapse rate and reducing the number of new enhancing lesions on MRI. Effects on long-term disability are becoming increasingly apparent, though these are harder to prove as this frequently has to be studied outside the confines of standard clinical trials given the long time intervals involved. For example, the BENEFIT trial (IFN Beta 1b) found that only 4.5% of patients who had been treated immediately developed secondary progressive MS at 11 years, compared to 8.3% of subjects who were initially in the placebo arm and whose treatment was therefore delayed by two years.

A VERY BRIEF SUMMARY OF IMMUNOLOGY AS IT RELATES TO MS THERAPIES:

Immune cells drive early injury in MS. Although a complete description of the immunopathogenesis of MS is beyond the scope of a broad overview of MS therapies such as this one, a general understanding of some of the most important immunological targets of existing therapeutics is crucial to their description (see next page Figure 1).

Lymphocytes are the primary arm of adaptive immune system. They generate a specific and targeted response against infections and any antigen they do not recognize as self. T-lymphocytes play a crucial role in helping to orchestrate a direct cellular immune response against antigens identified as "non-self". B lymphocytes serve to (1) regulate T cell activity, (2) present antigen to T cells and activate them (as circulating "antigen presenting cells) and (3) produce proteins (immunoglobulins) that are crucial to maintaining the ancillary humoral immune response (that uses proteins to target cells for destruction).

Lymphocytes are typically activated before being released into circulation. IL-2 receptor is expressed on the surface of T lymphocytes when they are activated (see **daclizumab**). They must also be rapidly generated via robust and prodigious replication especially during a sustained immune response (see **teriflunomide**).

Lymphocytes have to be trained in lymphoid organs to increase their capacity to recognize and eliminate non-self antigens. Lymphocytes that express a surface receptor known as CCR7 will remain trapped in the lymph node during periods of lymphocyte training and proliferation. T cells are also subdivided by the type of cytokines that they elaborate and the cell surface receptors they express. One basic and common distinction is between those T cells that are considered proinflammatory (Th1 and Th17) and those that help serve a regulatory function or participate in the humoral immune response (T-Regs and Th2 respectively) (see **interferon**). Classically MS was thought to be a disease mediated by loss of regulation of the Th1 subclass of T cells although greater understanding of immunology in combination with our therapeutic trial experience has challenged (and, in some respects, overturned) this concept.

As lymphocytes flow through blood vessels they are also subject to hydrodynamic flow stress. Therefore they would be incapable of migrating into target tissues for surveillance or recruitment unless they first interacted with the endothelial surface. The rapid flow of selected lymphocytes is interrupted by receptors which allow

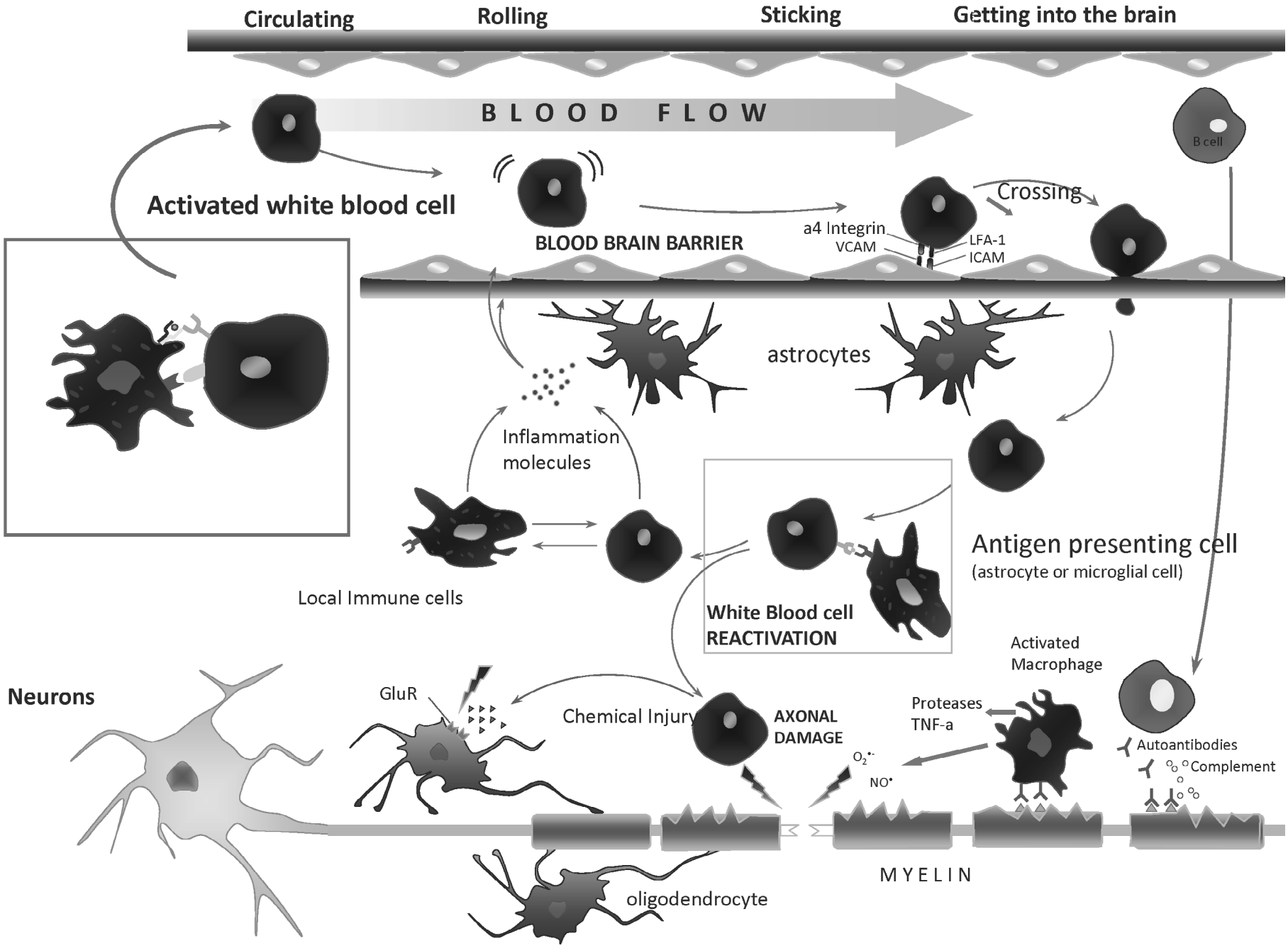
Circulating
Rolling
Sticking
Getting into the brain
BLOOD FLOW
B cell
Activated white blood cell
BLOOD BRAIN BARRIER
a4 Integrin
VCAM
LFA-1
ICAM
Crossing
astrocytes
Inflammation molecules
Local Immune cells
White Blood cell REACTIVATION
Antigen presenting cell
(astrocyte or microglial cell)
Activated Macrophage
Neurons
GluR
Chemical Injury
AXONAL DAMAGE
Proteases
TNF-a
Autoantibodies
Complement
MYELIN
oligodendrocyte

Figure 1

for direct interaction between the lymphocyte and the endothelial surface of the blood vessel. The crucial receptor controlling lymphocyte trafficking into the central nervous system is alpha-4- beta1 integrin (also known as VLA-4) (see **natalizumab**).

Immune cells frequently generate injury to targeted cells via oxidative mechanisms. The transcription factor nuclear (erythroid derived 2) related factor (NRF2) regulates an endogenous antioxidant pathway, and therefore suppression of Keap-1 mediated inhibition of this pathway can control immune mediated injury (see **BG12/dimethyl fumarate**).

A few more specific molecules:

- B cells express CD20 on their surface
- Most cells of immune lineage express CD52 (including T cells, B cells and natural killer CD8+ cells).
- CD25 is anther name for the IL2 receptor expressed on activated T cells.

EXISTING ANTI-INFLAMMATORY MS THERAPIES

INJECTABLE THERAPIES

Many of the older agents have unclear mechanism(s) of action. The interferons were initially designed and tested based on the theory that their anti-viral properties would treat an as-yet undiscovered viral infection which was responsible for MS. However, they are now thought to have a variety of effects, including inducing a shift from TH1- to TH2-type immunity, as well as preventing egress of circulating lymphocytes into the central nervous system. All three interferon formulations require injection and any clinically-meaningful differences between formulations have to do with route of administration (subcutaneous vs. intramuscular, IM) and/or the overall dose. Attempts to make an orally-available formulation of interferon have so far failed.

The precise mechanism of action of glatiramer acetate (GA, also known as copolymer 1) is also unknown. It is, in fact, the oldest drug in the disease-modifying therapeutic arsenal as it was originally discovered in the early 1970s by Michael Sela and colleagues at the Weissman Institute. It was first tested in patients in the early 1980s by Murray Bornstein. GA appears to alter T cell differentiation, restore regulatory T cell activity, and modify antigen presentation in response to blunt inflammatory injury.

The IFNs and GA constituted the mainstay of therapy in MS for over a decade (1992-2006). Collectively, they remain the most commonly used medications for the treatment of MS worldwide. They are modestly efficacious, and probably equivalently so (with the exception that less frequent dosing of IM IFN-β 1a is less efficacious than the higher dose IFNs and GA). They all have a well-established, outstanding long-term safety record but they are all associated with injection site reactions and other significant tolerability issues (such as flu-like symptoms, worsening spasticity and depression) that make them challenging for many patients. Interferons used in other settings (such as the treatment of hepatitis) are associated with the development of cotton wool spots, and these have been seen in a small but consistent group of patients using IFN-β for the treatment of MS.

Clinical trials over the last 10-15 years have indicated that these therapies are effective from disease onset and are, in fact, likely to be more effective the earlier they are initiated. As noted above, trials have indicated that increased dose and frequency of interferon administration result in greater efficacy than lower dose IM administration. However, in the face of competition from oral therapies, there has been a move in the last few years to try to reduce the frequency of injections as an alternative to standard dosing regimens.

Pegylated IFNβ (PegIFNβ) is a version of IFN with a longer half-life that allows for less frequent injections.The recent ADVANCE trial assessed two-weekly and four-weekly administration. Compared to placebo, there was a 36% reduction in the number of relapses and a 67% reduction in the number of new T2 lesions, as well as 86% reduction in new enhancing lesions ($p<.05$). This is the most recent drug approved for use in MS (late 2014).

Copolymer1 3x weekly: This is a reduced-frequency formulation of GA which was tested on 1,404 patients as part of the GALA trial.[8] This trial demonstrated that, compared to placebo, therapy was associated with a 34% reduction in relapse rate and a similar reduction in the development of new lesions on MRI. Lower-frequency GA has not yet been compared to the standard daily formulation of this medication.

Generic Copolymer 1: A clinical trial enrolling 796 subjects showed similar efficacy between branded copolymer1 (Copaxone®) and a generic form of the drug produced by Synthon pharmaceuticals.[9]

NEW ANTI-INFLAMMATORY MS THERAPIES

NATALIZUMAB (TYSABRI®)

Natalizumab is a monoclonal antibody that blocks trafficking of immune cells into the brain. The antibody binds to VLA4, a molecule expressed on the endothelial surface of blood vessels that is required for lymphocyte interaction with the blood vessel wall before crossing into the central nervous system. From clinical trials, natalizumab shows the strongest efficacy of any of the medicines available for the treatment of MS although it has not yet been compared head-to-head with any of the available MS therapies. The pivotal clinical trials leading to its approval showed a reduction in relapse rate of nearly 70% and a reduction in new disease activity on MRI of over 90%.[10-11] In addition, natalizumab showed a significant advantage

in preventing both decline in low contrast vision[12] and in worsening disability.

The most serious side-effect of natalizumab treatment is the potential development of progressive multifocal leukoencephalopathy (PML). To date, over 400 cases of PML have occurred in natalizumab-treated patients. The risk is higher in patients with prior exposure to immunosuppressants and longer periods of exposure. However, the greatest predictor of risk is the patient's serological status for the virus that causes PML (JC virus). Patients who are JC virus-positive may have a risk of developing PML of more than 1/100 (13/1000) whereas those who are negative have a risk which is lower than 1/20,000. PML often presents as cognitive disturbance or visual field defects. There are isolated cases of patients developing herpes zoster ophthalmicus (HZO) while on treatment with natalizumab, as well as cases of other herpes virus reactivation.[13] HZO appears to be treatable by only brief cessation of natalizumab or even with antiviral treatment with continuation of the drug. Discontinuing natalizumab abruptly has occasionally been associated with an immune reconstitution syndrome and aggressive recurrence of disease. This immunological rebound is one of the reasons that caution is used before starting natalizumab in patients with milder MS even if they are JC virus negative. As of late 2014 more than 130,000 patients have received this medication worldwide for MS.

FINGOLIMOD (GILENYA®)

This was the first oral agent to be approved for treatment of MS. It is taken as a once-daily pill. Prior to administration, patients must be assessed for cardiac risk, macular edema, and prior exposure to certain herpes virus infections (i.e. varicella zoster). Some clinicians also assess pulmonary function and look for any pre-cancerous skin lesions with a dermatologic assessment. The mechanism of action is much clearer than for some of the older agents. It modulates the sphingosine phosphate-based lipid biomessenger system and, as a consequence, has widespread biological effects. Probably the most important therapeutic effect is that it blocks CC7+ cells (see above) and so traps around 80% of circulating immune cells in the lymph nodes. Within hours after first dose administration circulating levels of lymphocytes drop substantially.

Fingolimod reduces relapse rate by 54% compared to placebo and by ~50% compared to IFN-β 1a. These reductions are associated with reduced disease activity on MRI and reduced sustained disability progression over the course of the pivotal trials.[14-16] Fingolimod has also shown efficacy in reducing decline in low contrast visual acuity. Fingolimod has shown reasonable effectiveness at controlling disease activity in patients transitioning off Natalizumab in at least 1 study[17]. It is currently being tested in progressive MS as well.

All patients on fingolimod appear to have a mild increase in macular volume on OCT.[18] A small subset of patients appear to develop cystoid or diffuse macular edema. It is unclear if fingolimod only unmasks pre-existing subclinical or mild macular edema or if it actually induces the condition in small subset of susceptible individuals. Macular edema was first identified as a risk in transplant patients long before the medication was ever used for the treatment of MS. In that setting the highest risk appeared to be in patients with pre-existing diabetes and, presumably, some degree of diabetic retinopathy. In renal transplantation trials the rate was 1.3 to 2.2 percent depending on dose. In at risk individuals the rate was as high as 30% for diabetics. In the MS cohort it appears as though diabetes, prior uveitis and the presence of a pre-existing epiretinal membrane and/or other evidence of vitreoretinal traction constitute the greatest risk for the development of macular edema, although diabetes was explicitly an exclusion criterion in the original MS clinical trials. The rate of macular edema was officially reported at 0.2% at the approved dose of 0.5 mg/day. Discontinuation of the medication is typically associated with resolution of macular edema. Some observers have noted that the highest period of risk is during the first year of treatment, although it is unclear if this is the only period of risk given that the medication is still relatively new. The American Academy of Ophthalmology has recommended a complete ophthalmologic exam at baseline and 3-4 months after medicine initiation. Repeat evaluation is recommended 6 months later and then annually thereafter presuming a negative evaluation. Standard exam is considered to be ophthalmoscopy with careful evaluation for macular thickening.[19] Many clinicians utilize OCT and with abnormal findings will also perform fluorescein angiography.

In the original clinical trials of fingolimod, two patients also developed major infections with herpes viruses, one with disseminated varicella zoster virus (VZV), the other with herpes simplex encephalitis. Therefore, all patients treated with fingolimod must have either been previously infected with, or immunized against, VZV and demonstrate maintained immunity (via assessment of their anti-VZV serological status) before initiating the drug. In addition, avoidance of live virus vaccinations (i.e., yellow fever, varicella zoster virus (VZV), influenza, etc.) is recommended while on fingolimod. Furthermore, if a patient requires steroids while on therapy (to treat an exacerbation, for example) many clinicians will prophylactically treat with valacyclovir given reported cases of herpes virus reactivation or systemic infection in patients in this setting.

When starting fingolimod concomitant treatment with class Ia and class III antiarrhythmics must be avoided given the transient heart rate slowing which occurs during administration of the first dose. Additional caution should be exercised with concomitant use of beta-blockers or calcium channel blockers, principally at medication initiation. As of late 2014 more than 100,000 patients have received this medicine worldwide for the treatment of MS.

DIMETHYL FUMARATE (BG12/TECFIDERA®)

Dimethyl fumarate (DMF) was developed as a treatment for MS following the observation in Germany that patients with both psoriasis and MS appeared to demonstrate reduced MS disease activity when they were treated with fumaric acid esters for their psoriasis. In two pivotal clinical trials, BG12 reduced relapse rate by approximately 50%.[20-21] DMF appears to work in two ways. First, it depletes glutathione which leads to production of the anti-inflammatory stress protein heme oxygenase 1. Second, it generates an antioxidant response via upregulation of the NRF2 pathway (see above). This is important as many immune cells use oxidative injury as means of damaging targeted cells. DMF was approved as a medication for the treatment of MS in March 2013. The medication is taken twice a day. It is associated with GI upset and flushing in between ¼- ½ of patients, which may become less pronounced with time. As of late 2014 more than 100,000 patients have been treated with this agent.

In late October 2014, Biogen-Idec announced that a patient treated with DMF monotherapy who had had sustained lymphopenia for > 3 years developed progressive multifocal leukoencephalopathy. This followed the description of at least two other cases of PML in patients treated for psoriasis with other fumaric acid ester formulations who also had lymphopenia. Although the package insert only s*uggests* a lymphocyte count 6 months before initiation of therapy and annually thereafter, many MS specialists check lymphocytes counts at least every 6 months after DMF initiation and stop patients who show signs of significant lymphopenia.

TERIFLUNOMIDE (AUBAGIO®)

This is a once-daily oral agent developed as an active metabolite of leflunomide, a drug used to treat moderate to severe rheumatoid arthritis and psoriatic arthritis. It inhibits synthesis of pyrimidines, specifically the nucleic acids cytosine, thymidine and uracil, and thereby blocks the development of rapidly-dividing cells like lymphocytes.

The medication was tested in 3 large clinical trials and showed modest efficacy similar to the older injectable agents. In fact, teriflunomide performed similarly to high dose subcutaneous IFN beta 1a (Rebif®). Tolerability is good and immediate side effects are minimal (apart from the relatively frequent complaint of hair loss).[22]

The principal issue affecting this class of drug is that they have been allocated to pregnancy category X (meaning that they are known to cause birth defects) and pose a risk to the offspring of both males and females of reproductive age.

MONOCLONAL ANTIBODIES THAT HAVE COMPLETED, OR ARE ABOUT TO COMPLETE, PHASE III CLINICAL PROGRAMS

DACLIZUMAB HYP

The results of large clinical trial enrolling 1800 patients treated with Daclizumab will soon be reported. This medication prevents the activation of T-lymphocytes by disrupting interleukin-2 signaling. It accomplishes this by binding to CD25, one of the subunits of the IL-2 receptor. A different infusible formulation of this medication was initially tested in patients who had broken through treatment with interferon. More recently, large-scale clinical trials are underway using a monthly subcutaneous injectable formulation, including one trial that is comparing the drug to weekly IM IFN β-1a. Early reports on the results from these trials are promising.

Interestingly, the medication has also been used to treat birdshot chorioretinopathy in a small clinical trial reported in the Archives of Ophthalmology.[23]

CAMPATH (LEMTRADA®)

Campath is a very broad class immunosuppressant that utilizes an antibody that targets CD52. The medication appears to be very effective at treating MS, although the phase III clinical trials were disappointing compared to phase II results.[24] However, the FDA raised serious concerns about the integrity of the clinical trial and the safety of the medication. There is a high rate of secondary autoimmunity seen in patients treated with Campath, including idiopathic thrombocytopenic purpura (ITP) and hyperthyroidism. Patient interest groups have generated an appeal and the parent drug company hopes to reverse an initial rejection by the FDA.

OCRELIZUMAB

Ocrelizumab is a humanized antibody that targets CD20 a molecule expressed on pre-B and B cells. This leads to the depletion of B cells and, contrary to initial expectations, appears to have a rapid and pronounced clinical effect on MS similar in magnitude to that seen with natalizumab. Phase III clinical trials are ongoing, but results from phase II trials demonstrating similar results with this and a related B cell depleting agent, rituximab, are promising.[25-26]

OTHER ORAL MEDICATIONS

Many other drugs with a similar mechanism of action to fingolimod are currently in the midst of late-stage clinical testing. These include RPC1063, ONO4641, and siponimod. All these medications could theoretically be associated with macular edema and/or increases in macular volume.

SYMPTOMATIC THERAPIES OF RELEVANCE TO NEURO-OPHTHALMOLOGISTS

DELAYED RELEASE 4-AMINOPYRIDINE (FAMPRIDINE, FAMPYRA®)

Fampridine is a potassium channel modulating medication approved for the treatment of walking in MS. Despite its principal indication for the treatment of motor dysfunction and gait impairment, patients also note some subjective visual improvement with the medication. Small trials are underway to assess if these visual effects are real and sustainable.

MEMANTINE (NAMENDA®)

Memantine is a low affinity, non-competitive antagonist of the NMDA receptor that also has agonist effects on D2 dopamine receptors and antagonist effects on serotonin 5HT receptors. Empirical evidence suggests that it is very useful in the treatment of acquired pendular nystagmus. Anecdotally, some patients with pendular nystagmus report complete disappearance of the associated oscillopsia on the medication, though clinical examination frequently demonstrates that lower amplitude nystagmus persists. For many patients, the effect is more dramatic than that which is seen with standard therapies used for this indication, i.e., baclofen and gabapentin. However, one group has reported the worsening of other MS symptoms in patients treated with high-dose memantine.[27]

VITAMIN D

Increasing evidence suggests that low vitamin D levels are associated with an increased risk of developing MS. Further evidence has recently suggested that low levels of vitamin D are also associated with increased disease activity in patients with MS.[28] However, it is not clear whether this association is a direct result of the activity of vitamin D or if the vitamin D is serving as a proxy for some other important biological factor. It is not clear whether vitamin D has an additive benefit when given with disease modifying treatments, and clinical trials are underway.

SODIUM INTAKE

Research published last year showed that a high sodium diet was associated with worsened disease in animal model of MS. A more recent observational study that estimated sodium intake based on urinary sodium excretion found that higher sodium intake was associated with 3-4x higher rate of MS exacerbations.[29]

EMERGING REPARATIVE THERAPIES

There are exciting new advances in the development of agents intended to restore or repair damaged myelin in patients with MS or following acute attacks. Clinical programs at various stages of development have undertaken approaches to use monoclonal antibodies or small molecules to achieve the restoration of normal myelin function and, hopefully, the protection of axons from long term degradation and loss. These include the agent Anti-LINGO and rhMIG22 as well as Phase II clinical trials of these agents have focused on using visual outcome as a primary efficacy measure for proof of concept. Additional discoveries of potential small molecule targets in MS could be considered particularly exciting and promising as we enter the age of reparative and restorative therapies in MS.

SUMMARY

The arsenal of available medications for the treatment of MS has expanded dramatically in the last 10 years. These advances have been catalyzed by a deepening understanding of the pathogenesis of MS and especially by major advances in clinical and laboratory immunology. In addition the ready availability of a phase 2 clinical outcome (Gadolinium-enhancing lesions on MRI) that predicts phase 3 clinical success and the fortunate success of many of the clinical trial programs in recent years has lead to a wide array of choices for managing patients with MS in 2015.

These enhanced options have also increased the complexity of managing patients with MS and exposed the importance of considering the balance between disease control and therapy related health risks in every patient. One clear and overarching principle that has emerged is that early control of immune injury in MS is indicated – and in this regard neuro-ophthalmologists are often on the front line as many patients come to see us early in the course of their disease. As we improve control of immune mediated injury in MS we are also now seeing the opportunity to embark into remyelinating and other reparative therapies to help tackle the elements of injury that are not addressed with immune targeting therapies.

CME ANSWERS

1. c, e and f
2. c and e
3. b
4. b
5. d

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THE RELATIONSHIP BETWEEN PDE-5 INHIBITORS AND NAION

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LEARNING OBJECTIVES

1. Review the mechanism of action of PDE-5 inhibitors
2. Discuss case reports of association between PDE-5 inhibitors and NAION
3. Review research studies investigating effects of PDE-5 inhibitors on ocular circulation and epidemiological studies of potential association of PDE-5 inhibitor use and NAION
4. Discuss medico-legal issues related to cases of NAION associated with PDE-5 inhibitor use
5. Review a prospective study of NAION and PDE-5 inhibitor use mandated by the FDA

CME QUESTIONS

1. Which of the following medications is not approved for use in the U.S.?

   a. Sildenafil
   b. Vardenafil
   c. Avanafil
   d. Udenafil

2. The Pfizer case-crossover retrospective study revealed an odds ratio of ____for an association between erectile dysfunction drug use and NAION.

   e. 1
   f. 2
   g. 3
   h. 4

3. The last FDA mandated update of the drug warning for sildenafil was in:

   a. 2001
   b. 2005
   c. 2010
   d. 2014

KEYWORDS

1. Erectile Dysfunction Drug
2. Non-arteritic Anterior Ischemic Optic Neuropathy
3. Phosphodiesterase 5 (PDE-5) Inhibitor
4. Pfizer
5. Sildenafil

INTRODUCTION

HISTORY OF ERECTILE DYSFUNCTION DRUG DEVELOPMENT AND MECHANISM OF ACTION

Sildenafil was first synthesized by pharmaceutical chemists working at Pfizer. It was initially studied for use in hypertension and angina. Phase I clinical trials suggested that the drug had little effect on angina but could induce penile erection. Sildenafil (Viagra®) was patented in 1996 and approved by the FDA for use in erectile dysfunction (ED) in March, 1998. Vardenafil (Levitra®) was approved by the FDA for treatment of erectile dysfunction in August, 2003 and tadalafil (Cialis®) in November, 2003. Avanafil (Stendra®) was approved in April, 2012. Udenafil (Zydena) is not FDA approved for sale in the United States, but is available in Korea, Russia and the Philippines.

Sexual stimulation causes a local release of nitric oxide in the corpora cavernosa. Nitric oxide activates guanylate cyclase, resulting in increased levels of cGMP, which causes smooth muscle relaxation, resulting in vasodilation and increased blood flow into the spongy tissue of the penis, thereby causing an erection. The ED drugs act by selectively inhibiting cGMP-specific phosphodiesterase (PDE) 5 in the corpora cavernosa, an enzyme that promotes degradation of cGMP. The molecular structure of sildenafil is similar to cGMP and it acts by binding competitively to PDE5, resulting in more cGMP and thus increased duration of erections. The half-life of sildenafil and vardenafil is 3-5 hours, while the half-life of tadalafil is 17.5 hours. Sildenafil also weakly inhibits PDE6 with an efficacy of about 1/10 of that for PDE5. PDE6 is present in the photoreceptors in the retina and is an important component of the phototransduction cascade.

The primary indication for sildenafil is treatment of erectile dysfunction. Other uses include treatment of pulmonary arterial hypertension (approved by the FDA

in 2005 as Revatio), and prevention and treatment of high-altitude pulmonary edema associated with altitude sickness. Tadalafil was also approved by the FDA in 2009 for treatment of pulmonary arterial hypertension (Adcirca), and for treating benign prostatic hyperplasia in 2011.

REVIEW OF CASE REPORTS OF ASSOCIATION BETWEEN PDE5 INHIBITORS AND NAION

The first case report of the potential association of an ocular side effect with sildenafil involved a third nerve palsy[1]. The first case of NAION associated with sildenafil use was reported in 2000 by Egan and Pomeranz[2], followed by a second case reported by Cunningham and Smith[3]. These cases were followed by two small case series reported in 2002 and 2005[4, 5]. Numerous other single case reports or case series have since been published[6-23]; table 1); some of these cases reported retinal vascular occlusions in addition to NAION[17] of isolated retinal vascular occlusions[24-26] and central serous retinopathy[27-32] have also been reported.

In addition, the FDA has compiled cases of vision loss associated with ED drug use that have been reported to it through its Med-Watch Program. Because the details of the vision loss are often incomplete in most of these cases, as the reports are provided by patients or other lay individuals, they cannot be relied upon to provide material for formal statistical analysis. However, they do provide an indirect indicator of the number of reported cases of NAION relative to the number of prescriptions dispensed for ED medications, as well as a sense of the magnitude of visual loss.

In 2005, an NBC news report revealed that the FDA had received 43 case reports of NAION associated with ED drug use; this information was confirmed by a report published on the FDA's web site as follows:

(From FDA Web Site) "As of May 18, 2005, a total of 43 cases of ischemic optic neuropathy (ION) among patients using the marketed PDE5 inhibitors (sildenafil, tadalafil, vardenafil) have been reported to the FDA's Adverse Event Reporting System. Since approval, 38 cases have been identified in association with sildenafil, 4 cases have been identified in association with tadalafil and one case has been identified in association with vardenafil. Most of these cases (25/43) appear to be the non-arteritic anterior ischemic optic neuropathy (NAION) subtype. Thirty-six of the 43 cases reported accompanying visual loss, and 26 of these 36 cases reported the visual loss as continuing or permanent. Most of the patients in these cases reported vascular risk factors for NAION that overlap with vascular risk factors for erectile dysfunction (such as age over 50, low cup to disc ratio, hypertension, diabetes, smoking, etc), making direct attribution to PDE5 inhibitors not possible. However, the clinical attributes of some of the cases (e.g., a temporal relationship in 19 sildenafil cases, 4 tadalafil cases, and the one vardenafil case, and the report of recurrent ocular symptoms that might reflect NAION in five sildenafil cases and one tadalafil case), raise concern with regard to the role of PDE5 inhibitors."

Since 2005, additional cases of ED drug-associated NAION have been reported in the peer reviewed medical literature, many of them from other countries around the world including India, Saudi Arabia, China, Korea, Egypt and Turkey. Two cases have been attributed to a Chinese herbal medicine containing sildenafil[11, 13]. Some cases have been attributed to sildenafil use for the treatment of pulmonary hypertension rather than ED[6, 15].

RESEARCH STUDIES INVESTIGATING EFFECTS OF PDE5 INHIBITORS ON OCULAR CIRCULATION

Research has been performed on healthy volunteers as well as on research subjects with known ED investigating possible effects of sildenafil on the arterial blood supply to the eye through the ophthalmic, posterior ciliary and central retinal arteries. Grunwald concluded that 100 mg sildenafil causes no significant change in optic nerve rim or foveolar choroidal blood flow[33] as measured by laser doppler flowmetry, and no effect on retinal vascular caliber[34] in 15 healthy male volunteers. Kurtulan et al[35] reported that 100 mg of sildenafil had no effect on ocular hemodynamics of the central retinal artery on the basis of color Doppler ultrasonography in 38 patients with ED. Koksal et al[36] reported that in 20 study participants with ED given 100 mg of sildenafil, peak systolic velocity, end-diastolic velocity and mean velocity were significantly increased one hour after drug intake in the ophthalmic and short posterior ciliary arteries, but not the central retinal artery. Dundar et al[37] found no changes in color Doppler hemodynamics in the ophthalmic, central retinal and short posterior ciliary arteries in 15 patients with ED received 50 mg sildenafil twice a week for 3 months. Paris et al[38] reported that in 12 normal adults after a 50 mg dose of sildenafil, an increase in pulsatile ocular blood flow occurred by causing a change in the choroidal vasculature. Pache et al[39] reported a significant dilatation of retinal arteries and veins in healthy subjects after 50 mg sildenafil using a retinal vessel analyzer. Polak et al[40] reported that sildenafil increases retinal venous diameters and retinal blood flow in healthy volunteers after 100 mg sildenafil using laser Doppler flowmetry and retinal vessel analyzer. McCulley et al[41] found that 200 mg sildenafil caused small inconsistent changes in choroidal thickness in healthy volunteers. These studies are summarized in Table 2. (see page 74)

In summary, the above studies show that sildenafil has little effect on the retinal, optic disk and choroidal arterial circulation in healthy individuals, while its effect in study participants with ED was variable depending on the study. No studies were specifically directed at individuals at high risk for NAION, i.e. individuals with a history of nocturnal hypotension, vasculopathic individuals with a small cup to disk ratio, sleep apnea, or history of NAION in the fellow eye. Such studies would be unethical. It does not appear that any studies have been published using the animal

model for NAION to determine whether or not ED drugs cause damage to the optic nerve.

EPIDEMIOLOGICAL STUDIES STUDYING PDE5 INHIBITOR USE AND NAION

Margo and French[42] reported that a case-control study of PDE5 inhibitors and NAION was feasible using a National Veterans Health Administration's pharmacy and clinical databases. McGwin et al[43] conducted a retrospective case control study with 38 cases of NAION and 389 controls who participated in a telephone interview regarding past and current use of Viagra and Cialis, but interviewers were not blinded to case status. They found a statistically significant association between ED drug use and NAION in those subjects with a history of myocardial infarction. Sobel and Cappelleri from Pfizer[44] criticized McGwin's conclusions based on methodological limitations such as study biases, sample size, and statistical analysis, ultimately resulting in a retraction of McGwin's study in 2011.

A new study[45] utilizing a pharmaco-epidemiological nested case-control study of a health claims database (looking at physician diagnostic codes and prescription medication dispensing) identified cases of NAION which were matched with corresponding controls and correlated with the prescription of PDE5 inhibitors. A conditional logistic regression model was used to estimate the likelihood of an association between NAION and the prescription of PDE-5 inhibitors. The authors concluded that there was no association between PDE-5 inhibitor prescription and NAION. One of the study's weaknesses was that it was limited solely to diagnostic codes and prescriptions identified in a database. No "real" data (i.e. patient cases of NAION or direct linkage of patients to an actual prescription record of ED drug use) were utilized in this study. Furthermore, the issuing a prescription for an ED drug is not necessarily indication guarantee that such the prescription was either dispensed or the medicine taken by the patient. In summary, there is no convincing epidemiological evidence linking NAION with ED drug use.

MEDICO-LEGAL ISSUES RELATED TO CASES OF NAION

After the first case series was published in 2002[4], a surge of initial inquiries was instigated by attorneys and patients requesting reviews of cases of vision loss associated with ED drug use. Many of these cases were either poorly documented (e.g. no recollection of time interval between last ED drug use and onset of vision loss) or were not cases of NAION. Over the next two years, more cases of NAION associated with ED drug use were reported. The documentation in these cases was more accurate and gave rise to a stronger suggestion of a temporal association between vision loss and recent ingestion of medication. The FDA paid closer attention to these cases as a result, but did not intervene at the time. After publication of the second case series in the Journal of Neuro-Ophthalmology in March 2005[5], the FDA began receiving pressure from the public and the media. A patient who lost vision due to NAION associated with sildenafil use decided to sue Pfizer and, together with his attorney, contacted CBS News to cover and publicize the story. The CBS news story aired on May 26, 2005, and was followed by coverage on NBC, ABC and CNN as well as newspaper and radio coverage the following day. That same day, the FDA announced that it was in discussions with Pfizer to update its Viagra® package insert to include vision loss.

One may wonder why the FDA delayed adding NAION to the list of other ocular complaints in the post-marketing data for sildenafil, particularly after cases were published in the peer-reviewed medical literature starting in 2000. After media coverage of the FDA announcement on May 27, 2005, Senator Charles Grassley became concerned about the lack of any substantive action by FDA and began his own investigation. Grassley's staff interviewed the safety evaluator from the FDA Office of Drug Safety, who had produced the original analysis of NAION in Viagra® users. By monitoring adverse event reports submitted to the FDA, the safety evaluator had concluded, as early as January 2004, that NAION was an important safety issue for Viagra® users. Her review had been sufficient to convince the deputy director of the Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products that the potential for NAION should be added to the Viagra® label. The NAION report was finalized in April 2004 and sent to the Office of New Drugs, the final arbiter of label changes. However, it wasn't until July 8, 2005, 13 months after the Office of New Drugs received documents from the safety evaluator, that the FDA finally published safety alerts for patients and healthcare professionals on its web site.

While all of this public attention was occurring, the attorneys handling the above mentioned lawsuit contacted other attorneys who were representing clients with similar cases against Pfizer, and decided to initiate multidistrict litigation to represent all of these cases as a group and proceedings commenced in 2006. By 2009 the case was dismissed based on insufficient evidence of causality between sildenafil use and NAION.

In 2010, the FDA sent Pfizer a warning letter accusing the company of actively downplaying cases of NAION reported:

(http://www.fda.gov/iceci/enforcementactions/warningletters/2010/ucm215405.htm). It is not clear exactly how many cases of NAION associated with ED drug use have been reported to the FDA to date either through the Med Watch Program or by the pharmaceutical firms themselves.

PROSPECTIVE STUDIES OF NAION AND PDE5 INHIBITOR USE MANDATED BY THE FDA

On July 8, 2005 the FDA mandated that the three pharmaceutical companies that marketed ED drugs place warnings on their drug inserts regarding the potential association between NAION and ED drug use. In addition,

the FDA mandated that Pfizer, Bayer and Eli Lilly each carry out observational studies to determine whether or not there was an association between ED drug use and NAION. Pfizer's study results were reported in August 2013. Studies by Bayer and Eli Lilly are still ongoing (see clinicaltrials.org).

Pfizer's study was a case-crossover retrospective study looking at definite and probable cases of NAION. The primary outcome measure was the number of cases of definite NAION that had been exposed to a PDE5 inhibitor during a 1-day case window (i.e. the day prior to symptomatic onset of vision loss) compared to twenty-nine 1-day control windows (i.e. the rest of the 30-day period prior to vision loss). [A case was considered "associated" if sildenafil or vardenafil was used on that day and/or the previous day, or if tadalafil was used that day and/or any of the previous 4 days (because of its longer half-life).] Other outcome measures were the total number of days exposed to ED drugs in definite or possible NAION cases, and the number of weeks exposed. 76 potential NAION cases with PDE5 inhibitor exposure were identified. Of these, 43 cases were deemed to be definite NAION with PD drug exposure occurring within the 30 days prior to onset of symptoms. Of these 43 definite NAION cases, 14 cases were exposed to PDE5 inhibitor during the day prior to symptom onset, while there were 248 documented instances of PDE5 inhibitor use over the 30 days prior to onset of symptoms. Based on conditional logistic regression, an odds ratio of 2.15 was calculated for developing definite NAION the day after exposure to an ED drug; in other words, a 2-fold increase in risk of NAION. For the combined definite and possible categories of NAION, 64 cases were identified, of which 22 cases were exposed 1 day prior to onset of symptoms, compared to 374 instances of PDE5 inhibitor use over the 30 days prior to symptom onset. These data yielded an odds ratio of 2.36.

The results suggest a degree of increased risk of developing NAION after ingestion of an ED drug but a more robust association has yet to be demonstrated. The major limitation of this study was that it relied on retrospective recall of ED drug use in a small number of participants.

In response to the results of Pfizer's prospective research study the FDA mandated an update to the drug warning for sildenafil in March 2014 (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/20895s039s042lbl.pdf). The following language was added:

"WARNINGS AND PRECAUTIONS"

"EFFECTS ON THE EYE

- Physicians should advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA®, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition and a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 in males aged ≥ 50. An observational study evaluated whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION. The results suggest an approximate 2 fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. From this information, it is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors [*see Adverse Reactions (6.2)*].
- Physicians should consider whether their patients with underlying NAION risk factors could be adversely affected by use of PDE5 inhibitors. Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore, PDE5 inhibitors, including VIAGRA®, should be used with caution in these patients and only when the anticipated benefits outweigh the risks. Individuals with "crowded" optic disc are also considered at greater risk for NAION compared to the general population, however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including VIAGRA®, for this uncommon condition."

SUMMARY AND CONCLUSIONS

In summary, 39 cases of NAION associated with ED drug use have been documented in peer reviewed publications, the details of which vary significantly in terms of the frequency with which ED drugs were ingested prior to onset of NAION, the dose of drug consumed, and the time interval between last use of an ED drug and onset of NAION. Many, though not all, cases had microvascular risk factors associated with NAION. There have not been any reported investigations of the effect of ED drugs on ocular circulation in individuals with microvascular disease and/or the "disk at risk," so it is not known whether such individuals carry a higher risk for development of NAION in association with ingestion of ED drugs. There are no convincing epidemiological studies linking NAION with ED drug use. However, Pfizer's case-crossover study reports a 2-fold increase in risk of NAION in individuals who ingested an ED drug.

Recommendations regarding NAION and ED drug use:

1. If NAION occurs, an inquiry should be made as to whether any PDE5 inhibitor medication has been used for treatment of erectile dysfunction (in men), pulmonary hypertension (men or women), or whether the patient has used any substance marketed for the purpose of enhancement of sexual experience, many of which have been determined by the FDA to include variable amounts of PDE5 inhibitor medications among their ingredients.

2. If so, the patient should be counseled as to (1) the future likelihood of development of NAION in the fellow eye, which is recognized from the IONDT to be approximately 15%, and (2) the possibility that continued PDE5 inhibitor use may additionally increase the risk of NAION. As above, the Pfizer observational study demonstrated at least a 2-fold increased risk. Whether or not this makes the overall potential risk of fellow eye involvement with continued PDE5 inhibitor use as high as 30% has yet to be determined.

3. Patients with a previous known history of occurrence of NAION in one eye should be cautioned regarding the use of PDE5 inhibitors for treatment of ED or pulmonary hypertension because of the increased risk of fellow eye involvement.

Table 1

Characteristics of reported cases of NAION occurring after erectile dysfunction drug use

Reference	Age	Risk Factors	Notes	Final acuity
6	7 months	CHD	bilateral PION	not known
7	52	DM	100 mg sildenafil used at least 2-3 times/month for 1 year	20/20, 20/40
7	50	DM, IHD	sildenafil routinely used for over one year (dose not known)	20/300, 20/100
7	52	DM	sildenafil regularly used 2-3 times/week for 2 years (dose not known)	20/25, 20/30
7	41	DM	sildenafil regularly used more than 2-3 times/week (dose not known)	20/100, 20/30
7	45	DM	sildenafil regularly used more than 2-3 times/week for 6 months (dose not known)	20/80, 20/30
7	38	DM, HLC	simultaneous bilateral vision loss after starting daily sildenafil (dose not known)	not known
7	56	HTN, HLC	sildenafil regularly used more than 2-3 times/week for 6-8 months (dose not known)	HM, CF
7	51	DM, HLC	sildenafil intake in the days prior to vision loss OU (dose not known)	20/25, 20/40
7	52	DM, HTN	sildenafil regularly used > 2-3 times/week for more than 1 year (dose not known)	20/60, 20/50
7	70	DM, HLC	sildenafil regularly taken for over 2-3 months (dose not known)	1/200, 1/200
8	60	DM	16 hrs after the 3rd of 3 daily doses of 50 mg sildenafil	20/50
9	51	HC	bilateral NAION 12 hrs post Viagra use	20/25 OU
10	55	none	8 months post continued use of sildenafil 4-5 times per month (dose not known)	20/20 OU
11	57	HTN	bilat PION, Chinese health product taken daily for 2 weeks	CF OD, HM OS
12	48	none	36 hrs post 25 mg, then 50 mg sildenafil	CF
13	76	HTN, HLC, stroke	Chinese herbal product 3 capsules prior to onset of vision loss	HM OD, CF OS
14	63	none	3 step sequential decline in vision (dose not known)	20/40
15	6	pulmonary hypertension	10 mg sildenafil TID x 15 months	LP
16	36	chronic renal failure	the next morning after ingestion of 100 mg sildenafil for each eye	20/25 OU
17	54	none	NAION and CAO a few hours after ingestion of 200 mg sildenafil	HM
18	69	none	18 hrs after ingestion of 50 mg sildenafil	20/20
19	48	none	after ingestion of 100 mg sildenafil daily x 2 days	20/20
5	59	none	a few hours after ingestion of 25 mg sildenafil	LP OD, HM OS
5	58	HC	one hour after ingestion after 50 mg sildenafil	HM
5	67	HTN	next day after ingestion of 50 mg sildenafil	20/200
5	69	HTN	24 hrs after ingestion of 100 mg sildenafil	20/125
5	50	none	30 hrs after ingestion of 100 mg sildenafil	20/160
5	66	HTN, HLC, DM	36 hours after ingestion (dose not known)	20/25
5	60	HTN, HLC	next morning after ingestion (dose not known)	20/20
4	52	prostate cancer, Crohns	60 minutes after ingestion of 50 mg sildenafil	20/20
4	69	HLC	45 minutes after ingestion of sildenafil	20/80
4	42	none	12 hours after ingestion of sildenafil (dose not known)	20/200
4	62	NAION OS	50 mg sildenafil weekly for 15 months	20/50
4	59	DM, smoking, CAD	several hours after ingestion of 50 mg sildenafil	20/25
20	59	none	7 days post 20 mg tadalafil	20/30
21	59	none	45 hrs post 20 mg tadalafil	20/20
22	67	HLC	5 episodes of challenge/rechallenge with 20 mg tadalafil	20/30
23	54	smoking	100 mg udenafil ingested 12 hrs prior to vision loss	20/20

Abbreviations: HM hand motions, CF, counting fingers, DM diabetes, HTN hypertension, HLC hyperlipidemia, CHD congenital heart disease, PION posterior ischemic optic neuropathy, IHD ischemic heart disease, CAD coronary artery disease, NAION nonarteritic anterior ischemic optic neuropathy, CAO cilioretinal artery occulsion

Table 2

Summary of Research studies investigating effects of sildenafil on ocular circulation

Ref	Number	Subject Type	Testing Modality	Summary of Findings
33	15	healthy volunteers	laser doppler flowmetry	no effect of 100 mg sildenafil on optic nerve or choroid
34	15	healthy volunteers	laser doppler flowmetry	no effect of 100 mg sildenafil on retinal vascular caliber
35	38	subjects with ED	color doppler ultrasonography	no effect of 100 mg sildenafil on central retinal artery
36	20	subjects with ED	color doppler ultrasonography	increased ophthalmic and posterior ciliary arterial flow velocity after 100 mg sildenafil
37	15	subjects with ED	color doppler ultrasonography	no effect of 50 mg sildenafil twice a week on ocular arterial flow
38	12	healthy volunteers	HRF, POBF	50 mg sildenafil caused choroidal blood flow changes
39	10	healthy volunteers	retinal vessel analyzer	50 mg sildenafil caused retinal artery and vein dilatation
40	12	healthy volunteers	laser doppler flowmetry	100 mg sildenafil increases retinal vein diameter and increases retinal blow flow
41	13	healthy volunteers	ultrasonography	200 mg sildenafil causes choroidal thickness changes

Abbreviations: ED erectile dysfunction, HRF Heidelberg retinal flowmetry, POBF pulsatile ocular blood flow

CME ANSWERS

1. d.
2. b.
3. d.

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BARIATRIC SURGERY AND THE NEURO-OPHTHALMOLOGIST

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LEARNING OBJECTIVES

1. Understand the types and complications of bariatric surgery
2. Describe the possible role of bariatric surgery for treatment of neuro-ophthalmic conditions
3. Evaluate patients with neuro-ophthalmic conditions after bariatric surgery for possible nutritional deficiencies

CME QUESTIONS

1. According the Society for bariatric surgery, bariatric surgery is indicated for which of the following:
    a. 30 year old man with BMI 32 kg/m^2 and type II diabetes
    b. 45 year old woman with BMI 34 kg/m^2 and type II diabetes
    c. 50 year old man with BMI 39 kg/m^2 and no weight-related comorbidities
    d. 25 year old woman with BMI 20 kg/m^2 and type I diabetes
2. Laboratory / symptomatic vitamin deficiencies following bariatric surgery are:
    a. Common / common
    b. Common / rare
    c. Rare / common
    d. Rare / rare
3. A patient with subacute optic neuropathy following bariatric surgery should be evaluated for
    a. Vitamin B12 deficiency
    b. Copper deficiency
    c. A compressive lesion
    d. All of the above

KEYWORDS

1. Bariatric Surgery
2. Nutrient Deficiency
3. Optic Neuropathy
4. Idiopathic Intracranial Hypertension
5. Obesity

INTRODUCTION

Bariatric surgery, in which the gastrointestinal tract is surgically manipulated with the goal of decreasing caloric absorption and ultimately causing weight loss, is relevant to neuro-ophthalmologists for two main reasons. First, it is a treatment option we can discuss with our patients who have weight-associated neuro-ophthalmic disease. Second, neuro-ophthalmic symptoms and signs may result from the nutrient deficiencies that can accompany altered caloric absorption.

There are a number of challenges in reviewing the relevant literature on bariatric surgery, particularly as it pertains to clinical neuro-ophthalmology. The literature spans a number of specialties, including ophthalmology, neurology, general surgery, obesity, endocrinology, nutrition, psychiatry and even neurosurgery. Furthermore, there is heterogeneity in the literature since bariatric surgery encompasses multiple distinct surgical procedures and some of these procedures are also used for non-bariatric indications. Another barrier is the relative rarity of the associated neuro-ophthalmic conditions, which makes both definitive epidemiological and treatment studies challenging. As a result, the articles that directly pertain to neuro-ophthalmology consist mainly of case reports and case series.

BARIATRIC SURGERY – WHO GETS IT?

Guidelines for the management of obesity, most recently published by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society,[1] recommend consideration of bariatric surgery in patients who are motivated and who have not responded to behavioral weight loss treatment (with or without pharmacotherapy) based on body mass index (BMI = (weight in kg)/ (height in m)^2) and the presence

of weight-related comorbidities. Specifically, the two categories warranting consideration are:

- BMI ≥ 40 kg/m^2
  e.g. 1.8m (6') tall weighing more than 130kg (285 lbs)
  or 1.6m (5'4") tall weighing more than 102kg (225 lbs)
- BMI ≥ 35 kg/m^2 + comorbidity
  e.g. 1.8m (6') tall weighing more than 113kg (250 lbs)
  or 1.6m (5'4") tall weighing more than 90kg (197 lbs)

What is considered to be a comorbidity varies from study to study. The most widely referenced bariatric surgery outcome scale includes hypertension, cardiovascular disease, type II diabetes, sleep apnea, obesity/ hyperventilation syndrome, osteoarthritis and infertility as major comorbid conditions. In this scale, idiopathic intracranial hypertension (IIH), venous stasis, gastro-esophageal reflux disease and urinary stress incontinence are considered to be minor comorbid conditions.[2] A more recent scale, which also includes IIH, does not distinguish between major and minor comorbid conditions.[3] This scale incorporates severity of each comorbidity using an integer rating scale from 0 to 5, where 0 means no symptoms, 1 or 2 means symptoms and 3 to 5 mean diagnosis with varying levels of treatment.[3] This scale is administered based on patient report. Consequently, a person can have a rating of 2 for IIH by reporting headaches even if no other testing has been performed and a rating of 3 by reporting a diagnosis of IIH. How the severity of any comorbid conditions might impact surgical decision-making is not yet clear.

Though classified as a weight-related comorbidity in the bariatric surgery literature, IIH remains a relatively rare disease in this population. In a prospective evaluation of comorbidities (assessed by interview) in 226 candidates for gastric bypass surgery, only 1 (0.4%) reported a diagnosis of IIH, while 201 had psychosocial impairment, 173 had musculoskeletal disease, 106 had hypertension and 50 had diabetes.[3] Two studies have evaluated the prevalence of IIH in patients undergoing bariatric surgery evaluation using a protocol of non-mydriatic fundoscopic photographic screening followed by full neuro-ophthalmic evaluation and appropriate clinical work up for those with photographic abnormalities. Krispel *et al.*[4] reported 7 (0.6%) of 1148 screened subjects had a history of IIH. 647 subjects (none with a history of IIH) were photographed and, of these, 606 photographs were interpretable. 17 were thought to have possible optic disc edema and 4/11 had confirmed mild papilledema with normal vision. The remaining 6 declined participation in dilated examination. 3 patients had complete work up with lumbar puncture and opening pressures of 24, 25 and 32 cm H_2O, respectively. 1 subject declined additional workup. The authors concluded that IIH was present in this population with a prevalence of 3/606 (0.5%), though this excluded 7 subjects with suspicious photographs who could not be completely followed up. In a similar study, Hamdallah *et al*. reported 4 (0.4%) of 1084 screened subjects had a prior diagnosis of IIH.[5] They photographed 568 patients, 532 photographs of which were interpretable. 16 subjects had images suggestive of possible optic disc edema and a further 27 suggested other ophthalmic findings. 4/11 had Frisén stage 1 disc edema on clinical exam and IIH was subsequently diagnosed in 3 (further specifics not given). 5 subjects with suspicious photographs did not complete the evaluation. Of note, two patients photographed with a prior diagnosis of IIH did not have disc edema. Also, two of the patients subsequently confirmed to have IIH with papilledema were actually asymptomatic. This casts doubt on any conclusions that are drawn from studies based solely on a survey of symptoms and patient report.

BARIATRIC SURGERY - WHAT IS BEING DONE?

Approximately 113,000 bariatric surgical procedures are performed annually in the U.S.[6] Bariatric surgery achieves weight loss through decreased caloric uptake by the body. This is accomplished through restricted food intake, malabsorption (i.e. bypassing a length of intestine), maldigestion (i.e. less exposure to stomach acids), and combinations thereof. There are multiple surgical techniques in use and these techniques are in constant evolution. Currently used techniques are outlined below and shown schematically in Figure 1.

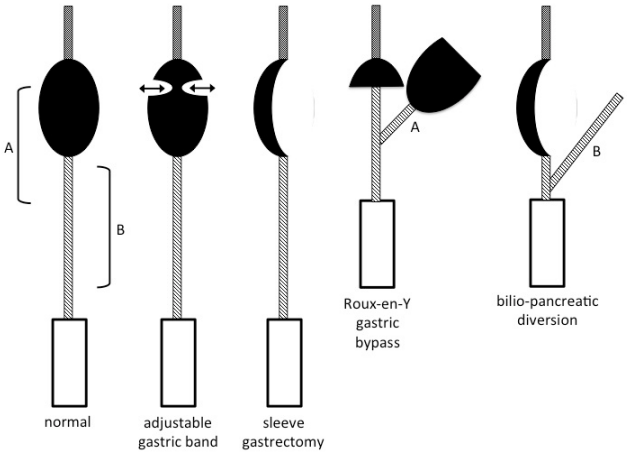

Figure 1: schematic of gastrointestinal tract showing esophagus (grey rectangle), stomach (black oval), small intestine (striped rectangle) and large intestine (white rectangle). Normal anatomy is illustrated on the left. Other illustrations show common bariatric surgical interventions. A and B indicate bypassed segments in Roux-en-Y and bilio-pancreatic diversion respectively.

Adjustable Gastric Band (lap band®, the band) involves laparoscopic placement of an adjustable band around the upper stomach. This restricts food intake and facilitates a feeling of satiety, which helps to reduce food consumed by the patient. Neither digestion nor absorption are affected. The band is adjustable via injection of saline through a subcutaneous port and is removable.[7] The hospital stay is short (outpatient or 24 hours) and the incidence of complications is reported to be 1% (major complications)

and 3% (minor complications) in the hands of an experienced surgeon.[1]

Sleeve Gastrectomy (the sleeve) involves laparoscopic removal of the greater curvature of the stomach to create a sleeve-like pouch. This restricts food intake and alters hormone patterns to promote satiety. It also impacts on digestion of food. The hospital stay is typically 2 days and complication rates range between those of gastric band and gastric bypass procedures.[7]

Roux-en-Y Gastric Bypass surgery (gastric bypass, RGB) involves dividing the GI tract at the stomach and at the jejunum, anastomosing the proximal stomach to the distal jejunum and attaching the removed section (distal stomach and proximal jejunum) approximately 1 m further down the small intestine. This restricts food intake, alters hormone patterns and decreases absorption in the proximal small intestine.[7] It can be performed laparoscopically, with a complication rate of 4-5% (major complications) and 2-18% (all complications).[1]

Biliopancreatic diversion (BPD) with or without duodenal switch (DS) involves the creation of a tubular stomach (similar to sleeve gastrectomy) and dividing the gastrointestinal tract at two points, specifically the proximal duodenum and the ileum. The stomach is anastomosed to the ileum and the bypassed section (consisting of 3/4 of the small intestine) is anastomosed to the ileum distal to this. The procedure can be performed laparoscopically. BPD restricts food intake, alters hormone patterns, alters digestion, and substantially decreases absorption.[7] Perioperative complication rates range from 2-8%.[1]

Guidelines for the perioperative nutritional, metabolic and non-surgical support of bariatric surgery patients were last published in 2013 by the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic & Bariatric Surgery.[8] These include recommendations for pre-operative psychosocial, nutritional and cardiopulmonary assessment. Post-operative meal initiation should be supervised by a registered dietitian and patients should receive counseling regarding appropriate food intake. Patients having undergone a gastric banding should receive supplementation with a multivitamin with minerals (including iron, folate and thiamine), calcium and vitamin D. In addition, patients status post other procedures should receive a second daily multivitamin with minerals and vitamin B_{12}. Patients status post BPD should also receive zinc supplementation. Supplementation can be oral with the possible exception of vitamin B_{12}, which may require subligual, parenteral, intramuscular or subcutaneous formulations to ensure adequate absorption. Vitamin B_{12} and urinary calcium should be monitored in all patients. In addition folate, iron, parathormone (parathyroid hormone) and vitamin D should be monitored after RGB and BPD, and vitamin A should be monitored after BPD. Thiamine, selenium, zinc and copper should be evaluated based on clinical findings (e.g. rapid weight loss, vomiting, or symptoms attributable to deficiency). However, studies show that in practice, testing does not meet these guidelines. One study based on claims analysis found that only 50% of patients had been tested for vitamin B_{12} and iron status post-operatively.[9] The practice of vitamin supplementation also varies widely.[10]

BARIATRIC SURGERY OUTCOMES

WEIGHT LOSS

Patients typically achieve weight loss of 20-35% 2-3 years after surgical procedures, this degree of weight loss being 14-37% greater than comparable non-surgical cohorts.[1] Evidence for longer-term success rates is less strong because there is a tendency for some weight to be regained by 10 years. Studies suggest that patients exhibiting similar weight loss after 2-3 years do better at 10 years following gastric bypass than gastric banding.

IDIOPATHIC INTRACRANIAL HYPERTENSION

Fridley *et al*. recently published a meta-analysis of 62 patients (11 case series and case reports) who had IIH and underwent bariatric surgery.[11] Lumbar puncture opening pressure was reported in 55 patients, ranging from 20 cm H_2O to 55 cm H_2O. Of 58 with documented pre-operative funduscopy, 42 had papilledema. Of 39 who had documented visual field testing, 25 had pre-operative field defects. The majority of patients had had RGB with a minority undergoing gastroplasty (6%) or gastric banding (5%). Five patients did not experience any improvement in their symptoms but the remainder did. Only 1 of 35 patients with pre-operative papilledema and a postoperative eye exam did not demonstrate resolution of the papilledema. The earliest documented resolution of papilledema occurred at 6 months postoperatively. All of the 12 patients with pre-operative visual field testing who also had postoperative visual field testing demonstrated stabilization or improvement in their visual fields. The authors noted that this remains class IV evidence for treatment of IIH with bariatric surgery and stressed the possibility of publication bias, meaning that case reports and series would be skewed towards those with positive outcomes.

When treating IIH, alternative treatments including direct medical/surgical management of the IIH should be considered, as well as non-surgical approaches to weight loss. Speed, complications, and effectiveness should all be considered when making individual treatment recommendations.[12]

WEIGHT-ASSOCIATED DISEASES

Recent guidelines on obesity management indicate that, in concert with weight loss following successful surgery, diabetic markers decrease, diabetic remissions increase, and diabetic incidence decreases. Similarly, the use of blood pressure medication decreases, hypertension remission

increases, cholesterol levels improve, and health-related quality of life improves. All of these effects are found, both within subjects and in comparison to subjects undergoing non-surgical treatments for weight loss.[1] There may even be a mortality benefit with the hazard ratio for mortality being less than 1 in persons undergoing bariatric surgery compared with obese control subjects.[8] There may be some variation in the degree of improvement based on the type of procedure – malabsorption procedures generally giving better results than purely restrictive procedures – though the strength of evidence for this is low.

In contrast to the long term improvements seen in weight-associated metabolic diseases, such as diabetes, following bariatric surgery, there may be negative effects in the short term, particularly with regard to diabetic complications. Relevant to neuro-ophthalmologists is the recent evidence that short-term improvements in glycemic control may be associated with paradoxical worsening of diabetic retinopathy. Thomas *et al*. identified 40 diabetic patients with funduscopic exams pre- and post-bariatric surgery.[13] Twenty-six showed no change, 5 showed regression and 7 showed progression of diabetic retinopathy after bariatric surgery. All those that showed regression had minimal background retinopathy prior to surgery. Of the 7 with progression, 1 had moderate background diabetic retinopathy that progressed to pre-proliferative diabetic retinopathy (PPDR) and 2 with PPDR pre-operatively had progression postoperatively characterized by worsening PPDR. None developed proliferative diabetic retinopathy. The patients with PPDR progression had higher pre-operative fasting glucose, higher pre-operative systolic blood pressure, and a greater magnitude of fasting glucose improvement post-operatively.

MEDICATION PHARMAKOKINETICS

Following bariatric surgery, drug pharmacokinetics are potentially altered via the same mechanisms that reduce nutrient absorption. Potential mechanisms include altered breakdown of drug salts resulting from exposure to a different pH, altered first-pass metabolism due to bypass of certain intestinal components, and altered processing of extended-release pharmaceutical products. This has not been comprehensively studied. Some examples include decreased phenytoin levels and increased atorvastatin levels following bypass-type surgeries.[14] Monitoring therapeutic effects and drug levels (where possible) following bariatric surgery is advised. The use of extended-release or sustained-release drug formulations is not advised in patients who have had bariatric surgery, particularly those of the bypass variety. As of September 2014, Pubmed did not list studies examining common neuro-ophthalmic medications (acetazolamide, topiramate, prednisone). NSAIDs should be avoided in patients with restrictive type procedures due to potential direct irritation of the gastric lining.[15]

NUTRITION

Vitamin and mineral absorption is altered following bariatric surgery via the same mechanisms that reduce caloric absorption. Contributing factors include maldigestion, malabsorption and intake deficiency (for example, decreased fat intake as recommended following bypass surgery). Though the literature describing and studying laboratory deficiencies is fairly comprehensive, that dealing with symptomatic deficiencies is less robust.

Laboratory abnormalities

Interestingly, many patients have vitamin and mineral deficiencies prior to bariatric surgery. One study of 232 patients found over 48% had a deficiency of at least one micronutrient pre-operatively, with vitamin B_{12}, zinc, vitamin D and selenium being the most common.[16] Following surgery, nutrient deficiencies are more common in patients with a bypass component to their operation.[9, 17] The type of bypass surgical intervention also has an effect. A study of 141 patients following bariatric surgery found copper deficiency in 50.6% of BPD patients, but only 3.8% of RGB patients.[18] Zinc deficiency was also more common in the BPD group.

Though multivitamins are routinely recommended following surgery, these are often inadequate to prevent laboratory deficiencies. Gasteyger *et al.* found that, of 137 patients who had undergone RGB and who were taking a standard multivitamin preparation, 98% required additional nutritional supplements by 2 years postoperatively.[19] The most common deficiencies were vitamin B_{12}, iron, vitamin D (in >50% of patients), folic acid (45% of patients), zinc, vitamin B_6, magnesium (12-13% of patients) and vitamin B_1 (4% of patients). This study excluded patients with pre-operative deficiencies and those non-compliant with follow up. Brolin *et al*. have suggested that some deficiencies, such as iron, are poorly remediated with oral supplementation.[20]

Symptomatic deficiencies

Despite the high incidence of laboratory nutrient deficiencies, and the well-described neurological consequences of vitamin and mineral deficiencies[21,22-24] (Table 1) (see next page), most laboratory nutrient deficiencies following bariatric surgery seem to be asymptomatic. On the other hand neurological syndromes attributable to nutrient deficiency can be observed despite normal serum nutrient levels (i.e. in the absence of laboratory nutrient deficiency). This is accounted for by the fact that serum nutrient levels may not reflect total body stores.

Brolin *et al*. reported in their study of 348 patients who had undergone RGB, including 37% with laboratory-proven vitamin B_{12} deficiency, that no patient was symptomatic.[20] In a report of 141 patients following RGB procedures with a high incidence of copper and zinc deficiency on the basis of blood levels, none had neurological symptoms.[18] Vitamin A may be the exception to the apparently low prevalence of symptomatic vitamin deficiencies following bariatric

surgery: a report of 90 patients found that 40-70% reported symptoms of night blindness 6 months after RGB.[25] However, this study did not include examination findings or visual function testing.

Thaisetthawatkul *et al.* performed an excellent study examining neurological complications following bariatric surgery, with a focus on peripheral neuropathy.[26] Based on medical record review at a single institution they identified 16% with symptomatic, electrodiagnostically-confirmed, peripheral neuropathy developing after bariatric surgery, compared with 4% in patients following cholecystectomy. In comparison with a cohort of patients who did not develop peripheral neuropathy after bariatric surgery features of jejuno-ileal bypass surgery (no longer performed) and prolonged nausea/vomiting/dumping/diarrhea were associated with neuropathy development, while vitamin B_{12} injections, multi-vitamin supplementation, calcium supplementation and attendance at a nutritional clinic were inversely associated with neuropathy development. It is not known if these conclusions can be extended to neuro-ophthalmic complications.

Abarbanel *et al.* published a prospective series of 500 patients followed over 20 months following Roux-en-Y gastric bypass (n=457) and gastroplasty (n=43) and noted neurologic complications in 23 patients.[27] All had normal neurological examinations pre-operatively.Diagnosis of complications was based on neurological examinations and testing prompted by patient complaint. One had acute severe neuropathy, electrical myotonia, nystagmus and facial diplegia, one had a myotonic syndrome, two each had burning foot syndrome, Wernicke-Korsakoff encephalopathy, and posterolateral myelopathy, three had meralgia paresthetica and twelve had symmetric polyneuropathy.

Table 1: Consequences of vitamin and mineral deficiencies[22-24]

Deficient Nutrient	Symptoms and Signs of Deficiency			Test
	Neuro-ophthalmic	Neurologic	Other	
Vitamin A	xerophthalmia, keratomalacia, nyctalopia		decreased immunity, dry skin	serum retinol
Vitamin B_1 thiamine	nystagmus, ophthalmoparesis, optic neuropathy	ataxia, amnesia, confusion, peripheral neuropathy	cardiac failure	clinical diagnosis; erythrocyte transketolase activity, whole blood thiamine
Vitamin B_2 riboflavin	Corneal vascularization	burning feet syndrome	magenta tongue angular cheilitis	serum B_2
Vitamin B_6 pyridoxine		polyneuropathy	anemia, nephrolithiasis, dermatitis	urine B_6, erythrocyte transaminase activity
Vitamin B_{12}	optic neuropathy	posterior & lateral myelopathy, dementia, depression, ataxia, polyneuropathy	anemia, atrophic glossitis	serum B_{12} level, methylmalonic acid, homocysteine
Folate		peripheral neuropathy, myelopathy	anemia	red blood cell folate, homocysteine
Vitamin D		myopathy, facial twitching, musculoskeletal pain	hypocalcemia, hyperparathyroidism	25-OH-Vitamin D, parathyroid hormone
Vitamin E	slow saccades, ophthalmoplegia	polyneuropathy, myopathy, spinocerebellar		markers of fat malabsoption
Copper	optic neuropathy	myelopathy, polyneuropathy, cognitive deficits	anemia, neutropenia, hepatosplenomegaly, kinky hair, depigmented skin, poor wound healing	serum copper, ceruloplasmin, 24-hour urine copper, erythrocyte copper-zinc superoxide level

(table continued on next page)

Table 1: Consequences of vitamin and mineral deficiencies[22-24] (continued)

Zinc	night blindness		dermatologic changes, alopecia, pica, immune , dysfunction, dysgeusia, rectile dysfunction	erythrocyte zinc levels
Iron		lethargy	anemia	iron studies
Selenium		skeletal muscle dysfunction fatigue	cardiomyopathy, diarrhea, metabolic bone disease	selenium level

The best-characterized syndrome relevant to neuro-ophthalmology is that of Wernicke's encephalopathy related to thiamine (vitamin B_1) deficiency. Singh *et al*. surveyed the literature and identified 32 reports of cases of Wernicke's encephalopathy occurring after bariatric surgery.[28] These occurred between 2 and 78 weeks after various bariatric surgical procedures. Many cases were associated with other neurological symptoms, most commonly sensory neuropathy. The diagnosis was clinical in the majority of cases, with thiamine levels being reported in only 6 patients (and low in only 4 of those). Erythrocyte transketolase levels were reported in 2 patients (but were low in only 1), thus highlighting the challenges which result when serum levels do not reflect body stores of a nutrient.

Other common neuro-ophthalmic presentations are optic neuropathy, nyctalopia, nystagmus, and ophthalmoparesis as outlined in Table 1. Case reports of neuro-ophthalmic syndromes post bariatric surgery highlight the challenges and complexities faced when trying to determine causality when possibilities include both multiple concurrent nutrient deficiencies as well as other non-nutritional conditions. Published cases that highlight these challenges include:

- A patient 10 months after BPD who developed cutaneous lesions, alopecia and blurred vision. The patient had bilateral optic disc pallor and delayed VEPs in the context of laboratory deficiencies of copper, zinc and selenium.[29]
- Out of 26 patients seen in a tertiary neurology referral setting with symptoms attributable to bariatic surgery, 2 had optic neuropathy associated with low serum vitamin B_{12}, elevated CSF IgG index and oligoclonal bands.[30] The authors proposed that the inflammation was induced by nutrient deficiency, though concurrent inflammatory disease seems a more likely alternative explanation.
- A patient with sequential optic neuropathies 3 years after a Roux-en-Y procedure had low serum vitamin E, borderline vitamin B_{12}/folate and positive testing for the LHON 11778 mutation.[31] The authors propose that the nutrient deficiencies provoked mitochondrial decompensation in this case.
- Bilateral optic neuropathy 10 years after Roux-en-Y in a patient using zinc denture cream were associated with low serum copper, iron, vitamin D, thiamine and pyridoxine levels but a normal vitamin B_{12} level.[32] In this case there was the possibility that zinc toxicity potentiated symptoms of hypocupremia.
- A symptom survey of 90 patients following bariatric surgery identified impaired night vision that increased in prevalence over time to 40-70% at 6 months, though many patients with symptoms had normal vitamin A levels.[25] Formal visual assessment was not performed, making interpretation of the symptoms challenging.
- Stroh *et al*. reported a patient with nyctalopia and central scotomas with documented vitamin A and D deficiency that responded to nutritional supplementation.[33] While the vitamin A deficiency could account for the nyctalopia, the etiology of the central scotomas was not clear.

CONCLUSIONS

- Bariatric surgery is a safe and effective treatment for weight loss in obese individuals. There is level I evidence that is associated with improvement in common weight-associated comorbidities such as diabetes and hypertension and level IV evidence that it is associated with improvement in IIH.
- Bariatric surgery does not preclude non-surgical weight loss treatment or directed treatment of comorbid conditions including IIH.
- Guidelines for selection of patients, pre-operative and post-operative management are published regularly by professional organizations and are an excellent resource for the non-bariatric specialist.
- Laboratory nutrient deficiencies following bariatric surgery are common and associated with the type of procedure performed, the type of nutrient supplementation.
- Clinical syndromes of nutrient deficiency following bariatric surgery are relatively rare and definitive diagnosis can be challenging due to limitations of

laboratory testing, overlap of clinical presentations, and coincident conditions.

- Evidence related to neuro-ophthalmic conditions and bariatric surgery is primarily case-based. Though this limits the strength of any conclusions that can be drawn, it also serves as inspiration for future neuro-ophthalmic research.

CME ANSWERS

1. c
2. b
3. d

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OBSTRUCTIVE SLEEP APNEA AND NEURO-OPHTHALMIC CONDITIONS

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LEARNING OBJECTIVES

1. Understand the clinical features of obstructive sleep apnea (OSA)
2. Describe the spectrum of systemic sequelae of obstructive sleep apnea
3. Explain the possible links between obstructive sleep apnea and optic nerve disorders

CME QUESTIONS

1. Which is not a risk factor for OSA?
   a. Obesity
   b. Male gender
   c. Hypertension
   d. Enlarged neck girth
2. The optic nerve head is potentially affected in OSA by:
   a. Direct hypoxia
   b. Impaired autoregulation of microvasculature
   c. Imbalance between vasoactive substances
   d. All of the above
3. The gold standard for diagnosis of OSA is:
   a. Berlin questionnaire
   b. History of snoring
   c. Still debated
   d. Overnight polysomnography in a sleep laboratory

KEYWORDS

1. Obstructive Sleep Apnea
2. Non-arteritic Anterior Ischemic Optic Neuropathy
3. Glaucoma
4. Papilledema
5. Idiopathic Intracranial Hypertension

1. INTRODUCTION

There has been an emerging interest in the link between obstructive sleep apnea (OSA) and ocular health over the last decade. Though the evidence for OSA playing a role in cerebrovascular disease risk seems clear, the same cannot be said for optic neuropathies. The association between OSA and glaucoma or non-arteritic anterior ischemic optic neuropathy (NAION) may be secondary to either direct hypoxia or to vascular dysregulation, either systemically or at the optic nerve head itself. Papilledema and increased intracranial pressure are also reported in OSA patients and are postulated to be due to increased cerebral perfusion pressure and cerebral venous dilation secondary to hypoxia and hypercapnia.

1.1 DEMOGRAPHICS AND RISK FACTORS

Obstructive sleep apnea (OSA) is characterized by intermittent upper airway obstruction during sleep resulting in apnea and hypoxia. The 1993 Wisconsin Sleep Cohort Study was the first to investigate the prevalence of OSA[1]. The authors reported a rate of 4% in middle-aged men, and 2% in middle-aged women (aged 30-60 years). Of concern, it was estimated in 1997 that up to 93% of women and 82% of men with moderate to severe OSA remained undiagnosed, so the earlier prevalence numbers may have been substantial underestimates of the true burden[2]. More recently, the prevalence of OSA in community-screened patients was found to be between 2% - 6% for moderate disease, and up to 14% for mild disease[3]. Other studies have reported rates of 10% for moderate disease in 30-50 year old men, and 17% in those over 50 years of age[4].

Those with OSA have a significantly higher body mass index (BMI) than those without OSA (31.4 versus 28.3 kg/m2, respectively)[5]. Even in countries with less overall obesity, including countries in Asia, the prevalence rates remain high e.g. 4% in middle-aged men in Hong Kong[6].

Other risk factors include: male gender, older age, post-menopausal women, upper airway abnormalities, family history, and enlarged neck girth[7, 8]. How male sex predisposes to OSA is not clear, though fat deposition in the upper airway and more central deposition than in women may be factors[8]. Men also have a longer airway independent of height, making it more prone to collapse. Obesity results in deposition of fat in the structures surrounding the upper airway, and may alter lung volumes and respiratory stability[8].

Smoking is also commonly linked with OSA, possibly through upper airway inflammation, reduced airway sensation and reduced arousal thresholds[4].

1.2 DIAGNOSIS AND MANAGEMENT

Overnight diagnostic polysomnography (dPSG) performed in a sleep laboratory is currently the reference standard for diagnosing OSA[5]. dPSG measures respiratory indices, the electroencephalogram, and limb movements during sleep. These measures assess both sleep state and respiration concurrently. The apnea-hypopnea index (AHI) is the sum of the apnea (reduction of oro-nasal flow to <10% of baseline for >10 seconds) and hypopnea (reduction of oro-nasal flow to <50% from baseline with a 4% oxygen desaturation and/or arousal from sleep) events occurring during each hour of sleep. However, the exact definition of hypopnea can vary internationally, as some investigators prefer to use a reduction in flow to <30% from baseline[8]. In most studies, OSA is defined as an AHI≥5, with an AHI of 5-15 considered to be mild OSA, 16 to 30 moderate OSA, and >30 severe OSA[7]. The respiratory disturbance index (RDI), another measure employed in the evaluation of OSA, is defined as the sum of apneas, hypopneas and abnormal respiratory events per hour of sleep. However, the terms AHI and Rd.I are oftentimes used interchangeably and the cut-off level for diagnosis of OSA also may vary between studies. Different indices appear to predict different effects on end organs, e.g., 4% desaturations predict hypertension, while the frequency of arousals predicts impaired memory[8]. Therefore the results of individual studies need to be interpreted with caution depending on the variables reported.

Overnight sleep studies in a laboratory are time consuming and expensive. There is increasing use of home-based diagnosis and treatment options. Randomized controlled trials have shown that home-based studies are no worse than studies performed in sleep centers for uncomplicated patients[8].

Nasal continuous positive airway pressure (CPAP) therapy is the treatment of choice, using airway pressure to splint the throat open, thereby reducing apneas and hypopneas. CPAP not only stabilizes the trans-mural pressure in the pharynx but also increases end-expiratory lung volume which further stabilizes the upper airway through traction. Nasal CPAP has been shown to be cost-effective when taking into account the cardiovascular and neurological sequelae of untreated OSA[9]. Compliance and adherence rates are approximately 60-70%; these rates can be improved with education and support. There is no evidence that full-face masks are better than nasal masks, so patient comfort and preference should be considered[8]. Alternatives to CPAP include positional therapy and oral splinting devices to advance the mandible or prevent obstruction of the airway by the tongue. Patients often express a preference for a trial of an oral device, particularly if their disease is mild. However, few data have been collected about the long-term efficacy of these devices. Finally, there is the option of upper airway surgery[8].

1.3 GENERAL CLINICAL SIGNIFICANCE

The fatigue and somnolence caused by OSA increases the risk of motor vehicle accidents by up to seven times compared to those without disease[10]. Depression and poorer quality of life have also been reported in OSA[11]. In particular, depression was associated with excessive daytime sleepiness and, though there was a positive linear trend for depressive symptoms to decrease with the effect of CPAP on sleepiness scales, this trend was not statistically significant[12].

A prospective observational cohort study showed that severe untreated OSA was associated with an increased incidence of fatal and non-fatal cardiovascular events compared to treated OSA patients and controls[13]. Nasal CPAP has been shown to have a positive effect on long-term survival in ischemic stroke patients, with 100% cardiovascular survival over 5 years in those treated for OSA compared to 89.9% survival in those not treated[14]. However, patients that adhere to CPAP treatment are more likely to adhere to other medical therapies so this effect may not have been due to the CPAP itself.

Other studies have reported inconsistent findings regarding the association between OSA and future risks of cardiovascular and all-cause mortality. A meta-analysis of six studies including 11,932 patients observed 239 cardiovascular deaths and 1,397 deaths from all causes. Pooled hazard ratios (HRs) of cardiovascular mortality were 1.40 (95% CI 0.77 to 2.53) for moderate OSA and 2.65 (95% CI 1.82 to 3.85) for severe OSA. Pooled HRs of all-cause mortality were 1.19 (95% CI 1.00 to 1.41) for moderate OSA and 1.90 (95% CI 1.29 to 2.81) for severe OSA. There was no significant difference in cardiovascular mortality in those treated with CPAP compared to healthy subjects (HR 0.82; 95% CI 0.50 to 1.33). It was concluded that severe OSA was a strong independent predictor for future cardiovascular and all-cause mortality. CPAP treatment was associated with decrease cardiovascular mortality compared to those with OSA who were untreated[15].

Regarding other health issues, a large Taiwanese study found that the risk of DVT and PE were, respectively, 3.5 and 3.97 times higher in an OSA cohort compared with age- and sex-matched controls[16]. The presence of OSA in patients with cancer appears to be associated with poorer outcomes, possibly due to altered immunosurveillance[17].

2. PHYSIOLOGY

2.1 BASIC SYSTEMIC PHYSIOLOGICAL CHANGES IN OSA

Variability in craniofacial structure and increasing body fat decrease the lumen of the pharyngeal airway. This predisposes to primary pharyngeal collapse during sleep when there is reduced activity of the upper airway dilator muscles[8]. Fluid retention and overnight shift of fluid from the legs to the neck, changes in lung volumes and alterations in central response to carbon dioxide levels are also linked to the likelihood of a patient developing OSA.

Intermittent upper airway obstruction in OSA results in hypoxia (reduced arterial partial pressure of oxygen, PaO_2) and hypercapnia (increased $PaCO_2$). This hypoxia results in sympathetic activation, oxidative stress, metabolic dysfunction, and systemic inflammation[18]. These are considered to be surrogate markers of cardiovascular risk as they are all intermediary mechanisms that can lead to increased rates of hypertension, ventricular dysfunction and early atherosclerosis.

OSA is increasingly recognized as an independent risk factor for hypertension, stroke and coronary heart disease[19]. Elevation in the odds of hypertension is observed, even in those with mild OSA[20]. Epidemiological studies suggest an association between OSA and increased atherosclerosis and large vessel endothelial disease[21] However, the mechanism of the link remains unclear. The Wisconsin Sleep Cohort Study showed that AHI was an independent predictor of hypertension, increased body mass index (BMI), insulin resistance and cardiac dysfunction[18].

OSA has also been found to be an independent risk factor for stroke in large epidemiological studies[22]. The relationship between OSA and small-vessel cerebrovascular disease is complicated by the fact that other risk factors, namely hypertension, diabetes mellitus and atherosclerosis, are also associated with OSA. Therefore, any relationship between OSA and small-vessel disease could be due to confounding factors[22].

The metabolic dysfunction found in OSA exacerbates obesity, with associated increased insulin resistance and non-alcoholic fatty liver disease[23]. Interestingly, obese patients without OSA do not show the same increase in markers of metabolic dysfunction. This suggests that OSA is an independent risk factor for these metabolic changes rather than OSA being an epiphenomenon of obesity.

2.2 PHYSIOLOGY OF OPTIC NERVE PATHOLOGY

The interactions between various physiological parameters during sleep, including ocular perfusion pressure, aqueous outflow in the supine position, and circulating hormone levels, complicate any assessment of the effects of vascular changes and intraocular pressure (IOP) fluctuations overnight. The association between OSA and glaucoma or non-arteritic anterior ischemic optic neuropathy (NAION) is postulated to be secondary to direct hypoxia or via vascular dysregulation at the optic nerve head[24].

a) Direct hypoxia

Repetitive apneic episodes might lead to direct anoxic damage to the optic nerve[25, 26]. As the AHI increases, more hypoxia results in reduced mean oxygen saturation. However Sergi *et al.* found no relation between ophthalmic measures of glaucoma and post-apneic falls of PaO_2, change in oxygen saturation, or the percentage of sleep time spent with oxygen saturation less than 90%[27].

b) Atherosclerosis and arterial blood pressure variation

OSA has been shown to be associated with hypertension[28], endothelial cell dysfunction[29], and autonomic dysfunction[30], all of which may alter ocular vascular regulation.

It has been demonstrated in both animal and human studies that OSA promotes cellular changes in the vascular wall, in particular the thickness of the carotid artery intima and media. The occurrence and progression of atherosclerotic plaques also appear to be related to the AHI in the absence of significant comorbidity[29]. Endothelial function is also affected by the oxidative stress of OSA, with resultant reduction in repair capacity and changes in vasomotor tone. However, these studies have focused on larger peripheral arteries[31]. The changes could also result in small vessel hyalinosis, thereby causing optic nerve head ischemia. Further histopathological studies focusing on the optic nerve are required.

Prolonged sympathetic overactivity is a characteristic feature of OSA, with bursts of sympathetic activity occurring before each nocturnal arousal and also during the day in response to sleepiness. However, the role of the sympathetic system in regulating cerebral and ocular circulation remains a matter for ongoing research efforts. Physiological research in humans indicates that brain perfusion is significantly distorted in OSA due to surges in blood pressure and blood velocity[32]. Repeated apneic episodes have been shown to have indirect effects on optic nerve head blood flow due to sympathetic surge-induced arterial hypertension[25, 26].

A recent multicenter study on patients with resistant hypertension and OSA showed that those treated with CPAP for 12 weeks experienced a decrease in 24-hour mean and diastolic blood pressure (3.1 mmHg and 3.2 mmHg, respectively) and an improvement in nocturnal blood pressure patterns compared to controls[33]. However, the long-term clinical health outcomes resulting from this response still need to be studied.

c) Impaired autoregulation at the nerve head

If cerebral perfusion pressure decreases due to increased intracranial pressure (ICP) during apneic episodes, then any cerebral hypoxia will be exacerbated. Furthermore, dynamic cerebral blood flow autoregulation is impaired in response to hypoperfusion in OSA patients[34]. These

fluctuations and impaired responses put the brain at risk of vascular damage and ischemia.

Doppler studies on the ophthalmic and central retinal arteries found no difference in the systolic and end-diastolic blood velocities between OSA patients and controls[35]. The posterior ciliary arteries and the choroidal vessels supply the pre-laminar and laminar portions of optic nerve head as the nerve travels through the sclera. Only the surface layer of the optic disc has capillaries derived from retinal arterioles, but even there it is not uncommon for this region to be supplied by choroidal vessels[36]. Given that most optic disc pathology is thought to arise from changes in the pre-laminar and laminar sections, the choroidal circulation is of interest. There is evidence from various human studies that retinal blood flow increases during hypercapnia[37-39]. A linear relationship exists between choroidal blood flow as measured using a laser Doppler flowmeter and $PaCO_2$. However, there is no effect of changes in PaO_2[40]. Compared to controls, one study found no difference in choroidal blood flow reactivity to different inhaled concentrations of O_2 or CO_2 in OSA patients, and no change after CPAP treatment[41]. However, this study did not look at the association with obesity or those who had a protracted course of OSA.

Data suggest that cerebral blood flow is abnormal in OSA, with surges of blood flow velocity[32]. Under normal conditions the changes in the pial arteries stabilize and counteract any changes in cerebral blood flow, but hypercapnia impairs the pial artery response to changes in cerebral blood flow[42]. The pial circulation supplies the orbital and intracranial segments of the optic nerve. Therefore, if the pial system at the optic nerve head can no longer compensate for changes in cerebral blood flow, impaired autoregulation at the nerve head may be the cause of ocular pathology in OSA.

d) Imbalance between vasodilator and vasoconstrictor substances

Intermittent hypoxia promotes production of reactive oxygen species, increased oxidative stress, activation of systemic inflammation, and decreased bioavailability of endothelial nitric oxide. Vascular dysregulation due to nitric oxide/endothelin imbalance or abnormal platelet aggregation also has indirect effects on optic nerve head blood flow[43].

Recent research has focused on the association between retinal microvascular dysfunction, cardiovascular disease, and OSA. Boland *et al.* found no association between OSA and the ratio of retinal arteriolar narrowing and venular widening[44]. However, retinal arteriolar changes were associated with hypertension while retinal venular changes were associated with inflammatory and metabolic abnormalities[45]. Shankar *et al.* analyzed retinal vessels independently, and found that AHI was associated with retinal venular widening independent of confounders, but was not associated with retinal arteriolar narrowing[21].

In a qualitative study of retinal photographs, changes resembling hypertensive retinopathy (arteriolar narrowing, arteriovenous nicking, and retinal hemorrhages) have been associated with AHI, independent of blood pressure[46]. These potential associations with microvascular changes in the retina are of interest when considering the link between OSA and optic nerve pathology because the same changes may also be occurring in the choroidal and posterior ciliary vessels.

2.3 CSF DYNAMICS IN OSA

An increase in cerebrospinal fluid (CSF) pressure has been observed in OSA, for which several mechanisms have been proposed[47].

a) Increased cerebral perfusion pressure

Increased systemic blood pressure seen in OSA may result in a secondary increase in cerebral perfusion pressure and, therefore, increased ICP. There is a strong correlation between the duration of apneic episodes and blood pressure fluctuations[47]. However, animal studies have shown that acute hypertension was tolerated with minimal perturbation of cerebral blood flow. However if there was pre-existing intracranial hypertension was there a loss of autoregulation in response to arterial hypertension[48]. Human work has shown in some cases that cerebral blood flow velocities are lower in patients with OSA than in normal controls[49], whereas other studies show a steady increase in cerebral blood flow during an episode of apnea[22].

b) Hypoxic and hypercapnia-related cerebral vasodilation

Vasodilation and increased brain water content from alteration in cerebral autoregulation may change intracranial volume. A reduction in brain volume of 4% without focal changes has been documented in OSA patients after treatment with overnight oxygen[50]. The increase in cerebral venous blood volume may be responsible, or partially responsible, for elevated ICP in OSA. During overnight CSF monitoring of three OSA patients, ICP was episodically elevated in parallel with apneic episodes and hypoxia[47]. In a subsequent study of patients with severe OSA, awake values of ICP were demonstrated to be elevated, with further increases in ICP related to apneic episodes while asleep[51]. Sustained elevation of ICP may lead to papilledema due to disruption of retrograde axonal transport at the optic disc.

Two patients with intracranial hypertension but no disc edema had overnight ICP monitoring, and dPSG. Both were obese (BMI >30 kg/m^2), had severe OSA with AHI >30 and had rapid sustained rises in ICP associated with hypoxemia. However, blood pressure did not change during these episodes, suggesting that cerebral vasodilation and increases in cerebral blood volume were the precipitating factors[52]. In another case series, a patient was shown to have CSF opening pressure on lumbar puncture of 16 cm H_2O during the day, but overnight ICP monitoring revealed pressures of 48 cm H_2O during episodes of oxygen desaturation[53]. The question remains as to whether these

intermittent changes in ICP alone would be sufficient to cause papilledema.

Apneic events are also associated with hypercapnia, which has been shown in some studies to lead to cerebral venous dilation. Hypercapnia has long been reported to decrease vascular resistance and increase cerebral blood flow[22]. However, recent data have altered our understanding of the dynamic cerebral blood flow changes that occur in OSA with changes in blood pressure[31]. Given the limited number of studies and the conflicting results, final conclusions cannot yet be drawn.

c) Mechanical factors

The mechanical airway obstruction in OSA leads to increased respiratory effort and increased intra-abdominal and intra-pleural pressures resulting in impaired cerebral venous drainage[54]. In turn, cerebral venous hypertension may theoretically reduce CSF re-absorption through the arachnoid villi, thereby increasing ICP.

3. NON-ARTERITIC ANTERIOR ISCHAEMIC OPTIC NEUROPATHY

NAION is an ischemic insult to the optic nerve head, with an annual incidence in persons ≥ 50 years of age between 2.3 and 10.2 per 100,000[55]. Typically found in patients over the age of 50, a small cup-to-disc ratio ("disc at risk") is presumed to be one of the major risk factors for NAION. NAION is also associated with acquired vascular risk factors such as systemic arterial hypertension, diabetes and atherosclerosis. Circulatory insufficiency within the optic nerve head is thought to precipitate NAION. However, the exact location of the vasculopathy remains unknown[56]. Histopathological studies have implicated the retrolaminar region as being the area of infarction, with fluorescein studies finding delayed filling in the pre-laminar optic disc[57]. Further research is needed to determine if, and how, OSA contributes to an isolated vascular insult or compartment syndrome within the optic nerve.

3.1 EVIDENCE FOR A LINK

In a review of 544 episodes of NAION, at least 73% were discovered upon first awakening leading to the hypothesis that nocturnal hypotension may be a precipitating factor[58]. However, the hypoxia of OSA promotes hypertension, producing a nocturnal non-dipping pattern otherwise known as "masked hypertension"[59]. Therefore, other vascular changes in OSA must be related to the NAION process if a link truly exists. As mentioned previously, vascular autoregulation may be hindered by sympathetic surges or imbalance of vasoactive substances such as endothelin-1 (vasoconstrictor) and nitric oxide (vasodilator)[60], thereby triggering NAION.

In two studies of NAION, 71%-89% of subjects had OSA diagnosed on dPSG (RDI >10 or AHI >15) compared to 18% of a control population[61, 62]. In addition, OSA was 1.5-2 times more frequent than other known risk factors such as hypertension and diabetes. However, in one of the two aforementioned studies, the 17 patients and controls were only matched by age and sex[59]. In the other study, the prevalence of OSA in NAION was compared to published population studies, showing a 4.9-fold increase in relative risk of OSA in NAION patients[61].

More recently, Arda *et al.* performed dPSG on 20 NAION patients and 20 controls matched for age, sex, body mass index (BMI), diabetes and hypertension. Of those diagnosed with NAION, 85% had OSA compared with 65% in controls. After controlling for hypertension and diabetes, the reported rates are much higher than expected in the general population; however, it is worth noting that these high rates may have been found because the authors used a low threshold of AHI (>5) to diagnose OSA[63].

In a prospective study, 27 NAION patients underwent dPSG within one month of symptom onset. Controls who were statistically similar for systemic risk factors and BMI[55] also underwent dPSG. A diagnosis of OSA was made, based on AHI >20, in 55.6% of NAION patients and 22.2% of controls. Using these stricter criteria for OSA than other studies, and appropriate matching for hypertension, diabetes, hypercholesterolemia and coronary artery disease, this study concluded that OSA should be considered a significant risk factor for NAION.

Studies using dPSG are time-consuming and generally have small sample sizes. By using the validated Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ), Li *et al.* were able to assess 73 NAION cases and 88 controls[64]. Their subjects included more women and patients with a higher BMI than previous studies. They still found an increased prevalence of presumed OSA, 30% versus 17.8% in those with NAION, and an odds ratio of 2.62 (95% CI 1.03-6.60) after controlling for confounders. However, a temporal relationship could not be established.

The prevalence of NAION in a population with diagnosed OSA has also been examined. In a large retrospective cohort study based on billing records, it was found that individuals diagnosed with OSA and not treated with CPAP had a 16% increased hazard of developing NAION[65]. This increased risk was not found in those with treated OSA. However, reports of patients developing NAION while undergoing CPAP therapy have also been published[66]. There are no studies that look at whether CPAP can prevent NAION in patients with other risk factors.

Given that there is no effective treatment for NAION, management of all potential risk factors including hypertension, diabetes and OSA is advisable, even though a direct causal relationship cannot be presumed based on evidence to date.

4. GLAUCOMA

The association between glaucoma and OSA has been widely reported. However, the results vary and a clear link is still uncertain. The prevalence of sleep-disordered breathing is between 20-50% in patients with primary open angle glaucoma (POAG)[67, 68] and normal tension glaucoma (NTG)[69]. The inverse is also reported, with 7.2% of sleep apnea patients having glaucoma, compared to the expected population rate of 2%[70]. However, other studies have found no difference between the prevalence of glaucoma in an OSA population and a control population. Geyer *et al*. found no relation between the Rd.I and intra-ocular pressure (IOP) or the presence of glaucoma[71].

While it is difficult to compare the various studies examining the association between glaucoma and OSA due to small numbers, lack of standardization in the criteria of OSA, and differing means of glaucoma assessment, the following provides a summary of the recent research.

4.1 EVIDENCE FOR A LINK

4.1.1 Normal tension glaucoma and retinal nerve fiber thickness changes

a) Retinal nerve fiber layer thickness

The link between OSA and glaucoma has been investigated by examining the preclinical changes in retinal nerve fiber layer (RNFL) thickness. The appearance of RNFL thinning suggests atrophy, presumably due to decreased ocular perfusion, hypoxia and vasospasm.

A trend for loss of RNFL thickness correlating with the severity of OSA was reported in a small group of patients by Kargi *et al.,* using scanning laser polarimetry[72]. In a study of 105 patients and 22 controls examined with Stratus ocular coherence tomography (OCT), Lin *et al*. also found that RNFL was thinner in patients with moderate/severe OSA (AHI >15) compared to those with mild OSA (5 < AHI < 15) and controls. The lowest saturation in overnight oxygen correlated with the greatest degree of RNFL thinning[73]. Within the moderate/severe OSA group, the peripapillary RNFL thickness in the superior and nasal quadrants of the optic disc was significantly decreased with increasing AHI. However, IOPs were higher in those with severe OSA than controls. Other studies have reported a significant decrease in RNFL thickness at the disc and the macular ganglion cell layer only in those with severe OSA, not mild or moderate disease[74].

While most studies have shown reduced thickness of RNFL, Nowak *et al.*, did not find any difference[75]. Some authors have raised concern that the earlier studies showing RNFL thinning in OSA included patients with elevated IOPs, which may have confounded the results because increased IOP is an independent risk factor for loss of RNFL. A recently-published report by Sagiv *et al.*, looked at the RNFL thickness of patients with recently-diagnosed OSA (RDI >20) but normal-appearing optic discs and normal IOPs[76]. The RNFL was thinner in OSA patients than in normal controls by 4-5 microns, though this did not correlate with disease severity. The changes, though diffuse, were most apparent in the superior and inferior quadrants.

A Spanish study[77] which included OSA and control patients with IOP <21 mm Hg and no glaucomatous visual field defects still found statistically-significant differences in IOP values (16.8 ± 2.9 mm Hg in OSA versus 15.2 ± 1.6 mm Hg in controls). OCT measures showed only nasal peripapillary RNFL thinning (74.7 ± 15.8µm versus 81.1 ± +/-16.6 µm), but no difference in thickness in the other quadrants. In addition, there was no difference in horizontal cup-disc ratios in OSA patients (0.48 ± 0.21 versus 0.48 ± 0.17) or vertical cup-disc ratios (0.43 ± 0.2 versus 0.42 ± 0.16).

The question remains as to whether such RNFL changes, if indeed they are related to OSA independently of IOP, are clinically significant and could eventually lead to normal tension glaucoma.

b) Normal tension glaucoma

Normal tension glaucoma (NTG) is a form of primary open angle glaucoma characterized by glaucomatous optic disc cupping in patients with IOP measurements consistently lower than 21 mm Hg. The visual field defects in NTG tend to be more central than in POAG, making it more difficult to distinguish from other optic neuropathies.

Progression of glaucomatous optic neuropathy may be due to either ongoing direct anoxic insult or to indirect changes to optic nerve head blood flow. Indeed, known risk factors for NTG include abnormal ocular blood flow and systemic hypotension, as well as disorders of coagulation, vascular disorders, migraine and autoimmune disorders[78].

Sergi *et al.* found evidence of NTG (loss of RNFL thickness and visual field changes) in 5.9% of OSA patients, compared to no patients at all in a control group[27].

A study from Hong Kong showed that ethnic Chinese patients with moderate to severe OSA had four times the rate of glaucomatous optic disc changes than matched controls (26% versus 6.8%) and that those with severe OSA (AHI ³40) had higher rates of disc changes than those with moderate OSA (AHI ³20)[79]. Visual field indices were also worse in OSA patients compared to controls. However, high-tension glaucoma was not significantly different between OSA and controls (3.66% versus 2.94%, respectively).

A recent prospective study compared OSA in NTG patients to age- and sex-matched controls who were also similar for body mass index (BMI), neck circumference, smoking and systemic risk factors[80]. The diagnosis of OSA (AHI >20) was made in a surprisingly high proportion (42%, or 10/24) of the NTG patients, compared to 12.5% (3/24) of the controls, prompting the authors to conclude that patients with NTG should be questioned about their sleep history.

4.1.2 Primary open angle glaucoma

Studies have shown that Rd.I is positively correlated IOP, visual field loss variance, glaucomatous optic disc changes,

and a diagnosis of glaucoma[69]. Higher IOPs have been documented in those with severe OSA (AHI >15) compared to controls (14.2 ± 3.5 versus 12.2 ± 3.6 mm Hg)[72]. Other studies have shown a positive correlation between IOP and increasing AHI scores[27, 35]. However, the inclusion criteria required an IOP <21 mm Hg[27] in one study, while another study[35] included 3/41 patients with IOPs > 21 mm Hg.

Other studies found no difference in IOP nor pulsatile ocular blood flow in patients with and without OSA[75]. Furthermore, no increase in IOP was seen at the end of prolonged apnea in OSA and NTG patients[81].

Bendel *et al*. examined 100 patients with moderate/severe OSA (AHI >15), and diagnosed glaucoma in 27%, a higher prevalence than expected[82]. However, there was no evidence for a relationship between AHI and IOP or the diagnosis of glaucoma (based on disc and field changes) - only increasing age correlated with a diagnosis of glaucoma.

Examining a subset of the Beijing Eye Study, data on snoring (as reported by the subject's life partner) and glaucoma were available for 3,146 patients[65]. "Severe snoring" was not associated with open-angle glaucoma, angle-closure glaucoma, cup to disc ratio or RNFL thinning. Another interview-based study found a higher prevalence of sleep-disordered breathing-related symptoms in 212 POAG patients than in controls[67].

A cross-sectional study that reviewed diagnoses given to patients in a managed care program found that there was no difference in the hazard of being diagnosed with POAG or NTG in those with OSA (regardless of CPAP treatment) and those without OSA[83]. Using diagnostic codes to identify co-morbidities, Girkin *et al.* found that individuals who developed glaucoma were more likely to have a previous diagnosis of sleep apnea than controls. However, after adjusting for other vascular and glaucoma risk factors (hypertension, migraine, diabetes) no significant difference was seen[84].

In a large, retrospective population-based study, Lin *et al.* compared the 5-year hazard ratio for developing open-angle glaucoma between 1,012 subjects with a diagnosis of OSA (based on dPSG) and 6,072 controls[60]. An ophthalmologist had reviewed all subjects, without making a diagnosis of glaucoma, in the 4 years prior to the "index" year. Records for OSA patients and controls were then examined from the index year for the next 5 years. After adjusting for multiple confounding factors, the hazard ratio for developing glaucoma after OSA was 1.67 times that of controls. This study concluded that OSA was independently associated with an increased risk of POAG. However, one drawback of the study was that it did not evaluate the relationship between glaucoma prevalence and OSA, but rather looked at the incidence during the period after OSA diagnosis.

A large, multi-center French study prospectively examined 9,580 OSA-suspects from a broad range of clinical settings[85]. A total of 6,754 patients had OSA (defined as AHI >15) and 330 had glaucoma (listed in their medical records as diagnosed by an ophthalmologist). The prevalence of glaucoma was 3.55% in all patients with OSA and 3.14% in patients (not statistically significant, p = 0.22). Patients with more severe OSA (AHI > 30) also had no significant difference in the prevalence of glaucoma, indicating that there was no dose-response relationship. To confirm the results further, a second analysis looked only at the patients treated with IOP-lowering eye drops versus non-glaucoma patients, and still found no significant difference in OSA. While the presence of OSA was not found to influence the risk of glaucoma, increasing age and arterial hypertension were associated. This study is of particular importance because it contains complete sleep study data for a large number of patients (rather than relying on diagnostic codes) and a control group.

In summary, the published data supporting a link between OSA and glaucoma are inconclusive (11 studies suggest an association while 6 do not[85]). A pathophysiological association is plausible and, though there does seem to be consistent evidence for loss of RNFL, the clinical significance needs to be reviewed. The direct link to NTG in OSA appears stronger than the case for high IOP-related POAG.

5. PAPILLEDEMA AND IDIOPATHIC INTRACRANIAL HYPERTENSION

5.1 EVIDENCE FOR A LINK

The first report suggesting a link between OSA and disc edema found resolution of disc edema after upper airway surgery in the setting of normal ICP[86]. A case series from Purvin *et al.*, described four patients with bilateral optic disc edema and OSA[53]. Treatment with CPAP has been reported to precede resolution of the disc swelling; though consistent with an association, this does not prove causality[53, 87].

In a study using diagnostic codes from a large managed care organization, Stein *et al*. found that, after adjusting for confounding factors, untreated patients with OSA had a 29% higher risk, and patients with CPAP-treated OSA had over twice the risk (105% higher), of having papilledema when compared to patients without OSA[83]. However, in seeming contradiction to this, the same paper reported similar rates of idiopathic intracranial hypertension (IIH) in those without OSA and CPAP-treated OSA, but that patients with untreated OSA had over twice the rate of IIH (103% higher) compared to those without OSA.

Marcus *et al*. found that, of 53 patients with IIH, 70% had evidence of sleep disturbance. Fourteen of these patients went on to dPSG, with 13/14 being diagnosed with OSA[88]. In a larger review of 721 IIH patients, Bruce *et al*. found 4%

of women had OSA compared to 24% of men[89]. Lee *et al*. found 6/18 men with IIH also had a diagnosis of OSA based on dPSG[87].

There has only been one small study looking at the prevalence of papilledema and symptoms of increased ICP in OSA patients. Of 95 recently-diagnosed OSA patients contacted, only 35 had had an eye examination, none of whom were found to have papilledema[54]. However, 34% gave a history of transient visual obscurations.

A study of non-mydriatic fundus photographs taken on 250 patients undergoing dPSG found no patient with optic disc edema (95% CI: 0%-3%)[46].

In a further study, patients with newly-diagnosed IIH underwent dPSG. The AHI values were then compared to the population-based expected AHI for each patient on the basis of age, sex, race, BMI and menopausal status. The prevalence and severity of OSA in IIH patients was not significantly different from predicted values[90].

A retrospective analysis of patients with IIH found that the prevalence of OSA was higher in these individuals than in an obesity-matched population[91]. While OSA is strongly associated with obesity and obesity, in turn, is known to be associated with IIH[92], the actual prevalence of IIH in OSA patients is unknown.

In a study of 41 Chinese OSA patients that was directed at investigating glaucoma, two were found to have disc swelling compared to none in the control population[79]. Increased macular thickness and increased disc area on OCT were seen in patients with mild-moderate OSA (5< AHI <30), and this has been hypothesized to be secondary to cell body swelling in hypoxic conditions. The increase in disc area was reported to be the most distinguishing feature between OSA and controls groups[76]. However, whether this was ischemic or due to papilledema remains uncertain.

CSF opening pressures on lumbar puncture in patients with normal tension glaucoma have been shown to be 3-4 mm Hg lower than those of controls[93]. If this "CSF pressure gradient theory" of NTG is valid, and OSA is associated with NTG, then it is difficult to explain a concurrent association of OSA with papilledema. What is interesting is that, though many OCT scans have been performed on patients with OSA, only two papers have reported finding any increased RNFL thickness.

6. CLINICAL DIAGNOSIS OF OSA

6.1 CLINICAL HISTORY AND USE OF SCREENING QUESTIONNAIRES

In a clinical outpatient setting, the most useful indicator for identifying patients with OSA is a history of nocturnal choking or gasping[3]. Though snoring is present in 94% of those with OSA, it is not useful in establishing a higher risk for diagnosis as not all snorers have OSA[5]. Other indicators include patient reports of awakening with a choking sensation, witnessed apnea (by the partner), non-restorative sleep, difficulty maintaining sleep, morning fatigue, and a headache on waking[8].

The potential number of patients with OSA is far larger than can currently be handled by available overnight sleep laboratories. Therefore, clinical questionnaires have been developed and tested as screening tools. The Berlin Questionnaire is the most commonly used, and has been validated in eight studies with overnight dPSG results[94]. Other tests include the Wisconsin Sleep Questionnaire, the Epworth Sleepiness Scale (ESS) and the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ). For surgical patients, the STOP-Bang (snoring, tiredness, observed apnea, high blood pressure, BMI, age, neck circumference and gender) checklist has also been used.

A review of all tools used for screening for OSA analyzed the results from well-selected published papers[94]. For the detection of moderate OSA (AHI >15), the Berlin Questionnaire showed the highest specificity in patients without a prior history of sleep disorders (an average of 70%, with results ranging from 38-95%). The sensitivity of detecting OSA (AHI >15) was highest with the STOP-Bang checklist (54-95% across studies). This same pattern was seen in using these tests to detect severe OSA (AHI >30). However, for mild OSA (AHI >5) the Wisconsin Sleep Questionnaire had the highest sensitivity and the Berlin Questionnaire the highest specificity. The STOP-Bang questionnaire was found to have the highest methodological validity, reasonable accuracy and easy-to-use features, but was developed as a pre-anesthetic/surgical screening tool. The Berlin Questionnaire has been found to be a useful screening tool in a general hospital/clinic setting and can be administered by nursing staff[95].

The Berlin Questionnaire is a validated scale that can be easily administered in clinic to reliably identify those likely to have OSA[96]. A low score identifies patients unlikely to have OSA, and this has been shown to be useful as a screening tool to exclude ophthalmic patients who do not need further investigation with sleep studies[97]. The accuracy of participants in completing the Berlin Questionnaire improved when bed partners and family members were available to assist in choosing the responses[95].

BERLIN QUESTIONNAIRE

Height (m) _____ Weight (kg)_____ Age_____ Male / Female

Please choose the correct response to each question.

CATEGORY 1

1. **Do you snore?**
   - ☐ a. Yes
   - ☐ b. No
   - ☐ c. Don't know

If you snore:

2. **Your snoring is:**
   - ☐ a. Slightly louder than breathing
   - ☐ b. As loud as talking
   - ☐ c. Louder than talking
   - ☐ d. Very loud – can be heard in adjacent rooms

3. **How often do you snore**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

4. **Has your snoring ever bothered other people?**
   - ☐ a. Yes
   - ☐ b. No
   - ☐ c. Don't Know

5. **Has anyone noticed that you quit breathing during your sleep?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

CATEGORY 2

6. **How often do you feel tired or fatigued after your sleep?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

7. **During your waking time, do you feel tired, fatigued or not up to par?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

8. **Have you ever nodded off or fallen asleep while driving a vehicle?**
   - ☐ a. Yes
   - ☐ b. No

If yes:

9. **How often does this occur?**
   - ☐ a. Nearly every day
   - ☐ b. 3-4 times a week
   - ☐ c. 1-2 times a week
   - ☐ d. 1-2 times a month
   - ☐ e. Never or nearly never

CATEGORY 3

10. **Do you have high blood pressure?**
    - ☐ Yes
    - ☐ No
    - ☐ Don't know

Details of the Berlin Questionnaire and STOP-Bang checklist are shown below: [94]

Berlin Questionnaire

Category 1: items 1, 2, 3, 4, 5.

Item 1: if 'Yes', assign 1 point

Item 2: if 'c' or 'd' is the response, assign 1 point

Item 3: if 'a' or 'b' is the response, assign 1 point

Item 4: if 'a' is the response, assign 1 point

Item 5: if 'a' or 'b' is the response, assign 2 points

Add points. Category 1 is positive if the total score is 2 or more points

Category 2: items 6, 7, 8 (item 9 should be noted separately).

Item 6: if 'a' or 'b' is the response, assign 1 point

Item 7: if 'a' or 'b' is the response, assign 1 point

Item 8: if 'a' is the response, assign 1 point

Add points. Category 2 is positive if the total score is 2 or more points

Category 3 is positive if the answer to item 10 is 'Yes' OR if the BMI of the

patient is greater than 30kg/m^2.

(BMI must be calculated. BMI is defined as weight (kg) divided by height (m)

squared, i.e., kg/m^2).

High Risk: if there are 2 or more Categories where the score is positive

Low Risk: if there is only 1 or no Categories where the score is positive

Additional question: Item 9 shold be noted separately. Answer all items as YES or NO

1. Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?
2. Do you often feel tired, fatigues, or sleepy during the daytime?
3. Has anyone observed you stop breathing during your sleep?
4. Do you have or you being treated for high blood pressure?
5. BMI >35kg/m2
6. Age > 50 years old
7. Neck cirumference >40cm
8. Gender - male

High risk of OSA: answering yes to three or more items
Low risk of OSA: answering yes to less than three items

6.2 DECIDING ON REFERRAL – WHEN TO BE SUSPICIOUS OF OSA

All patients with newly-diagnosed NAION, progressive normal tension glaucoma despite treatment, and patients with idiopathic intracranial hypertension (particularly men) not responding to typical therapy should be questioned about symptoms of OSA. Concurrent ophthalmic conditions associated with OSA should also increase suspicion – for example, floppy eyelid syndrome[98].

Any patient at risk of OSA based on clinical history and standardized questionnaires should be referred to a sleep specialist. However, those deemed to be at low risk based on history/questionnaires do not need routine referral.

While there appears to be to be a link between OSA and microvascular changes that could contribute to optic neuropathies, the question as to whether this is direct or confounding remains to be answered. Regardless of the direct pathology, treating OSA patients with CPAP does improve indirect measures of health and morbidity[99, 100]. Therefore, questioning patients with glaucoma, NAION and papilledema about symptoms and signs of OSA and referring appropriate cases for dPSG and appropriate management, makes clinical sense. However, the inverse question, i.e. whether all patients with OSA require ophthalmic review, is still the subject of further research.

Other ophthalmic patients of concern:
Patients with exudative age-related macular degeneration and diabetic macular edema with poor response to anti-vascular endothelial growth factor (VEGF) therapy have been shown to have significantly higher rates of OSA compared to age-matched controls[101]. Hypoxia induces secretion of VEGF, so the intermittent hypoxia of OSA may counteract the effects of anti-VEGF treatment.

Patients with floppy eyelid syndrome also need referral to a sleep specialist. Some studies have shown links between floppy eyelids, keratoconus and OSA[102] based on the Epworth Sleepiness Scale. However, others using the Berlin Questionnaire have not replicated these links[103]. In the largest study of 362 keratoconus patients, 18% had a prior diagnosis of OSA based on dPSG and 47% were at high risk of OSA based on the Berlin Questionnaire[104].

In a small study of patients with central serous retinopathy, OSA was diagnosed in 14/23 patients based on dPSG[105].

Other neurological patients of concern:
Impairment of attention, memory and executive function is seen in patients with OSA. However, results of CPAP treatment on improving these symptoms are mixed[106].

7. SOMEONE ALREADY DIAGNOSED WITH OSA

7.1 COMPLICATIONS OF TREATMENT

CPAP masks cover the nose and mouth, and must be fitted to each patient individually to prevent the leakage of air. In a large study of OSA it was found that patients using CPAP had high rates of ocular irritation, abnormal tear break-up time, and higher rates of conjunctivitis secondary to air leaks[107].

All OSA patients treated with CPAP, particularly overnight contact lens wearers, are at risk for bacterial keratitis. One theory is that air is forced up from the mask into the eye, with spread of bacteria causing infective keratitis of the dry cornea[108]. CPAP-associated retrograde air-escape via the nasolacrimal system has also been demonstrated to occur during treatment, with complications including dry eye, epiphora, air escape from the medial canthus and eyelid flutter. An increased risk of conjunctivitis and infective keratitis may be seen due to this phenomenon[109]. Four patients have been reported who experienced air regurgitation via Lester-Jones tube or a dacryocystorhinostomy ostium, with resultant dry eye complications[110]. Patients with orbital fractures have been reported to develop peri-orbital swelling and orbital emphysema with CPAP treatment[111].

Though OSA may be related to glaucomatous damage, one early study showed that before CPAP intraocular pressures in 18 glaucoma patients were, on average, 20.3 ± 6.3 mm Hg but that, after treatment with nasal CPAP, they increased to 22.3 ± 5.7mm Hg[112]. A more recent study demonstrated that IOP was higher than baseline after one month of CPAP treatment, with a greater diurnal fluctuation pattern and a reduction in ocular perfusion pressure during therapy. Thirty minutes after cessation of CPAP, a significant decrease in IOP was noted[113].

7.2 WHAT TO LOOK FOR IN A PATIENT WITH OSA

Modifiable risk factors should be addressed in all patients. Initially, it is recommended that patients avoid alcohol and

muscle-relaxant drugs due to their potential to reduce respiratory drive. Studies have shown that a 10 kg reduction in body weight can result in an improvement of symptoms and a reduction of 5 apnea-hypopnea events per hour[114].

When patients with known OSA are seen in the clinic, they should be assessed for complications of floppy eyelid syndrome and dry eye. Careful funduscopy for evidence of diabetic or hypertensive retinopathy changes should be performed, as retinal arteriolar changes have been shown to be independently associated with OSA severity[46]. Optic nerve function and structural tests should also be performed in a standard fashion, with further OCT and visual field tests as indicated by the appearance of the optic disc.

Results of large population-based studies do not support the recommendation for conducting systematic glaucoma screening in patients with OSA[85]. In one large study evaluating billing records, the increased risk of NAION and IIH reported in patients with untreated OSA led the authors to conclude that OSA patients should undergo ophthalmologic screening[83]. However, in a prospective fundus photography study, no difference in the prevalence of glaucoma, NAION or optic disc edema was found between those with and without OSA. Therefore, this study did not support routine ophthalmoscopic screening of OSA patients for optic neuropathies[46].

8. FUTURE DIRECTIONS FOR RESEARCH

8.1 THE UNANSWERED QUESTIONS

Much of the data relating to OSA and its association with any of the optic neuropathies is difficult to interpret due to small numbers of patients, inadequately matched controls, and the variability of what constitutes a diagnosis of OSA. Larger studies are limited in their conclusions by the cross-sectional or retrospective nature of their data. In particular, difficulty arises with the numerous potentially confounding factors that occur in patients with OSA, including obesity, hypertension and diabetes. It is difficult to separate out the direct effects of OSA from these epiphenomena as each may individually contribute to optic nerve pathology.

A more uniform set of diagnostic criteria for published studies should be established to allow direct comparison between study results. Larger prospective population studies, with appropriate control groups and formal dPSG at a time point close to ophthalmic assessment, are also required.

Further work into the blood supply of the optic nerve head and the pathophysiological aberrations and adaptations associated with OSA is necessary. The complex interaction between hypoxia, blood pressure, sympathetic activity, and the cardiovascular and neurological changes associated with OSA will also require further investigation. Translational research is necessary, as animal models of OSA are being developed. Also, investigation into the genomics of OSA and biomarkers of disease may prove beneficial.

From the patient perspective, future research also needs to address comfort and adherence to CPAP therapy, and to explore newer therapies such has hypoglossal nerve stimulation. Further work is also required for therapies to address co-morbid risk factors as well as weight loss strategies and lifestyle modification. The effect of these various therapies on quality of life is also important.

CME ANSWERS

1. c
2. d
3. d

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AUTOIMMUNE OPTIC NEUROPATHIES (SORTING IT ALL OUT)

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LEARNING OBJECTIVES

1. Understand the diagnostic criteria for chronic relapsing inflammatory optic neuropathy (CRION)
2. Distinguish CRION from other related optic neuropathies
3. Learn how to manage CRION

CME QUESTIONS

1. Which of the following would be unusual for CRION?
   a. Bilaterality
   b. Severe visual loss of 20/200 or worse
   c. Pain
   d. Spontaneous recovery
2. Which of the following are not used for treating CRION?
   a. Corticosteroids
   b. Rituximab
   c. Vitamin B_{12}
   d. Mycophenolate
3. True/False: A patient with presumed CRION has a positive antibody test against aquaporin 4. The patient therefore has NMO and not CRION.

KEYWORDS

1. Chronic Relapsing Inflammatory Optic Neuropathy
2. Neuromyelitis Optica
3. Immunosuppressives
4. Optic Neuritis

INTRODUCTION

Chronic relapsing inflammatory optic neuropathy (CRION) is an uncommon cause of visual loss that is at the same time a common cause of frustration to the neuro-ophthalmologist. As suggested by its appellation, CRION is an optic neuropathy with inflammatory features (pain, response to corticosteroids) that relapses when corticosteroids are withdrawn. This occurs chronically over months to years. When a specific etiology is found, such as similarly-behaving sarcoidosis, by definition CRION is not present.

CRION can affect both eyes simultaneously or sequentially, or in some cases remain unilateral. The degree of visual loss is frequently severe, partly because the recognition of the steroid dependence is not always promptly achieved. In patients who are initially diagnosed with typical optic neuritis and not given corticosteroids, the first clue to the atypical nature of the disease is that spontaneous visual recovery was minimal or absent.

EPIDEMIOLOGY

Much of our understanding of the clinical course of CRION is from case reports and case reviews. Two large reviews were published in 2014, one summarizing 122 cases from the literature[1] and one out of France with 20 cases of CRION within a larger population of 62 cases of relapsing optic neuritis.[2] The Table below summarizes these two studies.

Attribute	Petzold and Plant	Benoilid et al	Comments
Gender	71% female	75% female	Missing data on gender in many patients in Petzold and Plant
Age (mean)	36	29±13 years	
Ethnicity	45% non-white	3% non-white	Missing data on ethnicity in many patients in Petzold and Plant
Final visual acuity	Median 20/60	Mean 20/40	33% worse than 20/200 in Petzold and Plant

NOSOLOGY

There are several disorders that overlap in some ways with the clinical manifestations of CRION. The most common is typical optic neuritis, either associated with multiple sclerosis or as a clinically isolated syndrome. The hallmark of the differentiation of typical optic neuritis from CRION is that there is usually spontaneous recovery in the former, albeit hastened by the administration of corticosteroids. When typical optic neuritis recurs, it is usually in the setting of other inflammatory events in the central nervous system, most commonly in a pattern consistent with multiple sclerosis.

Autoimmune optic neuropathy is closely related to CRION, with a strong response to corticosteroids, relapses when corticosteroids are withdrawn, and no manifestations of multiple sclerosis. A distinctive factor of autoimmune optic neuropathy is the presence of markers of other autoimmune diseases, such as autoantibodies, evidence of autoimmunity on skin biopsy, but without symptoms or signs (such as arthritis or rash) that would lead to the diagnosis of a classical autoimmune disease such as systemic lupus erythematosus. It is unclear whether the presence of autoimmune markers means that autoimmune optic neuropathy is truly different from CRION, or that the signs of an autoimmune process have simply not yet become evident in CRION. Extended follow-up of CRION patients has not yet demonstrated a clear propensity for other autoimmune diseases.

Neuromyelitis optica (NMO) is diagnosed (2006 criteria;[3] soon to be updated) on clinical and radiological criteria, namely optic neuritis and transverse myelitis, and two or more of the following: anti-aquaporin 4 antibodies, brain MRI that is not consistent with multiple sclerosis, and a spinal cord lesion three or more vertebral segments in length. A typical case of CRION may have optic neuritis and MRI non-diagnostic for multiple sclerosis, but does not have the spinal cord disease nor the presence of the anti-aquaporin 4 antibodies. However, there are occasional cases of CRION which can became positive for those antibodies, suggesting that there is overlap in the diagnosis of CRION and NMO.[4] However, this does not mean that the two diseases are etiologically or pathophysiologically linked, and it is difficult to distinguish NMO taking time to declare itself from CRION that happens to be aquaporin 4 antibody-positive.

*Neuromyelitis optica spectrum disorder*s are a family of disorders of which NMO is a subset, but for which not all diagnostic criteria are fulfilled or for which there are additional features unrelated to NMO. As with NMO, neuromyelitis spectrum disorders share some features with CRION, specifically the optic neuritis and the non-self-limited time-course, indicating that there is a spectrum of findings which are shared among these entities. Without an adequately sensitive and specific biomarker, it is difficult to definitively state that these syndromes are truly different from each other or whether they are different manifestations of the same underlying pathophysiology.

There are many other inflammatory disorders of the central nervous system that are steroid responsive and can recrudesce when off steroids. The most common is sarcoidosis, but other inflammatory syndromes involving the optic nerve (e.g. those associated with Wegener granulomatosis, systemic lupus erythematosus, or vasculitis) can respond to steroids or other immunosuppressive agents, and therefore mimic some of the aspects of CRION. Interestingly, some of these are radiologically different from CRION and typical optic neuritis in that the dura is preferentially inflamed, hence the moniker optic perineuritis. How this translates into an underlying pathophysiological distinction is unclear.

This picture of overlap with other disorders suggest that we do not yet have a clear understanding of what exactly makes CRION a distinct entity. For the sake of convenience, it is reasonable to use the following case definition:[1]

Factor	Requirement
History	Optic neuritis with at least one relapse
Clinical	Objective evidence for loss of visual function
Laboratory	Seronegative for anti-aquaporin 4 antibodies
Imaging	Contrast enhancement of the acutely inflamed optic nerve(s); optic nerve atrophy at later stages
Treatment	Response to immunosuppressive treatment and relapse on taper or discontinuation

(Adapted from Petzold and Plant[1])

ONTOLOGY

The hallmark of CRION is the dependence on steroids to prevent relapses. This raises the question of whether endogenously produced cortisol normally maintains protection against the onset of an autoimmune event in most people, but that patients with an autoimmune disease such as CRION may have insufficient baseline levels of cortisol (and perhaps other endogenous anti-inflammatory molecules) to maintain a stable immune system. The fact that patients with CRION can have a specific daily dose of prednisone below which a relapse will occur (see Posology section) is consistent with this model.

This hypothesis could be tested by determining whether patients with Addison disease are at higher risk for developing optic neuritis or other central nervous system inflammatory diseases. Unfortunately, a study like this would be contaminated because Addison disease is associated with autoimmune processes itself. Another way to test this hypothesis would be to see if patients with surgically-induced hypocortisolemia are at increased risk for autoimmunity. However, such patients are almost always already treated with corticosteroid supplementation.

PATHOLOGY

In some cases where patients have completely lost vision in one eye and the disc is completely pale, indicating a low likelihood of recovery, and the other eye has progressive visual loss despite immunosuppressive agents, then the no-light-perception optic nerve can be biopsied. In a case managed by the author of this syllabus, a scant inflammatory infiltrate was found. Whether this reflects the same disease process as when there is better response to steroids and immunosuppressives is unclear.

ETIOLOGY

It is unknown what predisposes patients to have CRION. As mentioned in the section on epidemiology, there is a certain age range which is characteristic, but so far no true predisposing factor has been identified that increases relative risk to any great degree.

PATHOPHYSIOLOGY

The pathophysiology of CRION is known only with respect to some aspects of inflammation and axonal damage. The presence of gadolinium enhancement on MRI demonstrates breakdown of the blood nerve barrier, presumably through disruption of endothelial cell tight junctions from inflammation. The pathological features of mild inflammation seen in optic nerve or dural biopsies do not point to any particular pathophysiology.

From the neurobiological point of view, the relentless thinning of the retinal nerve fiber layer, which consists of the axons of retinal ganglion cells, and the decrease in the ganglion cell complex in the macula, which contains retinal ganglion cell bodies amongst other inner retinal neurons, suggest that the retinal ganglion cells are the final common pathway for loss of vision in CRION. This is confirmed by the decreased diameter of the optic nerve within the dural sheath on MRI. Together, these findings imply an axonal loss that progresses retrograde and/or anterograde away from the site of pathology. This is theoretically similar to what happens with other optic neuropathies, and is therefore not specific to CRION, nor does it imply a specific type of axonal damage in CRION. On the other hand, studies of diffusion tensor imaging suggest abnormalities in the white matter (including optic chiasm) of patients with CRION that are not seen on standard MRI signal sequences.[5]

POSOLOGY

By definition, patients with CRION are treated with corticosteroids, usually from first symptom or sign and with high intravenous doses such as methylprednisolone 1 gm per day for the first few days followed by oral prednisone at 1 mg/kg/day. It is only with the decrease or cessation of corticosteroids that the relapse of what might otherwise appear to be typical optic neuritis will intimate the diagnosis. The methodology for management of the corticosteroid dose as it is tapered may in some cases decrease the likelihood of relapse or prolong its occurrence. Unlike the treatment of typical optic neuritis, where a rapid taper based on the Optic Neuritis Treatment Trial or similar precedents are used, with CRION a slow taper over weeks to months may yield better outcomes. This is especially true as the dose of prednisone (or similar medication)

comes close to twice the equivalent physiological cortisol levels (e.g. 10 mg daily of prednisone). At this point, a taper based on decreasing the daily dose by one mg every 1-4 weeks may delay or even prevent the relapse. Under the circumstances of a slow taper, it is not unusual for a relapse, if it occurs, to take place at a highly specific dose of drug, e.g. 8 mg daily. Going below the specific dose for an individual patient therefore appears to trigger a relapse at a dose threshold that is idiosyncratic to the patient.

Given the likelihood that a relapse will occur when the corticosteroid dose is lowered or stopped, coupled with the debilitating effects of long-term corticosteroids, patients with CRION are almost always eventually placed on other immunosuppressive drugs or regimens as corticosteroid-sparing agents. Almost all have been used at some point, and there is no general agreement on which work best. The impracticality of carrying out traditional randomized clinical trials in a rare and highly variable disease like CRION means that the recommendations for therapy are of moderate to low quality. In the end, n of 1 studies are considered acceptable mechanisms for finding the best treatments for patients with CRION.

In most practitioners' hands, an immunosuppressive drug with the least side effects is typically tried first, e.g. methotrexate or mycophenolate. If the immunosuppressive does not allow corticosteroids to be tapered off, therapies with more potential for adverse effects are next tried. These include azathioprine, intravenous immunoglobulin, plasmapheresis, rituximab, and cyclophosphamide. Anti-TNF-alpha agents such as infliximab have been used,[6] although this class of drugs has also been associated with multiple sclerosis-like syndromes, including optic neuritis. Standard multiple sclerosis drugs such as beta-interferons are not used frequently because there has been some suggestion that they may exacerbate the problem.

Many patients require a combination of treatments. For example, monthly plasmapheresis, rituximab, and a low dose of prednisone successfully controlled one patient with progressive visual loss and steroid complications.

The following Table, adapted from Palace et al[7] and using Greenberg et al,[8] was developed for NMO syndromes, but reflects current practice in many groups for the treatment of CRION.

Drug	Dosing
Azathioprine (po)	2.5–3.0 mg/kg target (increase slowly)
Methotrexate (po)	15–25 mg once weekly
Mycophenolate (po)	1 g twice daily
Rituximab (iv)	1000 mg at days 1 and 14, repeated every 6 months or if monthly CD19 counts increase above 2% of baseline

A PRACTICAL APPROACH TO MANAGING CRION

The first step is to distinguish this uncommon disease in the large haystack made up of other optic neuropathies. For the patient who presents with pain on eye movements and findings of an optic neuropathy of subacute onset in an age group that suggests idiopathic or multiple sclerosis-related optic neuritis, standard protocols for diagnosis and treatment should be followed. An exception is if there is a particular red flag such as bilateral optic nerve involvement, non-Caucasian ancestry, or simultaneous involvement of other central nervous system structures such as the cervical spinal cord).

In most cases, the consideration of CRION is raised when the patient does not recover vision after the initial episode or that the visual loss continues to progress over time. Under these circumstances, a standard workup for other optic neuropathy should be done, including MRI of the anterior visual pathways if not previously performed, laboratory workup for inflammatory, infectious, hereditary, toxic, and nutritional causes, and lumbar puncture. Because sarcoidosis can be difficult to diagnose and the clinical course can mimic CRION, gallium scanning or positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (PET-^{18}FDG) should be performed.

Assuming a negative workup for an infectious or neoplastic disease, corticosteroids should be promptly initiated. Once there is clinical response, a slow taper can be initiated after the visual loss has stabilized or improved. With progressive visual loss despite corticosteroids or where there is history of severe visual loss in the other eye, the institution of another immunosuppressive should be considered.

If there is relapse when corticosteroids are tapered, then the diagnosis of CRION becomes more likely. Assuming a negative workup for neuromyelitis (no anti-aquaporin 4 antibodies and no spinal cord involvement), then CRION is most likely. Under these circumstances the treatment regimens discussed in the posology section should be considered.

CME ANSWERS

1. d
2. c
3. False

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NON-MYDRIATIC FUNDUS PHOTOGRAPHY

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LEARNING OBJECTIVES

1. List epidemiologic associations between retinal microvascular abnormalities and cardiovascular and neurologic disease
2. Describe key research findings related to the use of non-mydriatic ocular fundus photography in ophthalmic and non-ophthalmic settings
3. Explain the implications of the increasing use of ocular fundus photography on patient care, medical education, and clinical research

CME QUESTIONS

1. Retinal microvascular findings have been associated with the long-term risk of:

    a. Heart failure
    b. Incident stroke
    c. Dementia
    d. a & b
    e. a, b, & c

2. True or false: For ophthalmologists, fundus photography provides higher sensitivity, specificity, and inter-reviewer agreement for diabetic retinopathy than ophthalmoscopy.

3. The Fundus Photography vs. Ophthalmoscopy Trial Outcomes in the Emergency Department (FOTO-ED) study found that among patients presenting to the emergency department of one university hospital with headache, focal neurological deficits, visual changes, or markedly elevated blood pressure:

    a. About 10-15% had findings of urgent relevance (optic disc edema, isolated intraocular hemorrhage, grade IV hypertensive retinopathy, retinal vascular occlusion, and optic disc pallor)

    b. Emergency physicians examined these patients with the direct ophthalmoscope less than 15% of the time

    c. When photographs were provided, emergency physicians reported them to be helpful over a third of the time

    d. Emergency physicians, without additional training, were able to identify about 50% of the emergent abnormalities on fundus photographs seen during the course of the study

    e. All of the above

KEYWORDS

1. Ocular Fundus Photography
2. Non-Mydriatic
3. Telemedicine
4. Emergency Medicine

INTRODUCTION

Examination of the ocular fundus is a fundamental component of the general physical examination and critical to the diagnosis of life- and sight-threatening medical conditions among patients with certain presenting complaints, such as headache. In addition, population-based studies have shown the prognostic value of retinal microvascular findings in cardiovascular and neurologic disease. Yet, the examination of the ocular fundus is infrequently and inadequately performed in most non-ophthalmic settings. Non-mydriatic ocular fundus photography is a promising alternative to direct ophthalmoscopy, particularly when combined with telemedicine. The Fundus Photography vs. Ophthalmoscopy Trial Outcomes in the Emergency Department (FOTO-ED) study is discussed as an example of the use of non-mydriatic ocular fundus photography in an acute, non-ophthalmic setting. The implications of non-mydriatic fundus photography on medical education, patient care, and clinical research are also addressed.

THE OCULAR FUNDUS – A UNIQUE VIEW OF THE BRAIN AND ITS MICROVASCULATURE

Ophthalmoscopy is a key element of the physical examination. Despite the rapid progress that has been made in various diagnostic medical technologies (e.g., neuroimaging), visualization of the ocular fundus is often the only diagnostic clue to the identification of potentially

serious ophthalmic and neuro-ophthalmic diseases. Examination of the fundus is necessary for the diagnosis of various disorders causing acute visual loss that require urgent management (e.g., retinal detachment), the detection of warning signs of impending visual loss and potentially catastrophic neurologic complications (e.g., papilledema, central retinal artery occlusion, anterior ischemic optic neuropathy), and to determine the severity of certain medical conditions (e.g., hypertensive crisis).

Fundus examination should be routine in the detection of vision- and life-threatening signs in patients presenting with headache, focal neurologic deficits, and severely elevated blood pressure, and in the evaluation of patients with acute visual changes. Indeed, several life-threatening intracranial disorders, such as intracranial mass, cerebrospinal fluid shunt malfunction, hydrocephalus, meningitis, and cerebral vein thrombosis often present to the emergency department with headache and associated papilledema,[1,2] which in the absence of ophthalmoscopic examination may go undetected. Failure to examine the ocular fundus for papilledema is of particular concern in the setting of idiopathic intracranial hypertension (IIH), which most commonly presents with headache, generally has an otherwise unremarkable physical examination and neuroimaging, and can lead to permanent severe visual loss in up to 10% of cases.[3-5]

The value of ophthalmoscopy in neurologic disease is hardly surprising when one considers the anatomic and physiologic homology of the brain and ocular fundus. Indeed, the ocular fundus 1) consists of central nervous system tissues, i.e., the optic nerve and retina, and 2) their supporting vasculature, containing both large and small vessel components that are supplied by the anterior cerebral circulation like the majority of the brain. The retinal and cerebral microvasculatures share embryological origins and are very similar anatomically and physiologically.[6] Both are barrier circulations sharing mechanical (luminal tight junctions) and metabolic components (e.g., transport proteins: GLUT-1, P-glycoprotein, and transferrin), and both circulations also have autoregulatory mechanisms to maintain constant blood flow in the face of changes in systemic blood pressure.[7] However, the ocular fundus has the unique distinction of being the *only CNS structure, as well as the only part of the body's microvasculature, that can be directly visualized* allowing us to easily observe the retinal microvascular changes that occur when homeostasis is disturbed. As blood pressure increases, vasoconstriction (arteriolar narrowing) occurs. As retinal autoregulatory mechanisms fail, blood and fluid leak from vessels (microaneurysms and hemorrhages) and ischemia ensues (cotton wool spots). In addition, retinal thromboembolic events can be directly visualized as emboli and vascular occlusions.[8]

RETINAL MICROVASCULAR CHANGES PREDICT LONG-TERM CARDIOVASCULAR AND NEUROLOGIC OUTCOMES

Numerous studies have related retinal microvascular changes with the long-term risk of cardiovascular disease. Chronic arteriolar changes, characterized by generalized arteriolar narrowing and arteriovenous nicking, are markers of long-term, cumulative damage from hypertension based on their association with blood pressure measured 5-8 years before retinal photography.[9] Conversely, focal arteriolar narrowing, retinal hemorrhages, microaneurysms, and cotton-wool spots are markers of acute hypertension based on their association only with concurrently obtained blood pressure measurements.[9,10] Retinal microvascular changes are also associated with increased risks of left ventricular hypertrophy,[10] ischemic heart disease,[10] congestive heart failure,[11] renal dysfunction,[12] and cardiovascular mortality.[12,13] In fact, retinal microvascular changes have been associated with twice the risk of incident congestive heart failure, even among otherwise low-risk individuals,[11] and sub-analyses of the Beaver Dam Eye Study have found that individuals with retinal microaneurysms, exudate, and retinal hemorrhages are twice as likely to die from cardiovascular events as those without these signs.[13]

From a neurologic perspective, retinal microvascular abnormalities are strongly associated with long-term risk of stroke.[6,14] Indeed, the large, middle-age-population-based Atherosclerosis Risk in Communities Study (ARIC) study found that retinal microvascular abnormalities, particularly microaneurysms and soft exudates, predict subclinical strokes independent of the patient's hypertensive and diabetic status.[15] Other investigators have also found a similar relationship between hypertensive retinopathy and silent brain infarction in patients without a history of stroke or TIA, independent of the patient's current hypertensive status.[16] Likewise, multiple population-based studies have similarly found a relationship between retinal microvascular changes and stroke, after controlling for traditional stroke risk factors.[10,17,18] In particular, retinal microvascular changes that are more reflective of acute blood pressure changes (i.e., focal arteriolar narrowing, retinal hemorrhages, microaneurysms, and cotton-wool spots) tend to portend a higher risk of incident stroke than those that appear to be markers of cumulative long-term hypertensive damage (i.e., generalized retinal arteriolar narrowing and arteriovenous nicking).[6,9,10]

Microvascular changes are also associated with dementia, as cerebrovascular cognitive impairment, typically related to small vessel disease with resultant white matter lesions and lacunar infarctions, causes 20% of dementia. Retinal microvascular changes correlate with magnetic resonance imaging (MRI) signs of cerebral white-matter lesions, and retinal exudates correlate with the presence of lacunar infarction.[7] The ARIC study investigated the relationship between retinal microvascular abnormalities and cognitive

impairment in a stroke-free population and found that the presence of retinal microvascular abnormalities (retinopathy, microaneurysms, retinal hemorrhages, and exudates) was independently associated with lower cognitive function.[7,19] Microaneurysms and retinal hemorrhages were the most consistent findings linked to diminished cognitive function.[7] The ARIC investigators also found that retinopathy and arteriovenous nicking on photography obtained at baseline were independently associated with 10-year cerebral ventricular enlargement, but not 10-year sulcal widening, suggesting a microvascular etiology for subcortical, but not cortical cerebral atrophy.[20]

OPHTHALMOSCOPY – USEFUL, BUT NEGLECTED

Despite its diagnostic and prognostic value, ocular fundus examination is often neglected by non-ophthalmic physicians due to several factors: 1) limited training in performing the technical skill,[21,22] 2) inability to recognize important ophthalmoscopic findings and interpret their relevance,[23,24] and 3) increasing demands on physician's time, coupled with under appreciation of the value of the examination.[25] U.S. third-year medical students in one study attempted direct ophthalmoscopy only 11% of the time in which an ocular fundus examination was clinically indicated.[26] Forty-seven percent of medical student clerks at one Canadian university had minimal confidence in their ability to use direct ophthalmoscopy to examine the ocular fundus through an undilated pupil,[27] and 43% of general practitioners surveyed in the United Kingdom lacked confidence in using the direct ophthalmoscope.[22] In a survey of hospital physicians, all said that ophthalmoscopy was important but only 3 of 72 performed it routinely. Half of these physicians indicated they would perform ophthalmoscopy for patients with diabetes, hypertension, visual impairment, and neurologic symptoms, but on review of 100 case notes, ophthalmoscopy was documented on only 3 patients; 9 with diabetes and 35 with hypertension had no ophthalmoscopy reported. When a subset of these physicians were tested with the direct ophthalmoscope, they correctly diagnosed abnormalities less than 50% of the time.[24] In a study of pediatric physicians at a university-affiliated hospital, 9 of 11 residents and 1 of 5 senior physicians responded "one to three times" and the rest said "never," when asked how many times they had examined an ocular fundus during the last year.[23] In a study asking patients whether they recalled being examined with a tendon hammer, ophthalmoscope, and stethoscope, over half of the patients could not recall having ophthalmoscopy performed, while 95.7% recalled being examined with a stethoscope.[28]

NON-MYDRIATIC FUNDUS PHOTOGRAPHY – AN ALTERNATIVE TO OPHTHALMOSCOPY?

Non-mydriatic digital retinal imaging has several advantages compared to ophthalmoscopy. For example, studies of non-mydriatic fundus photography in diabetic retinopathy screening (the most extensively studied area in retinal imaging) have found it to have higher sensitivity, specificity, and inter-examination agreement than ophthalmoscopy, even among ophthalmologists.[29,30] In contrast to ophthalmoscopy, non-medical personnel can assist by obtaining high-quality images for later review, even after only limited training. One study comparing images obtained by a trained ophthalmic photographer (with 20 years of experience) and two non-professional photographers (one with 2 days and the other with 1 hour of training) found no difference in the image quality based on the ratings of two retina specialists.[31]

Non-mydriatic fundus photography is already routinely used to screen for treatable, sight-threatening eye diseases, such as diabetic retinopathy, within at-risk populations.[32] Indeed, there is level I evidence that single field fundus photography can identify patients with diabetic retinopathy who require referral for ophthalmic evaluation and management.[33] The capabilities of ocular fundus photography have also been shown both in the diagnosis of referral-warranted retinopathy of prematurity and in the telemedical diagnosis of cytomegalovirus retinitis in HIV-positive patients in underserved countries, although assessment of both of these conditions typically requires pupillary dilation.[34,35]

THE FUNDUS PHOTOGRAPHY VS. OPHTHALMOSCOPY TRIAL OUTCOMES IN THE EMERGENCY DEPARTMENT (FOTO-ED) STUDY

The importance of timely and accurate ocular fundus examination is particularly evident in the emergency department (ED) where failure to correctly evaluate the ocular fundus places patients at risk for poor outcomes and exposes their caregivers to significant medicolegal liability.[36] Yet, even in the ED, examination of the ocular fundus is not consistently performed. For example, two studies of headache management in the ED found documentation of ophthalmoscopy in only 37–48% of cases.[37,38] Non-mydriatic ocular fundus photography appears to overcome many barriers to an adequate ophthalmoscopic examination in the ED because many physicians are reluctant to perform routine dilation of patients for ophthalmoscopic examination, pupillary dilation takes up to 30 minutes, and most patients prefer not to have their pupils dilated.[24] In addition, neurologic patients represent a unique population in which pupillary reflexes can be critical for monitoring clinical status. We hypothesized that the undilated views of the ocular fundus provided by non-mydriatic ocular fundus photography would be useful in overcoming important obstacles to appropriate patient examination in the ED. Therefore, the FOTO-ED study was developed as an interdisciplinary project between neuro-ophthalmology and emergency medicine in order to improve ophthalmologic care in the ED by evaluating whether non-mydriatic fundus photography was a better alternative to direct ophthalmoscopy.

The FOTO-ED study was conducted in 2 phases between April 2009 and August 2011. The first phase evaluated the routine clinical use of direct ophthalmoscopy by ED physicians, whereas the second phase evaluated the routine use of non-mydriatic ocular fundus photography as interpreted by the ED physicians. In both phases, all patients had non-mydriatic ocular fundus photographs obtained. The inclusion criteria for the FOTO-ED study were adult patients presenting to the ED with a presenting complaint or condition of one or more of the following: headaches, focal neurologic deficits, diastolic blood pressure (DBP) ≥120 mmHg, or acute visual changes. Patient demographics, including age, gender, race, presenting vital signs, height, and weight, were prospectively collected in the ED. Photographs of the posterior pole of the ocular fundus (optic disc, macula, and major retinal vessels) were obtained from both eyes of enrolled patients at presentation by trained nurse practitioners or a medical student using a commercially available, Food and Drug Administration–approved, non-mydriatic ocular fundus camera (Kowa nonmyd-D series cameras; Kowa Optimed, Inc., Torrance, CA). The images were automatically electronically transferred to a Health Insurance Portability and Accountability Act-compliant database for review. Throughout the FOTO-ED study, relevant ocular fundus abnormalities were defined as optic disc edema, isolated intraocular hemorrhage, grade III/IV hypertensive retinopathy, retinal vascular occlusion, and optic disc pallor.

Phase I – Only Direct Ophthalmoscopy Available to Emergency Physicians

In the first phase of the FOTO-ED study,[39,40] 350 adult patients were enrolled. The median age of patients was 44.5 years (interquartile range [IQR] 31–59 years), and 220 (63%) were women. The presenting complaints and conditions were headache in 228 (65%), acute focal neurologic deficit in 100 (29%), acute visual change in 92 (26%), and DBP ≥120 mmHg in 21 (6%). Patients could have more than one presenting complaint or condition. The performance of ED physicians and the findings on direct ophthalmoscopy were prospectively recorded, with the physicians unaware of the photography results.

During routine evaluation, ED physicians performed direct ophthalmoscopy on only 48 of the 350 patients (14%; 95% confidence interval [CI]: 10–18%). In 44 enrolled patients, relevant ocular findings (13%; 95% CI: 9–17%) were identified with the use of non-mydriatic fundus photography by the neuro-ophthalmologist reviewing the images: 13 cases of optic nerve edema, 13 cases of intraocular hemorrhages, 10 cases of hypertensive retinopathy (grade III or IV), 4 cases of arterial vascular occlusion, and 4 cases of optic nerve pallor. Eleven of the findings were known before patients presented to the ED. Of the remaining 33 relevant findings, 6 were identified by ophthalmologic consultants, but the other 27 neither had a consult requested nor were identified by the ED physicians. Thus, 82% (95% CI: 65–93%) of the findings unknown at the time of ED presentation were missed by routine ED care. For each photography session, the nurse practitioner rated the ease and speed of fundus photography and patients rated the ease, speed, and comfort of non-mydriatic photography on a 10-point Likert scale (10 best) and mean scores for each scale were 8.7 or better. The quality of the photographs was of some diagnostic value for 97% of enrolled patients. Median photography time was 1.9 minutes (IQR: 1.3–2.9).

We concluded from the first phase that direct ophthalmoscopy was infrequently and poorly performed in the emergency department and that non-mydriatic fundus photography was a feasible alternative to direct ophthalmoscopy.

Phase II – Fundus Photography Provided to Emergency Physicians

Among 478 patients screened for eligibility, 354 were enrolled in phase II of the FOTO-ED study.[41] Eighty-six patients were ineligible (56 too ill, 13 non-focal neurologic complaints, 14 unable to be located, 3 other reasons), and 33 patients refused participation. Using the EMR automated screening process, 345 of the enrolled subjects (97%) were identified, with the remainder identified by active surveillance by study personnel. Five eligible patients (3 headache, 2 focal neurologic) who triggered the automated process were missed by study staff.

The median age of the patients was 45.9 years (IQR: 33–57) and 251 (71%) were women. Two hundred six patients (58%) had headache, 123 (35%) had focal neurologic symptoms, 56 (16%) had acute visual changes, and 21 (6%) had DBP ≥120 mm Hg (patients were allowed to have more than 1 presenting complaint). Thirty-five patients (10%; 95% CI: 7%–13%) had relevant findings identified by neuro-ophthalmologist review of the photographs, including 6 patients with disc edema, 6 with grade III/IV hypertensive retinopathy, 7 with isolated intraocular hemorrhages, 15 with optic disc pallor, and 1 with a retinal vascular occlusion. Among the 354 enrolled patients, the ED physicians reviewed the photographs of 239 patients (68%) and reported that the photographs were helpful in their evaluation of 125 patients (35%; 95%CI: 30%–41%). The ED physicians identified 16 of the 35 relevant findings (46%) during their review of the fundus photographs.

We concluded that non-mydriatic fundus photographs were used by ED physicians more frequently than they performed direct ophthalmoscopy (68% vs. 14%), that their detection of relevant abnormalities improved (46% vs. 0%), and that ocular fundus photography often assisted with ED care even when the photographs were normal (e.g., the absence of papilledema in a patient with potential shunt malfunction). The increased frequency of both viewing

the fundus and diagnosing abnormalities was particularly remarkable given that the emergency physicians had not received any additional training.

BEYOND THE EMERGENCY DEPARTMENT

Education

Non-ophthalmic physicians have also read non-mydriatic photographs for diabetic retinopathy screening in two large-scale projects.[42,43] The first study reported the characteristics of 742 patients referred for ophthalmic care by 24 trained general practitioners who reviewed the photographs for evidence of diabetic retinopathy within a nationwide screening program in Singapore, but the article did not discuss false negatives (missed diagnoses).[42] In the other study,[43] four trained general practitioners in Spain deemed the photographs of 2036 of 2750 patients (74%) normal and sought ophthalmologic consultation for the remainder. Among those sent for review, 392 (55%) did not have diabetic retinopathy, suggesting that the general practitioners had a low threshold for referral to avoid false negatives. Ophthalmologists also reviewed a sample of 240 of the patients that the general practitioners had read as normal and found that 16 of these (7%) had diabetic retinopathy, but that only two patients (1%) had treatable diabetic retinopathy. The authors concluded that the general practitioners had acceptable sensitivity (particularly relevant for a screening technique), but were concerned about specificity and recommended additional training to avoid inappropriate referrals.[43]

The demonstration that non-ophthalmic physicians are capable of reviewing photographs for key conditions in various settings, combined with the technical advantages of non-mydriatic fundus photography over direct ophthalmoscopy, suggest that non-mydriatic photography may be an acceptable (and in some cases a better) alternative to direct ophthalmoscopy. Moreover, it seems likely that educational efforts at the allied health, medical school, and post-graduate levels may be best directed at teaching students and clinicians how to read photographs rather than how to perform the technical skills of direct ophthalmoscopy. In fact, two longitudinal studies by Lippa et al. of a sustained, multi-year ophthalmology curriculum emphasize the difficulties of teaching direct ophthalmoscopy in a way that has a lasting effect.[26,44] For example, while there was initially a 46% documentation rate of ophthalmoscopy in one of the medical students' third year rotations, there were no documented funduscopic examinations during the students' fourth year internal medicine clerkship. In addition, only 23% of the students had purchased an ophthalmoscope by completion of medical school.[44] Of further concern, 13% to 16% of students stated that a direct ophthalmoscope was not important for clinical duties, and 5% to 6% stated that there was a "dearth of opportunities" for its use in clinical encounters.[44]

We have investigated the use of fundus photography as an alternative to direct ophthalmoscopy in the education of medical students. We studied 138 first-year medical students,[45] 119 (86%) of whom completed all required elements for the study. For learning ophthalmoscopy, 85 (71%) preferred humans to patient simulators. For learning relevant features of the ocular fundus, 92 (77%) preferred photographs to ophthalmoscopy on simulators or humans. The students' accuracy was better when interpreting fundus photographs than when performing ophthalmoscopy on simulators, and their performance improved after specific teaching about assessing fundus photographs before testing ($P = 0.02$). Examination of the ocular fundus was found to be easier and less frustrating when using photographs than when using ophthalmoscopy on simulators or humans. Eighty-four students (70%) said they would prefer to have fundus photographs instead of using the ophthalmoscope during upcoming clinical rotations.

In a one-year follow-up study of the same students,[46] 107 (90%) of which participated, the students' self-reported median frequency of fundus examination over the preceding year was <10% (interquartile range: 0%-20%). Of 107 students, 85 (79%) felt uncomfortable with ophthalmoscopy, 47 (44%) stated they would not perform ophthalmoscopy during general physical examinations, and 81 (76%) stated they would prefer using photographs over ophthalmoscopy for fundus examination. Students continued to be more accurate using photographs than ophthalmoscopy and still preferred photographs for examining the ocular fundus. Although both groups performed significantly worse in identifying relevant fundus features than they did 1 year prior, the difference was equal in the 2 groups and likely related to a lack of fundus examination skill reinforcement in the interim. Most students felt uncomfortable with ophthalmoscopy, which may cause avoidance of ocular fundus examination in clinically appropriate situations. Of concern, 20% of students cited discouragement by their clinical preceptor as their primary reason for not performing ophthalmoscopy, which suggests that postgraduate education may be needed to create a long-term change in the use and performance of fundus examination.

Alternatives to Physician Photography Readings

As technology continues to advance, one can ask the controversial question of whether the general physician of the future even needs basic fundus interpretation skills. In fact, Bhargava *et al.* reported on 367 diabetic patients assessed by both non-physician graders and family physicians compared to a reference standard of a retinal specialist. They found that the non-physician graders with one year of rigorous training followed by yearly auditing had better agreement with the retinal specialists

(kappa =0.66) than the family physicians who had two hours of training followed by re-education every two years (kappa=0.40). The non-physician graders also had better sensitivity (70%) than the family physicians.[47]

While it is promising that the majority of diabetic retinopathy screening could be offloaded from retinal specialists and general practitioners to non-ophthalmic readers, developments in automated, computerized reading takes this one step further, by potentially taking the task of reading photographs completely out of the hands of human reviewers. Although efforts to develop automatic methods to identify features of diabetic retinopathy have been ongoing for over 20 years,[48] only recently have they begun to achieve levels of diagnostic capability comparable to ophthalmologists.[49] For example, two groups have recently reported sensitivity of at least 90% with 100% specificity using their comprehensive assessment algorithms.[50,51] Automatic detection and severity assessment of optic disc edema using photographs has also shown promising results.[52]

Improving the Mobility of Non-Mydriatic Fundus Cameras

A major limitation of table-top cameras is that they are unable to assess patients who are too ill or too young to sit at the camera. Technology is already addressing this issue with several new, portable devices for retinal photography, some of which are non-mydriatic, such as EyeQuick (Eye Quick, El Paso, TX; http://www.eyequick.com), VersaCam (Nidek Co., Ltd., Fremont, CA; http://www.nidek-intl.com/products/diagnosis/ds-10.html), and Pictor Plus (Volk Optical, Mentor, OH; http://www.volk.com/pictorplus). Many of these devices can also capture video for the assessment of dynamic phenomena (e.g., spontaneous venous pulsations). In addition to these dedicated devices, special adapters are available that allow the attachment of smartphones to ophthalmoscopes and slit lamps (e.g., iExaminer [Welsh Allyn, Skaneateles Falls, NY; http://www.welchallyn.com/en/microsites/iexaminer.html]), albeit generally for mydriatic photography (see also "Smart Phoneography" on http://eyewiki.aao.org/). However, these devices are substantially more difficult to use than a tabletop camera, have narrower fields of view, and can only obtain photographs of lower quality. Further scientific and technological progress in imaging science and engineering will be required to produce the ideal "digital ophthalmoscope." Continued improvements will facilitate the examination of very young pediatric patients, sicker patients in the ED and other settings, and patients in intensive care units.

Telemedicine

Advancements in telemedicine, particularly via nearly ubiquitous mobile devices (e.g., smartphones and tablets), will allow expert reviewers to assess emergent images in a timely fashion. For example, in a subanalysis of the FOTO-ED study, a five-point overall quality rating assigned by two reviewers to the same 100 photographs on a desktop computer and the iPhone 3G was compared. A very high intra- and inter-rater agreement on the iPhone (kappa=0.96) and high agreement of the same reviewer between the two devices (0.82-0.91) was found. Notably, both reviewers on average rated the same image as higher quality on the iPhone compared to the desktop computer (chi square >36, p<0.001).[53] Likewise, Kumar et al. found that the ophthalmologists who reviewed images of patients for the telemedical diagnosis of diabetic retinopathy had very high agreement (kappa=0.9) and gave high scores to the image quality on the iPhone 4.[54] These studies suggest that today's mobile devices already possess the quality needed for tele-ophthalmology.

CONCLUSION

Further advancements in non-mydriatic fundus photography and telemedicine not only have the potential to improve patient care, but may also facilitate clinical research in areas that are currently intractable. The expansion and validation of non-mydriatic fundus photography and its interpretation by non-ophthalmic reviewers and by telemedicine may offer the early diagnosis required for clinical trials in neuro-ophthalmology analogous to emergent stroke treatment trials for conditions such as central retinal artery occlusion, anterior ischemic optic neuropathy, and traumatic optic neuropathy.[55] In addition, these techniques hold promise for risk stratification and predictive health in both acute and chronic neuro-ophthalmic diseases, such as transient ischemic attack, although their role remains to be fully elucidated.

CME ANSWERS

1. e
2. True
3. e

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IMAGING OF HORNER SYNDROME

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LEARNING OBJECTIVES

1. Review the literature regarding imaging of Horner syndrome in adults and children
2. Provide recommendations for imaging of Horner syndrome in adults and children

CME QUESTIONS

1. True/False: Horner syndrome in adults and children can be managed conservatively, without the aid of imaging.
2. True/False: Non-directed imaging in adults with Horner syndrome never finds an underlying cause.
3. True/False: Urine VMA/HVA is a insufficient screen for neuroblastoma in children with Horner syndrome.

KEYWORDS

1. Horner Syndrome
2. Carotid Dissection
3. Neuroblastoma

INTRODUCTION

The goals of this talk are to review the literature regarding imaging of Horner syndrome in adults and children, and to provide practical recommendations for imaging of Horner syndrome in adults and children.

Table 1 (see below) outlines the differential diagnosis of Horner syndrome according to localization and frequency.[1] The ganglion referred to is the superior cervical ganglion; thus "preganglionic" refers to the second-order neuron and "postganglionic" to the third-order neuron.

The diagnosis of Horner syndrome in adults and children is often a clinical one based upon examination findings, with cocaine or apraclonidine used only to confirm the oculosympathetic paresis. Hydroxyamphetamine is becoming more difficult to acquire because of decreasing commercial availability. This, coupled with the high false-negative and positive rate of the hydroxyamphetamine test, will encourage clinicians in most instances to localize the Horner syndrome and make management decisions clinically, based upon clues in the history or examination. An imaging study typically will be pursued next, and the localization and clinical setting will dictate the modality and region to be evaluated.[2,3]

TABLE 1. Causes of Oculosympathetic Paresis (Horner Syndrome), According to Affected Neuron and Frequency.[1]

	Common	**Uncommon**
First-order (central) neuron	Lateral medullary stroke Spinal cord lesion	Hypothalamic, midbrain, or pontine injury
Second-order (preganglionic) neuron	Pancoast tumor Brachial plexus injury Iatrogenic trauma Neuroblastoma	Cervical disc disease
Third-order (postganglionic) neuron	Carotid dissection Carotid thrombosis Cluster headache Cavernous sinus lesion "Small vessel ischemia"	Intraoral trauma

ADULTS WITH HORNER SYNDROME

Published studies. The question at hand is, in an adult patient with a relatively newly acquired (<1 year), isolated Horner syndrome of unknown etiology, what types of imaging should be ordered? Unfortunately there are no prospective studies to answer this question. I am aware of only two relatively large published retrospective studies addressing this issue in the last 15 years.

Almog et al.[4] retrospectively studied 52 patients with Horner syndrome. In 32 (62%) the etiology was already known at presentation, with trauma being the most common cause in this group. In 11 (21%), targeted imaging was performed and revealed an etiology in 7 of the 11 with carotid dissection and cavernous sinus masses most commonly identified. In the remaining 9 (17%), nontargeted imaging (MRI of brain, neck and CT or MRI of upper thorax in all 9 and neck vascular imaging in 2) was revealing in only 1 (11% of this group). A previously unknown thyroid malignancy was identified. The authors concluded, "When the etiology is not known and clinical information is insufficient to allow a targeted imaging evaluation, an etiology is rarely discovered. Even so, nontargeted imaging is warranted because life-threatening conditions, such as thyroid malignancies, may rarely be detected."

Mollan et al.[5] retrospectively analyzed forty-seven clinically isolated cases of Horner syndrome. Although the total number of patients without localizing clues on history or exam was not provided, 4 such patients were found to have responsible pathology: 2 with carotid dissections, 1 with a Pancoast tumor, and one with a C1 benign aneurysmal bone cyst. Three patients were evaluated with a history of Horner syndrome for greater than one year and found to have pathology: 2 with carotid dissections, and one with a cervical sympathetic paraganglioma.

So what is the clinician to do? Recommendations for imaging span between observation and a "shotgun" approach with imaging along the entire sympathetic chain.[6] Based upon recent studies, sensible algorithms have been suggested by various experts.[7,8] Both suggest that pharmacologic testing can be confirmatory, hydroxyamphetamine testing no longer has a prominent role, and imaging to some degree should be performed in a directed fashion. Standard chest x-ray and carotid ultrasound are probably inadequate compared to CT and MR.[8]

In my opinion, there are two situations that mandate a directed radiologic investigation regardless of clinical or pharmacologic localization (because neither is perfect). First, in any middle-aged or elderly patient, especially one with a history of smoking, with an isolated, unexplained Horner syndrome, chest CT or MRI should be performed to rule out an apical lung tumor. Second, Horner syndrome accompanied by ipsilateral headache, eye pain, or dysgeusia, with or without ipsilateral cerebral or ocular ischemic symptoms, requires MRI and MRA (or CT and CTA) of the neck to exclude a carotid dissection or thrombosis. Axial T1-weighted MR images through the neck are especially important in this setting, as the hematoma within the vessel wall may be visualized with this modality. (see below)

Other situations can be governed by suspected localization aided by the presence of additional clinical signs or symptoms. Sweating on the face may be reduced in first- and second-order lesions. Brainstem or spinal cord signs suggest involvement of the first-order neuron. Arm pain, or a history of neck or shoulder trauma, surgery, or neck lines, point to injury of the second-order neuron. Horner syndrome accompanied by ipsilateral facial pain or headache is characteristic of disorders that affect the third-order neuron.

1. *First-order neuron*. If the process is thought to be first order because of the presence of cerebral, posterior fossa, or spinal cord signs, then the neurologic findings should guide the investigation. For instance, accompanying hemianesthesia or ataxia mandate brain MRI to exclude a brainstem lesion. On the other hand, a sensory level or paraparesis accompanying a Horner syndrome should be evaluated with a spine MRI, with and without contrast.

2. *Second-order neuron*. If a presumed preganglionic Horner syndrome is isolated or associated with brachial plexopathy, screening chest CT or MRI, with and without contrast, with attention to the lung apex and neck is indicated.

3. *Third-order neuron*. If the lesion can be localized to the postganglionic neuron, in addition to an MRI and MRA of the neck to exclude a carotid dissection or thrombosis, we recommend an MRI of the brain to exclude a cavernous sinus lesion. The additional presence of a third, fourth, or sixth nerve palsy or trigeminal neuropathy ipsilateral to the Horner syndrome would be highly suggestive of such a localization. However, the evaluation of postganglionic Horner syndromes is often unrevealing, and in such instances the Horner syndrome is felt to be benign.

MRA or CTA of the neck is essential for establishing the diagnosis and defining the extent of dissection. Lumen narrowing of the internal carotid usually begins 2 cm distal to the carotid bifurcation and extends rostrally for a variable distance. Dissection of the extracranial ICA almost always ends before the artery enters the petrous bone, where mechanical support limits further dissection.[9]

Axial MR T_1- and T_2-weighted images through the neck may demonstrate a characteristic crescentic hyperintensity, representing a mural hematoma, constricting the true lumen of the internal carotid artery. One of our neuro-radiologists at the University of Pennsylvania, Dr. Ronald Wolf, communicated to me that he prefers "MRA, or more specifically MRA with MRI to give optimal attention to

vessel walls, often simply with fat saturated T1-weighted axials. CTA is OK, but MRI/MRA is better for vessel wall hematoma detection. IV contrast is not absolutely necessary, but tends to be given for MRA per routine (first noncontrast MRA, followed by bolus contrast MRA) because the bolus contrast acquisition is fast, robust, and less sensitive to motion. The noncontrast is retained in protocol in case bolus is mistimed or other issue with IV contrast bolus."

Others have suggested CT/CTA is adequate for combined soft-tissue imaging of the neck and visualization of the carotid artery.[7] CT/CTA may be easier to obtain, requires less imaging time, is less susceptible to motion degradation, and is less expensive than MRI/MRA. CT however requires radiation and contrast allergy must be considered. In the end, the decision to order CT/CTA or MRI/MRA in this clinical setting may be dependent on the setting and the institution. In one study,[30] CTA and MRA were felt to be equivalent for the evaluation of internal carotid artery dissection.

Although there are rare exceptions,[5] most causes of Horner syndrome of more than one year in duration are benign and imaging would not be mandatory. A work-up in these instances may depend on the level of concern between the patient and physician.

So my protocol for evaluating adult patients with Horner syndrome <1 year in duration is as follows:

1. Localize clinically, +/- confirm with cocaine or apraclonidine.
2. Chest imaging in middle-aged or elderly patients, or in those with a history of smoking.
3. Emergent vascular neck imaging in anyone with ipsilateral headache, eye pain, or dysgeusia.
4. In localizable cases, pursue directed imaging. Perform emergently if brainstem stroke or carotid dissection considered. Non-emergent otherwise.
5. In non-localizable cases, non-emergent:
    i) Combined chest, neck, and vascular neck imaging (conservative approach).
    ii) Combined head, neck, chest imaging and vascular neck imaging ("nontargeted", "shotgun" approach that I prefer).

CHILDREN WITH HORNER SYNDROME

Published studies. Like in adults, all published studies within the past two decades looking at the evaluation of children with Horner syndrome are retrospective.

George et al.[10] retrospectively reviewed 23 children with Horner syndrome presenting during the first year of life. One was found to have a ganglioneuroma of the left pulmonary apex and another with a cervical neuroblastoma. They recommended urinary VMA levels and follow-up in isolated cases and further investigation if the Horner syndrome was acquired or associated with other signs such as increasing iris heterochromia, a palpable cervical mass, or cranial nerve palsies.

Jeffery et al.[11] retrospectively studied 73 children with Horner syndrome, of whom 11 had acquired, non-surgical Horner syndrome. In this group, neuroblastoma (2), rhabdomyosarcoma (1), brainstem vascular malformation (1) and demyelination (1) were found. The authors concluded that "all acquired pediatric Horner syndrome patients without a known etiology require thorough evaluation because of the frequent association of serious underlying disease."

In another retrospective study of children with Horner syndrome of unknown etiology,[12] responsible mass lesions, such as neuroblastoma, Ewing sarcoma, and juvenile xanthogranuloma, were found in 6 of 18 (33%) of patients. Of interest, the MRI was found to be more sensitive than urine testing in this setting, as all the newly diagnosed neuroblastomas in this study were detected on imaging but had normal VMA and HVA levels.[12]

In a population-based study, Smith et al.,[13] retrospectively analyzed 20 children diagnosed with Horner syndrome in a Olmsted County over a 40 year period. Birth, surgical, or other trauma was the cause in 13 (65%) of patients. None had an underlying mass lesion. The remaining 7 were idiopathic. The study has been criticized for its possible lack of generalizability.[14]

Other issues particular to children with Horner syndrome. Even children with a history of birth trauma or those with Horner syndrome at birth ("congenital") should be evaluated, as these patients may still harbor an underlying neoplasm.[11,15,16] The presence or absence of iris heterochromia should not influence the work-up.

Testing with apraclonidine has been suggested in children with Horner syndrome,[17,18] but reports of drowsiness and unresponsiveness in children less than two years of age tested with this agent,[19] and in those treated for glaucoma[20] with the similar drug brimonidine,[21] have discouraged us from using it in this population. In our experience dry eye and mild irritability are the only side effects from the use of cocaine eye drops in children.

Although excess production of catecholamines or their metabolites occurs in 90% of all neuroblastomas,[22] in low-risk neuroblastomas such as those causing Horner syndrome, as few as 40% may be associated with elevated urinary catecholamine metabolite (vanillylmandelic acid

[VMA] and homovanillic acid [HVA]) levels.[23] Only "spot" urine samples, rather than large collections, are needed. As stated above, in Mahoney et al.'s series, of the patients found to have neuroblastoma, VMA and HVA levels were normal in all. Thus screening urinary VMA and HVA tests may be relatively insensitive in detecting neuroblastomas causing Horner syndrome in children.

There have been rare cases of Horner syndrome associated with neuroblastomas arising from the adrenal glands and in the lower thoracic sympathetic chain.[10,24,25] In George et al.'s case, CT of the neck and chest imaging was negative.[10] How distant tumors affect the oculosympathetic pathway is uncertain, but a more generalized disorder of sympathetic neuronal maturation has been proposed.[25,26] Alternatively, a small cervical metastasis may have been missed without MRI of the neck, as neuroblastoma may be multifocal (John Maris, MD, personal communication). Because of the uncertainty of the relationship with these non-cervical neuroblastomas with the Horner syndrome, currently we are not recommending abdominal imaging as part of the evaluation.

Carotid dissection is uncommon in children although carotid dysgenesis may be a cause of congenital Horner syndrome.[12]

Children with pharmacologically-confirmed oculosympathetic paresis with no obvious cause and normal imaging and urine testing are given the diagnosis of idiopathic Horner syndrome. One suggested etiology in these cases is regressed neuroblastoma.

Suggested protocol. As in adults, although there are rare exceptions, most causes of Horner syndrome in children of more than one year in duration are benign and imaging would not be mandatory. A work-up in these instances may depend on the level of concern between the parents and physician. The protocol applies to children with Horner syndrome which is acquired or present at birth, with or without a history of birth trauma.

So my suggested protocol for evaluating children with Horner syndrome <1 year in duration is as follows:

1. Palpate the neck, upper chest, and axillae for masses.
2. Localize the Horner syndrome clinically, confirm with cocaine or apraclonidine (above age 2 years only for the latter). If cocaine cannot be obtained, and the child is less than 2 years of age, then one will have to proceed presumptively.
3. In localizable cases with confirmed Horner syndrome, non-emergent directed imaging.
4. In non-localizable cases with confirmed Horner syndrome, non-emergent evaluation to exclude neuroblastoma and other responsible mass lesions.[12]
   i) Combined chest and neck MRI (conservative approach) and urine VMA and HVA
   ii) Combined head, neck, chest imaging and vascular neck imaging ("nontargeted", "shotgun" approach that I prefer) and urine VMA and HVA.

CME ANSWERS

1. False
2. False
3. True

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NEURO-OPHTHALMOLOGY OF OUTER SPACE

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LEARNING OBJECTIVES

1. Describe the history, clinical findings, and possible pathogenic etiologies of neuro-ophthalmic findings discovered in astronauts after long-duration space flight
2. Discuss the terrestrial implications of such findings
3. Describe potential countermeasures to decrease risk to future missions and our astronauts

CME QUESTIONS

1. Which of the following neuro-ophthalmic findings have been seen after long duration space flight?

    a. Anisocoria
    b. Optic disc edema
    c. Ocular motor cranial neuropathy
    d. Bitemporal hemianopsia

2. Which of the following fundus findings have been documented in astronauts after long duration space flight?

    a. Choroidal folds
    b. Retinal vein occlusion
    c. Angle closure glaucoma
    d. Retinal artery occlusion

3. Which of the following have been seen radiographically in long duration space flyers?

    a. Globe flattening
    b. Venous sinus thrombosis
    c. Suprasellar mass
    d. Intracranial hemorrhages

4. Which of the following is the refractive error shift that has been seen most frequently in long duration space flight astronauts?

    a. Myopic shift
    b. Hyperopic shift
    c. Astigmatic shift
    d. Higher order aberration shift

KEY WORDS

1. Astronaut
2. Optic Disc Edema
3. Choroidal Folds
4. Papilledema
5. Hyperopic Shift
6. Long Duration Space Flight

INTRODUCTION

Physiologic and pathologic systemic responses and novel but dramatic ocular changes are known to occur in the microgravity environment of outer space. The precise effects of the long duration space flight environment on the human eye and brain remain ill-defined but over the last decade, the United States National Aeronautics and Space Administration's (NASA) Space Medicine Division has documented varying degrees of optic disc edema, globe flattening, choroidal folds, cotton wool spots (CWS), and hyperopic refractive error shifts in astronauts during and after long-duration space flight. In addition, neuroradiographic and ultrasonographic findings have demonstrated structural correlates to the clinical findings experienced by our long duration space flyers including flattening of the posterior globe and increased cerebrospinal fluid signal in the optic nerve sheaths. Although there have been some similarities of these radiographic and neuro-ophthalmic clinical findings with terrestrial idiopathic intracranial hypertension (IIH), there have also been clear differences. The clinical features of this unique patient cohort during space travel suggest specific neuro-ophthalmologic responses that might be inherent to long duration exposure to the microgravity space environment. We described our clinical experiences in a prior report and we proposed at that time that these neuro-ophthalmic findings may represent pathologic processes related to intraocular, intra-optic nerve, intraorbital, intravascular, or intracranial changes.[1] There is also a cephalad fluid shift experienced by our astronauts during microgravity exposure that might be the key to the underlying pathogenesis. Alternatively, increased intracranial pressure (ICP), translaminar pressure differences between intraocular pressure (IOP) and ICP, or

alterations in the cardiovascular or cerebrovascular systems have also been proposed as potential alternative but not necessarily mutually exclusive pathogenic mechanisms.

The objectives of this presentation include: 1) To describe the neuro-ophthalmic changes seen in astronauts after long duration space flight; 2) To detail the possible hypotheses for an etiologic mechanism including intravascular, intracranial, intraorbital, intrasheath, and intraocular changes related to long duration space flight and microgravity; 3) To compare and contrast terrestrial IIH and postoperative ischemic optic neuropathy (ION) with the findings in long duration space flyers and[4] to discuss the possible implications of our space flight findings for these terrestrial neuro-ophthalmic disorders.

In 2013, Mader et al. described the history, clinical findings, and possible etiologies of ophthalmic findings discovered in astronauts after long-duration space flight on the International Space Station (ISS).[1] This retrospective, observational report described the neuro-ophthalmic findings in 7 astronauts as well as an analysis of post-flight questionnaires about in-flight vision changes in approximately 300 additional astronauts. All 7 subjects underwent complete eye examinations before and after their ISS mission, including cycloplegic and/or manifest refraction and fundus photography. Six underwent post-mission optical coherence tomography (OCT) and magnetic resonance imaging (MRI); 4 had lumbar punctures (LP). After 6 months of space flight, 7 astronauts had ophthalmic findings, consisting of optic disc edema in 5, globe flattening in 5, choroidal folds in 5, CWS in 3, nerve fiber layer thickening by OCT in 6, and decreased near vision in 6 astronauts. Five of 7 astronauts with near vision complaints had a hyperopic shift of +0.50 diopters (D) between pre/post-mission spherical equivalent refraction in 1 or both eyes (range: +0.50 to +1.75 D). These 5 cases also showed a structural correlate of globe flattening (axial hyperopic shortening) on orbital MR and ultrasound imaging. Lumbar punctures (LP) performed in the 4 cases with optic disc edema documented opening pressures (OP) of 22, 21, 28, and 28.5 cm H2O performed 60, 19, 12, and 57 days post-mission, respectively. The 300 post-flight questionnaires documented that approximately 29% of short (space shuttle) duration and 60% of long-duration mission flyers on ISS had experienced a degradation in distant and near visual acuity. Although most of the visual changes were reversible or correctible to 20/20, some refractive error changes remained persistent even years after flight. Table 1 (see next page) (reprinted with permission from[1] summarizes the neuro-ophthalmic findings in 7 ISS crew members. In addition, NASA follows longitudinally the health of the astronaut corps in the Lifetime Surveillance of Astronaut Health (LSAH) program. Table 2 (see next page) demonstrates the in-flight and post flight refractive changes from shuttle and ISS flyers in the LSAH. Figure 1 (see below) shows an example of fundus photography documentation of preflight and post-flight development of optic disc edema in one long duration space flyer. Figure 2 (see below) demonstrates the orbital MRI (T2 weighted) findings of flattening of the posterior globe, CSF fluid in the optic nerve sheath, and an elevated optic disc. Figure 3 (see next page) shows choroidal folds OU in a long duration flyer post flight which were not present on fundus photographs preflight.[1]

Figure 1: Preflight and Postflight optic disc photos demonstrating development of optic disc edema after long duration space flight (with permission from Ophthalmology 2011;118:2058-69.).

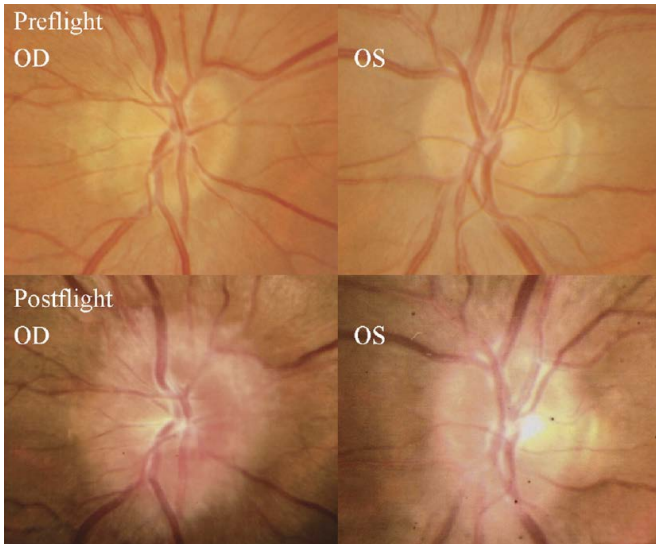


Figure 2: Orbital MRI showing cerebrospinal fluid in the optic nerve sheath, elevation of the intraocular optic nerve (long black arrow) and flattening (gray arrows) of the posterior globe (with permission from Ophthalmology 2011;118:2058-69.).

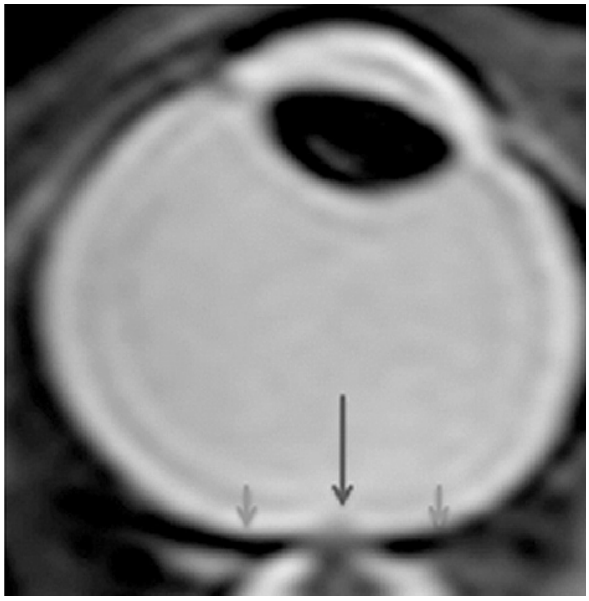


Table 1. Neuroophthalmic Changes in Astronauts

ISS Crew Member	Mission Duration (mos)	Refractive Change		Intraocular Pressure (mmHg)		Fundoscopic Examination Postflight
		Preflight	*Postflight*	*Preflight*	*Postflight*	
1	6	OD: −1.50 sph OS: −2.25 − 0.25 × 135	OD: −1.25 − 0.25 × 005 OS: −2.50 − 0.25 × 160	15 OU	10 OU	Choroidal folds OD Cotton wool spot OD
2	6	OD: +0.75 OS: +0.75 to 0.25 × 165	OD: +2.00 sph OS: +2.00 − 0.50 × 140	14 OU	14 OU	Bilateral disc edema OD > OS Choroidal folds OD > OS Cotton wool spot OS
3	6	OD: −0.50 sph OS: −0.25 sph	Plano Plano	10 OU	10 OU	Bilateral disc edema OD > OS Small hemorrhage OD
4	6	OD: −0.75 to 0.50 × 100 OS: plano to 0.50 × 090	OD: +0.75 − 0.50 × 105 OS: +0.75 − 0.75 × 090	15/13	11/10	Disc edema OD Choroidal folds OD
5	6	OD: −5.75 to 1.25 × 010 OS: −5.00 − 1.50 × 180	OD: −5.00 − 1.50 × 015 OS: −4.75 − 1.75 × 170	14/12	14/12	Normal
6	6	OD: +0.25 OS: +0.25 to 0.50 × 152	OD: +2.00 − 0.50 × 028 OS: +1.00 sph	14 OU	14 OU	Disc edema OD Cotton wool spot OS
7	6	OD: +1.25 sph OS: +1.25 sph	OD: +2.75 sph OS: +2.50 sph	16 OU	12/14	Disc edema OU Choroidal folds OD > OS

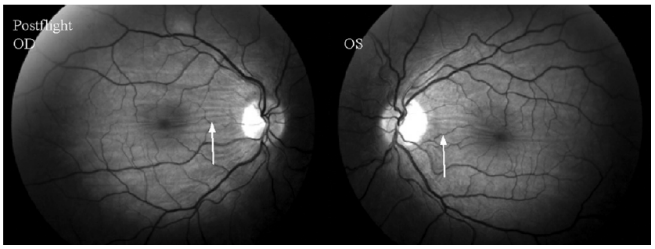
CSF = cerebral spinal fluid; MRI = magnetic resonance imaging; NFL = retinal nerve fiber layer; OCT = optical coherence tomography; OD = right; Disc edema was graded with the modified Frisén scale.

Table 2. Reported In-Flight Subjective Visual Changes and Postflight Refraction Changes of National Aeronautics and Space Administration Astronauts (Not Including International Partners) from 1989 to 2009

Description	Shuttle % (n)	ISS-Long Duration % (n)
Decreased DVA		
Total (n)	581	44
None	93.5 (543)	88.1 (39)
Mild	5.7 (33)	2.4 (1)
Moderate	0.9 (5)	4.8 (2)
Severe	0 (0)	4.8 (2)
Decreased NVA		
Total (n)	581	44
None	76.7 (448)	52.3 (23)
Mild	17.6 (103)	13.6 (6)
Moderate	5.5 (32)	27.3 (12)
Severe	0.2 (1)	6.8 (3)
Refraction change		
Total (n)	587	44
None	88.9 (522)	65.9 (29)
Mild	9.2 (54)	25.0 (11)
Moderate	1.9 (11)	2.3 (1)
Severe	0 (0)	6.8 (3)

DVA = distance visual acuity; ISS = International Space Station; NVA = near visual acuity.
Source: Lifetime Surveillance of Astronaut Health (LSAH) Program, NASA Johnson Space Center.

Figure 3: Choroidal folds in macula (arrows) OU (with permission from Ophthalmology 2011;118:2058-69.).



DISCUSSION

Although optic disc edema, globe flattening, choroidal folds, and hyperopic shifts have been reported in terrestrial IIH, the neuro-ophthalmic findings in our long duration space flyers at NASA seem to have unique and somewhat perplexing clinical and radiographic differences when compared with IIH.[1-12] First, our affected space flyers do not report the typical and classic symptoms of increased ICP seen in terrestrial IIH (e.g., headache, pulse synchronous tinnitus, or diplopia).[1] Second, although choroidal folds and hyperopic shifts are sometimes seen in terrestrial IIH, these findings seem to be a more common finding in our returning astronauts. Third, distal retinal CWS are also not a typical component of IIH and yet they are present in our cohort. Finally, although several reports have described the ultrasonography, OCT, MRI and CT scan findings in IIH that include flattening of the posterior globe and CSF enlargement of the subarachnoid space (SAS) around the ON sheath these structural findings seem more

pronounced (especially relative to the lack of symptoms) in our astronauts than in typical IIH.[3-5, 8, 10, 13] In IIH, the elevated subarachnoid CSF pressure caused by intracranial hypertension is believed to be directly transmitted from the intracranial compartment to the intraorbital compartments through the perioptic SASs.[8, 11] This increased ICP causes a distension of the ON sheaths and secondary stasis of axoplasmic flow leading to axonal swelling and resultant bilateral optic disc edema, which we call papilledema on Earth.[8, 12]

It remains unclear whether the optic disc edema seen in our astronauts after long duration space flight actually represents true papilledema or not. LP OP (admittedly performed days to weeks after return to Earth) have been borderline high but uniformly unimpressive for elevated ICP that we typically see in IIH. Elevated intrasheath CSF pressure is thought to cause the subarachnoid compartment to exert an anterior force that indents the posterior sclera resulting in posterior globe flattening, redundancy and folding of the choroid, and axial shortening with a secondary hyperopic shift. This CSF fluid in the optic nerve sheath may account for the radiographic findings of both terrestrial IIH and the findings in our astronauts.

Since the end of the US space shuttle program, NASA astronauts must now make the return to Earth from the ISS via the Russian Soyuz. This return in Kazakhstan (in the former Union of Soviet Socialists Republics (USSR)) makes the political and operational logistics for measuring OP in our astronauts immediately upon landing or even within a few days more difficult. Thus, when NASA physicians have been able to perform an LP it is often delayed to well beyond the return date. We have reported some elevated OP measurements of 28.5 and 28 cm H2O at 57 days and 12 days, respectively, in some astronauts after returning to Earth. Although these OPs were only mildly elevated, these LP results could represent the downslope of a CSF pressure spike that may have existed during microgravity exposure on ISS. It should be noted that we have no experience with and very limited capability for performing an LP in space.

The possible mechanisms of an IIH-like syndrome in our astronauts may involve a rise in cephalad venous pressure brought about by microgravity fluid shifts. Prior head-down and microgravity studies have documented that cerebral arterial diameter and blood flow velocity are autoregulated and do not change significantly during space flight[14, 15] but microgravity fluid shifts have been documented to cause jugular vein distension,[16–19] possibly implicating cerebral venous congestion as a mechanism. The traditional understanding of ICP regulation on Earth assumes that CSF is largely produced in the choroid plexus and drainage depends on the pressure difference between the CSF and the venous system.[20–22] Perhaps venous stasis in the head and neck (valveless veins as opposed to valves in the lower extremity veins preventing flow against gravity), produced by cephalad fluid shifts during space flight, might be a cause of impairment of CSF outflow, lymphatic outflow, or cerebral venous outflow reduction or congestion which could increase ICP.[23]

Another alternate hypothesis is that the rate of CSF formation and absorption (outflow) is a balance between hyperosmolar plasma in high pressure capillaries, and the subsequent absorption of the formed hypo-osmolar interstitial fluid by the low-pressure venules that are in anatomic proximity to the high-pressure capillaries.[1, 24] Thus, in a microgravity environment interstitial venous stasis at the level of low pressure CSF venules and a subsequent decrease in the osmotic drive toward absorption may occur.

Yet, another possible explanation of these findings is that the ON head edema may not be ICP related papilledema. Instead it may be that the intraocular and intraorbital findings are the result of localized CSF events occurring at the level of the intraorbital ON with or without a rise in CSF pressure in the entire CSF system. This might explain the lack of significantly higher ICP on the LPs that have been performed to date and also the lack of typical symptoms of increased ICP in our astronauts as compared with terrestrial IIH. The OP is assumed to be equal throughout the CSF system but this may not necessarily be the case. In addition, impaired exchange of fluid between the intracranial CSF and that in the SAS of the ON has been proposed as a possible mechanism to explain persistent papilledema and visual loss in patients with terrestrial IIH despite a functioning lumboperitoneal shunt (LPS) and also might be the explanation for "normal or near normal" OP in some patients who clearly have clinical IIH on Earth.[27–29] In the past, clinicians (including me) blamed these "normal" OPs on "improper" LP technique or "multiple sticks" that produced artifactually lower ICP. In some of these cases of IIH, bolt 24 hour ICP measurements confirmed elevated ICP despite prior normal OP measurements using LP.

The role of CSF stasis rather than elevation of ICP is also an intriguing hypothesis. It has been suggested that CSF is constantly produced and absorbed in the entire CSF system as a consequence of filtration and reabsorption of water volume through the capillary walls into the surrounding brain tissue.[24] This implies that the CSF exchange between each portion of the CSF system and the surrounding tissue may depend on pathophysiologic conditions that predominate locally within those compartments.[24] Animal studies have also documented a potential role of lymphatic drainage of CSF via the ethmoidal lymphatic system[30] and there may be analogous lymphatic drainage pathway in the dura of the CSF outflow pathway of the optic nerve in the orbit.[27] We have also seen impaired olfactory function in terrestrial IIH and in the head down tilt position (perhaps analogous to the cephalad fluid shift seen in our astronauts) and this might support the hypothesis

of a role for lymphatic drainage outflow abnormalities at the level of the olfactory system and cribiform plate.[31] Thus, these orbital ON lymphatic drainage systems may be affected by initial cephalad directed flow and then persistent microgravity exposure could lead to secondary lymph stasis, which could produce increase in ON sheath pressures within the unique cul de sac–like anatomically closed system. Our neuro-ophthalmology colleagues, Dr. Killer et al have proposed such a theory of a terrestrial IIH compartment syndrome with a bottleneck in CSF passage between the orbit and optic canal and we believe this to be a compelling hypothesis for the findings that we see in our astronaut cohort.[27]

Although theoretically ocular hypotony (i.e., low IOP) could produce similar findings to our cases (e.g., choroidal folds and optic disc edema) we do not believe that hypotony is at play in our astronauts. Although there is an initial spike in IOP on exposure to microgravity this is followed by a decrease in IOP over a period of days.[31] No long-term studies of IOP have been performed in microgravity to document specific trends but we have not found any evidence of low or high IOP in our astronauts. Head-down bed rest studies suggest that the initial spike in IOP is followed by a leveling[32] or lowering[33, 34] of IOP over a period of days. The initial spike in IOP supports the hypothesis that there is choroidal expansion brought about by cephalad fluid shifts.[32,35] The subsequent decrease in IOP after the initial IOP spike may be the result of a compensatory decrease in aqueous volume. However, we have not seen any support for IOP as the causative factor in microgravity/space flight related optic disc edema.[32, 37, 38]

Likewise, the etiology of the hyperopic shift supports the cephalad fluid shift hypothesis. The phenomenon of hyperopic shift is so common that NASA astronauts over the age of 40 years are routinely offered the use of plus lens "Space Anticipation Glasses" preflight should they experience a hyperopic shift during the mission. The hyperopic shift usually occurs after weeks or months in space, has a gradual onset, is variable in magnitude, and strangely may persist for months to years after return to the 1-G Earth environment. Although one long-duration, head-down study documented a decrease in near visual acuity after 4 to 5 days of head-down tilt,[39] another similar study noted no visual changes.[40] As postulated previously, choroidal expansion on top of the normal aging related presbyopia process in those flyers over age 40 years may lead to a progressive shortening of the axial length that could theoretically cause a hyperopic shift.[41] Although changes in corneal refractive power after exposure to changes in atmospheric pressure and oxygen partial pressure could be a possible mechanism considerable prior work has shown that normal, non-post-refractive surgery corneas are not subject to refractive changes during exposure to changing environmental conditions of spaceflight.[42-44] Likewise, we do not believe that intraocular fluid shifts are producing any lenticular changes as the etiology for the hyperopic shift.

Instead, we hypothesize that choroidal expansion at least partially accounts for the hyperopic shift. The spongy, highly vascular choroid is normally approximately 0.3 mm in thickness; is drained by the vortex veins; and is likely sensitive to impeded outflow produced by microgravity and cephalad fluid shifts. Choroidal volume changes in microgravity may also be responsible for the abrupt increase in IOP (within 30 seconds) in orbital and KC-135 parabolic flights as well as head-down studies.[31, 32, 35] The cephalad fluid shift could also cause venous congestion in the neck and head that might lead to a rise in vortex vein pressure[32, 35] and perhaps decreased choroidal drainage and stagnation or pooling of blood in the choroid.[46]. Choroidal vasculature alterations have been reported in highly myopic eyes[47] on Earth. A shortening of the distance between the macula and the lens of 0.33-mm anteriorly at the macula would lead to a 1-D shift toward hyperopia. For patients with permanent refractive error change, this choroidal pooling may gradually expand the delicate collagen lamella of the choroid beyond its normal anatomic structural boundaries such that the choroid becomes permanently distended even on return to the 1-G environment and in the presence of normal venous backpressure. The choroidal folds that we see might be the structural marker of this change. Newell hypothesized that visible choroid folds may occur as a result of a combination of variable anatomic attachments of the choroid to Bruch's membrane and some factor that causes congestion in the choriocapillaris.[48]

Even more intriguing, unilateral CWS have been noted (n=3 astronauts) after exposure to extended microgravity. CWS are thought to be accumulations of cytoplasmic debris caused by focal obstruction of orthograde and or retrograde axoplasmic transport[29] and they may leave a permanent retinal defect[49, 50] and are thought to reflect precapillary arteriolar closure.[50, 51] Although CWS are nonspecific, they are well known to occur in a number of conditions including diabetes mellitus, HIV retinopathy, Purtscher retinopathy, high-altitude retinopathy, and hypertensive retinopathy.[52-56] None of these clinical conditions offer insight into why these findings occur in our astronauts but it has been postulated that perhaps local asymmetric microgravity related changes in CSF flow within the intraorbital portion of the ON may lead to a biochemically altered CSF that may cause a metabolic toxicity to the ON and set the stage for focal arteriolar closure in the retina. The role of radiation exposure including cosmic rays in space or during extravehicular activity outside of the ISS remains unknown and the CWS may not be directly related to the other neuro-ophthalmic findings seen in our astronauts.

Recently we described an astronaut with two long-duration (6 months) exposures to microgravity. Before and after his first long-duration space flight, he underwent complete eye examination, including fundus photography. Before and after his second flight, 9 years later, he underwent preflight fundus photography, OCT, ocular ultrasonography, brain

MRI and then in-flight fundus photography and ultrasound. After his first long-duration mission, the astronaut was documented to have eye findings limited to unilateral choroidal folds and a single CWS. During the subsequent 6-month mission, he developed more widespread choroidal folds and new onset of optic disc edema in the same eye. This bothersome finding suggests that the effects of repeated exposure to space flight and microgravity might be cumulative.[57]

Finally, the findings in our astronauts might also have some bearing on further understanding of the pathogenesis or treatment of terrestrial IIH and another condition with cephalad fluid shift as a risk factor, ischemic optic neuropathy (ION) after spine surgery. Spine surgery in the prone position produces a similar morphologic change in the head, face, and neck (postoperative facial edema) as the cephalad fluid shift experienced by our astronauts. In terrestrial patients who have lost vision due to ION after spine surgery the impaired venous return in the orbit has been hypothesized as a potential risk factor. Likewise in our head tilt down studies similar hypotheses about cephalad fluid shift as a pathogenic mechanism have been suggested. This raises additional questions about possible pathogenic mechanisms for optic disc edema in terrestrial causes of disc edema without elevated ICP. Further study is necessary to determine the etiology for the findings in our long duration space flyers. It is hoped that we will be able to document a single or predominant mechanism and propose specific countermeasures in preparation for a return to longer duration space flight including the possibility of future missions to ISS or to asteroids, a return trip to the moon, or perhaps a future manned mission to the planet Mars.

CME ANSWERS

1. b
2. a
3. a
4 b

DISCLOSURES

* Although Dr. Lee has served as a neuro-ophthalmology consultant for NASA and the contents of this specific manuscript were vetted and reviewed by NASA, the views and opinions represented here are those of the author as well as content already within the public domain and thus do not necessarily represent the views of the space agency (NASA) or the United States government.

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AUTHOR REFERENCES

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PLATFORM SESSION I

Monday, February 23, 2015 ● 5:00 p.m. - 7:00 p.m.
Moderators: Laura Balcer, MD, MSCE & Beau Bruce, MD, PhD

Monday, February 23, 5:00 - 5:15 p.m.

Lipocalin-2 Expression in Demyelinating Optic Neuritis of Experimental Autoimmune Encephalomyelitis Model and their Pivotal Role

Bo Young Chun[1], Jong-Heon Kim[2], Youngpyo Nam[2], Seungwoo Han[3], Kyoungho Suk[2]

[1]Department of ophthalmology, Kyungpook National University Hospital, Daegu, Korea, [2]Department of Pharmacology, Brain science and engineering institute, Kyungpook National University School of Medicine, Daegu, Korea, [3]Division of Rheumatology, Department of Internal Medicine, Daegu Fatima Hospital, Daegu, Korea

Introduction:
The purpose of this study is to determine the role of lipocalin 2 (LCN2) in experimental autoimmune optic neuritis (EAON) model. We compared degrees of neuro-inflammation between LCN2 knock out (KO) mice and wild type (WT) littermates by histological analysis of demyelination, reactive astrocytosis and proliferation of microglia.

Methods:
EAON was induced by subcutaneous immunization with emulsified mixture of myelin oligodendrocyte glycoprotein (MOG35-55) peptide in LCN2 KO mice and WT littermates. Mice were examined daily and scored for disease severity. At post-immunization day 17, mice were killed and their eyes were enucleated. Comparison of degrees of demyelination, activated neuroglial cells and profiling of cytokines and chemokines between LCN2 KO mice and WT littermates following EAON induction was done by immunohistochemistry and real-time PCR respectively.

Results:
EAON was well induced in WT littermates, however, LCN2 KO mice were resistant to the EAON induction. The expression of LCN2 was notably increased by reactive astrocytosis in the optic nerve of WT littermates. A remarkable reduction of demyelination and astrocytosis of the optic nerve was demonstrated in the LCN2 KO mice. Restrained microglial activation compared to WT littermates was also observed in the optic nerve of LCN2 KO mice. LCN2 KO mice showed a markedly reduced M1-related gene expression associated with an attenuated toll-like receptor signaling.

Conclusions:
In this study, the significant induction of LCN2 expression was observed in the optic nerve of the EAON mice compared to naive mice and was mostly detected in reactive astrocytosis. These results imply that LCN2 may be a critical mediator of autoimmue inflammation in EAON.

References: None.

Keywords: Experimental Autoimmune Optic Neuritis, Lipocalin 2, Demyelination, Reactive Astrocytosis, Microglial Activation

Financial Disclosures: The authors had no disclosures.

Grant Support: Supported by the 2012 Cheil-nammyung Foundation Research Fund

Monday, February 23, 5:15 - 5:30 p.m.

Preliminary Safety and Tolerability Results Of A Recombinant Adeno-Associated Viral Vector Serotype 2 (rAAV2/2) Containing The Human Wild-Type Mitochondrial NADH Dehydrogenase 4 (*ND4*) Gene, In Patients With Leber Hereditary Optic Neuropathy Due To The G11778A Mitochondrial DNA Mutation

Catherine Vignal [1,2], Géraldine Honnet [3], Anne Galy [4], Nitza Thomasson [4], Marisol Corral Debrinsky [5], Scott Uretsky [4], Jean-Philippe Combal [4], Serge Fitoussi [4], Jose A. Sahel[1,5]

[1]CHNO, Paris, France, [2]Fondation Rotschild, Paris, France, [3]Genethon, Evry, France, [4]GenSight-Biologics, Paris, France, [5]Institut de la Vision, Paris, France

Introduction:
Our goal is to report the results of a first-in-man safety trial of gene therapy in patients with Leber Hereditary Optic Neuropathy (LHON).

Methods:
Two cohorts each comprised of 3 patients with the G11778A ND4 mutation and severe visual loss (≤20/200) received ascending doses of intravitreal (IVT) recombinant adeno-associated viral vector (rAAV2/2) containing the wild-type ND4 gene.

Baseline general and ophthalmic examinations, laboratory and EKG parameters were obtained. Paracentesis (6/6) and intra-ocular pressure (IOP) lowering treatment (5/6) preceded IVT. In-patient observation for 24-hours post-IVT ensued with IOP measurement at 0.5, 2, 4, and 24-hours. Follow-up visits including vital signs, IOP, ophthalmic examinations, laboratory evaluation, immune-monitoring and assessment of adverse events (AE, SAE) are conducted at 0.5, 1, 2, 4, 8, 12, 24, 36 and 48-weeks post-IVT. Bio-dissemination in blood, urine and tears were evaluated for two weeks post-IVT. The first cohort received 9E+09vg/eye. A data safety monitoring board evaluated the safety of this dose before escalation to 3E+10vg/eye in the second cohort.

Results:
8 LHON patients were screened, 6 were included (time since vision loss 7.5-254 months). No SAE or treatment-related systemic AE occurred. 5/6 patients had non-sustained, topical-treatment responsive, elevated IOP; 3/5 patients within 4-hours post-IVT and 2/5 patients at 2-weeks post-IVT [elevated IOP range: 23-34mmHg]. 3/6 patients experienced mild anterior chamber inflammation between 4 and 8 weeks post-IVT requiring topical treatment in 2/3. Visual acuity remained unchanged.

Conclusions:
Overall safety and tolerability of a single IVT injection of rAAV2/2 was good. Post-IVT IOP elevation (mechanistic) and mild ocular inflammation (pre-clinical studies) occurred as expected; both were mild and reversible with local treatment. These results allowed for dose escalation necessary to identify the highest tolerated dose of IVT-rAAV2/2 that will be used in our upcoming study of clinical efficacy in more recently affected LHON G11778A patients.

References: None.

Keywords: Leber Hereditary Optic Neuropathy, Mitochondrial Genetic Disorder, Gene Therapy, Adeno Associated Viral Vector, Safety and Tolerability Trial

Financial Disclosures: Catherine Vignal: Consultant for Gensight-Biologics. Anne Galy, Nitza Thomasson,Scott Uretsky, Jean-Philippe Combal and Serge Fitoussi: Gensight-Biologics employees. Jose Alain Sahel: Gensight-Biologics Share Holder and Consultant

Grant Support: None.

Monday, February 23, 5:30 - 5:45 p.m.

Clinical Features of OPA1-Related Optic Neuropathy: A Focus on Genetic Modifiers

Eric D Gaier[1,2], Katherine Boudreault[3], Isao Nakata[3], Maria Janessian[2], Elizabeth Delbono[2,4], Simmons Lessell[3,5], Dean Cestari[3,5], Janey L Wiggs[1,2,4,5], Joseph F Rizzo[3,5]

[1]Department of Ophthalmology, Boston, MA, USA, [2]Howe Laboratory, Boston, MA, USA, [3]Department of Neuro-Ophthalmology, Boston, MA, USA, [4]Department of Glaucoma, Boston, MA, USA, [5]Harvard Medical School, Boston, MA, USA

Introduction:
Dominant optic atrophy (DOA) is the most common hereditary optic neuropathy, and known mutations in *OPA1* account for 40-60% of cases. Previous studies investigating clinical features in DOA patients with *OPA1* mutations have been limited to a few mutations and few include *OPA1* copy number variant (CNV) analyses or mitochondrial genomic analyses. We hypothesized that some clinical presentations depend upon both *OPA1* status and the background mitochondrial haplogroup.

Methods:
This is an updated retrospective case series of 86 patients with bilateral optic atrophy referred for genetic testing at a tertiary care center using selective exon capture followed by next generation sequencing for *OPA1* and the mitochondrial genome. Patients were also screened for CNVs involving *OPA1* using Multiplex Ligation-dependent Probe Amplification (MLPA) analysis and array CGH (comparative genomic hybridization). Mitochondrial haplogroups were defined by mitochondrial genome analysis. Clinical features, including visual acuity, Ishihara testing, automated visual field testing and dilated funduscopy, were analyzed by *OPA1* mutation and mitochondrial haplogroups.

Results:
Twenty nine cases were found to have *OPA1* disease-causing mutations including 4 novel sequence mutations and 6 CNVs. *OPA1*-positive patients were younger at symptom onset but had less severe visual field deficits than *OPA1*-negative patients. Four of 21 *OPA1*-positive cases had mitochondrial haplogroup “J”, compared to 4/34 *OPA1*-negative cases. Three of those four with *OPA1* mutations and haplotype “J” had extraocular neurological symptoms, consistent with a DOA+ phenotype.

Conclusions:
This is the first study to include CNV testing and mitochondrial group analyses in clinical studies of DOA. Mitochondrial haplogroup “J” may interact with *OPA1* genotype affecting DOA phenotype although further study of larger datasets will be necessary to confirm this. By continuing to study the interactions between genetic and clinical features of DOA, we will expand our knowledge of DOA pathophysiology to guide diagnostic decision-making and testing of potential disease-modifying treatments.

References: None.

Keywords: Genetic Disease, Optic Neuropathy, Visual Fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Monday, February 23, 5:45 - 6:00 p.m.

Cytokine Mechanisms in Giant Cell Arteritis

Brian R Younge[1], Gene Hunder[2], Cornelia M Weyand[3]

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Introduction:
In a series of 41 patients with pathologically corfirmed giant cell arteritis (GCA) cytokine studies were undertaken from both tissue and blood samples to determine T-cell mechanisms prior to and after treatment began.

Methods:
Cytokine analysis was done on both tissue and blood samples by culture and flow cytometry to determine the major mediators of inflammation and the response of the Th1 and Th17 cells to treatment. Groups of 10 patients were studied after treatment was begun at intervals of 3, 6, 9 and 12 months with repeat biopsy (the other side) and blood studies.

Results:
Pathologic reversal of inflammatory response takes 9-12 months or sometimes longer in 20 percent of the patients studied. The CD4 T cells are the primary mediators of the inflammatory response. Th1 cells that produce interferon gamma, among other cytokines and Th17 cells that produce interleukine-17 among other cytockines are markedly upregulated in active GCA. Steroids only affect the Th17 line of cells and their respective cytokines, but do not affect the Th1 cells nor their cytokines.

Conclusions:
The rapid clinical response to steroid treatment in GCA is largely explained by the sharp reduction of Th17 cells and their respective cytokines. Persistence of the disease both pathologically and biochemically for several months may be explained by the failure of Th1 cells to respond to steroids. Targetting specific cytokines in future holds promise for improved treatments that may improve the biochemical response and reduce the need for prolonged steroids.

References:
1. Deng J, Younge B, Olshen R, Goronzy J and Weyand C. The17 and Th1-cell responses in giant cell arteritis. Circulation. Feb 23, 2010

Keywords: Cytokines, Th1 Cells, Th17 Cells, Giant Cell Arteritis

Financial Disclosures: The authors had no disclosures.

Grant Support: Research to Prevent Blindness

Monday, February 23, 6:00 - 6:15 p.m.

Retina Examination with Curcumin for Tau Tangles and Beta Amyloid in Alzheimer's Disease

Umur A. Kayabasi[1], Robert C. Sergott[2]

[1]World Eye Hospital, Istanbul, Turkey, [2]Wills Eye Hospital, Philadelphia, PA, USA

Introduction:
Our aim was to detect tau tangles and beta amyloid plaques in retina for the early diagnosis of Alzheimer's Disease (AD).

Methods:
We examined 30 patients with mild cognitive insufficiency (MCI) and 15 age-matched healthy controls. Retina was examined by fundus autofluorescein (FAF) and optical scanning tomography (OCT) tests. FAF detected lipofuscin which contained beta amyloid in AD and the layer of the accumulations was detected by OCT. Patients who had retinal lesions were given curcumin with proprietary curcumin-phosphatidylcholine phytosome complex for three days and FAF-OCT tests were repeated. All the suspicious cases for AD were sent for brain PET- CT imaging.

Results:
In 22 patients, tau tangles and plaques were observed on OCT. Curcumin stained the retinal lesions in all 22 patients. Since curcumin binded to beta amyloid, it was proven that the plaques were related to AD. All 22 patients had brain PET- CT results consistent with bilateral temporo-parietal hypometabolism. Tau tangles and curcumin staining was not seen in the control group.

Conclusions:
Our study suggests that tau tangles and beta amyloid plaques can be seen in retina in an easier way and probably earlier than the brain changes in AD. This is the first study that reveals tau tangles and beta amyloid imagings in alive AD patients with FDA approved devices.

References: None.

Keywords: Tau Tangles, Beta Amyloid, OCT, FAF, Alzheimer's Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Monday, February 23, 6:15 - 6:30 p.m.

Role of the Optic Canal Size on the Severity of Papilledema and Visual Outcome in Idiopathic Intracranial Hypertension (IIH)

Samuel Bidot[1], Lindsay Clough[1], Amit M Saindane[2], Nancy J Newman[1,3,4], Valerie Biousse[1,3], Beau B Bruce[1,3,5]

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Introduction:
High-grade papilledema is a risk factor for visual loss in IIH, but factors contributing to the severity of papilledema remain unclear. We recently found an association between larger bony optic canal size and worse papilledema among IIH patients with highly asymmetric papilledema.[1] Our goal was to confirm these results in a large sample of IIH patients.

Methods:
Retrospective review of definite IIH patients with 1-mm isotropic volumetric pre- or post-contrast T1-weighted brain MRI allowing for optic canal measurement seen between 2009 and 2014. Clinical characteristics/HVF results were reviewed; papilledema was graded according to the modified Frisen scale[2] on fundus photographs. Cross-sectional area of the optic canals was measured independently 3 times by two readers and averaged for each canal. For each patient, we included the optic canal measurement on the eye with worst papilledema or on the right eye in case of symmetric papilledema. Logistic regression modeling was applied.

Results:
69 IIH patients were included [mean age: 33; 91% women; 65% black; 94% with BMI≥25]. The inter-grader agreement for optic canal measurement was strong (intraclass correlation: 0.77 [95%CI: 0.69-0.83]). Mean±SD optic canal size was 22.9±5mm^2. Controlling for age, gender, BMI, race, and CSF opening pressure, each mm^2 increase in canal size was associated with a 0.37 dB reduction in automated perimetry mean deviation (p=0.04); this was likely mediated by the increased odds of grade 4-5 papilledema or optic atrophy in patients with larger canals (OR: 1.24 [95%CI: 1.06-1.46; p=0.007] for grade 4-5 papilledema or atrophy vs. grade <4 papilledema per mm^2 increase in canal size).[3]

Conclusions:
Poorer visual field outcomes and severe papilledema or secondary optic atrophy were associated with a larger optic canal. This suggests that larger optic canal size may be a factor facilitating transmission of CSF pressure to the optic disc, leading to more severe papilledema with resultant worse visual loss.

References:
1. Bidot S, Bruce BB, Saindane AM, Newman NJ, Biousse V. Asymmetric papilledema in idiopathic intracranial hypertension. J Neuroophthalmol (In press)

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Keywords: Idiopathic Intracranial Hypertension, Neuroimaging, Optic Canal, Papilledema

Financial Disclosures: The authors had no disclosures.

Grant Support: Supported in part by an unrestricted departmental grant (Department of Ophthalmology) from Research to Prevent Blindness, Inc., New York, and by NIH/NEI core grant P30-EY06360 (Department of Ophthalmology). Dr. Bidot receives research support from Berthe Fouassier Foundation (Paris, France) and Philippe Foundation (New York, New York, USA). Dr. Bruce receives research support from the NIH/NEI (K23-EY019341).

Monday, February 23, 6:30 - 6:45 p.m.

A New Pupil Light Reflex Test for Detecting Optic Neuropathy Independent of the Fellow Eye Which Highly Correlates to Visual Field Volume

Randy H Kardon[1,2], Susan Anderson[1,2], Jade Grimm[1], Matt Thurtell[1,2], Michael Wall[1,2], Pieter Poolman[1,2]

[1]University of Iowa College of Medicine/Ophthalmology and Visual Sciences, Iowa City, IA, USA, [2]Iowa City VA Medical Center and the Center of Excellence for the Prevention and Treatment of Visual Loss, Iowa City, IA, USA

Introduction:
Our purpose was to develop and test a new paradigm for detecting optic nerve disease in one eye, independent of the fellow eye, so that patients with bilateral involvement can be diagnosed and monitored using objective pupil responses. We also sought to determine which stimulus light condition and pupil response parameter (transient vs. sustained contraction) would provide the greatest difference between normal and abnormal eyes and the highest correlation with visual field sensitivity.

Methods:
39 patients seen in the neuro-ophthalmology clinic and 44 normal subjects were prospectively tested by computerized pupillometry (NeurOptics DP2000, Irvine, CA) using a 1 second red or blue light stimulus at 1 lux and 400 lux. The percent pupil contraction from baseline pre-stimulus size was calculated for the transient, initial response to the light stimulus and the sustained pupil contraction at 6 seconds following offset of light. Visual fields were obtained using standard kinetic Goldmann perimetry and the volume of visual field sensitivity was determined and correlated with pupil responses.

Results:
We found the greatest statistically significant separation between eyes of normal subjects vs. those with optic neuropathy occurred with the transient pupil contraction using the 1 second, 400 lux blue light, compared to the sustained post-illumination contraction. In response to 400 lux blue light, the transient contraction gave the highest correlation with volume visual field (r=0.85) compared to the sustained contraction (r=0.52).

Conclusions:
The transient pupil contraction to bright blue light provides an objective, easily recordable reflex, which correlates well with visual field sensitivity. Under these stimulus conditions, both photoreceptor input and direct activation of photosensitive retinal ganglion cells summate the visual field input to the brain. This approach provides a clinical tool for estimating visual dysfunction that has important applications for remote diagnosis and monitoring of vision threatening disorders.

References: None.

Keywords: Pupils, Optic Neuropathy, Visual Field

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Grant Support: Funding (grants) from NEI R009040554 R01 EY018853 Funding (grants) Department of Defense TATRC Funding (grants) VA Rehabilitation Research and Development

Monday, February 23, 6:45 - 7:00 p.m.

Color Vision Deficits in Multiple Sclerosis

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Introduction:
Color vision deficits have been reported in multiple sclerosis (MS) in the absence of optic neuritis (ON). Demyelination of the optic nerve in ON probably causes color-vision deficits by affecting the parvocellular-Red/Green (PC/RG) and koniocellular-Bue/Yellow (KC/BY) pathways. The evidence for selective deficits in PC/RG versus KC/BY pathways, however, is inconclusive. Moreover, the mechanism of color vision deficit in MS without ON demyelination is unclear. In this study we investigate color vision deficits in early versus late MS in the PC/RG versus KC/BY pathways.

Methods:
Participants were either early-MS (<1 year after diagnosis, 16 subjects) or late-MS (5-10 years after diagnosis, 15 subjects) with no history of ON. Twenty controls completed the study. Contrast detection thresholds were measured for Achromatic, RG and BY sinewave gratings with spatial frequencies (SF) of 0.5 and 2 cycles-per-degree (cpd) using an orientation discrimination two-alternative forced-choice staircase task.

Results:
We found a significant difference ($p<0.05$) in RG contrast thresholds at the low SF (0.5 cpd) in early- versus late-MS (mean=2.7 +/_ 0.15 and 3.9 +/_ 0.16, respectively). Early-MS subjects were similar to the controls. At 2 cpd, mean BY contrast thresholds in early- and late-MS groups were significantly higher than in the controls (BY threshold=5.85% (controls), 9.79 %(early-MS), and 9.04% (late-MS)).

Conclusions:
Here we report for the first time that color contrast sensitivity for RG versus BY color vision is differentially affected in early- versus late-MS. The BY axis is affected in both conditions but the RG axis is affected only in late-MS. These findings are important because 1. BY versus RG color tests may be used in differentiating MS chronicity, 2. Help understand the mechanism of color sensitive pathway involvement in MS in the absence of demyelination, and 3. Show that standard Ishihara color tests are not sufficient in testing MS patients as they exclude the BY axis.

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Keywords: Multiple Sclerosis, Color Vision, Parvocellular, Koniocellular

Financial Disclosures: The authors had no disclosures.

Grant Support: Manitoba Medical Service Foundation

North American Neuro-Ophthalmology Society

41st Annual Meeting

February 21-26, 2015
Hotel del Coronado • San Diego, California

Program Schedule

TUESDAY, FEBRUARY 24, 2015

6:00 a.m. – 6:45 a.m.	**Yoga Class**	**Spreckels Complex**
6:30 a.m. – 12:30 p.m.	**Registration**	**Ballroom Foyer**
6:30 a.m. – 7:30 a.m.	**Breakfast**	**Crown Room**
6:30 a.m. – 12:15 p.m.	**Exhibits**	**Crown Room**
6:30 a.m. – 7:30 a.m.	**JNO Editorial Board Meeting**	**Hanover Room**
7:00 a.m. – 7:30 a.m.	**YONO Committee Meeting**	**Garden Room**
7:00 a.m. – 7:30 a.m.	**CME Committee Meeting**	**Executive Room**
7:30 a.m. – 12:00 p.m.	**SCIENTIFIC PLATFORM PRESENTATIONS: SESSION II [3.75 CME]**	**Ballroom**
9:15 a.m. – 9:30 a.m.	**Update: The Journal of Neuro-Ophthalmology** *Lanning Kline, MD, Editor-in-Chief & Jason Roberts, PhD, Managing Editor*	
9:30 a.m. – 10:00 a.m.	**Coffee Break**	**Crown Room**
12:15 p.m. – 4:15 p.m.	**The USS Midway Tour**	**Depart from Orange Avenue Lawn**
12:15 p.m. – 4:15 p.m.	**San Diego Zoo Excursion**	**Depart from Orange Avenue Lawn**
12:15p.m. – 5:15 p.m.	**Balboa Park/Museums Excursion**	**Depart from Orange Avenue Lawn**
12:15 p.m. – 5:00 p.m.	**NANOS Board Meeting**	**Windsor Room**
6:00 p.m. – 9:30 p.m.	**POSTER SESSION**	**Grande Ballroom**

Guests are welcome. Event is complimentary for attendees but guests must purchase tickets. Tickets are available for purchase for $50 per person.

PLATFORM SESSION II

Tuesday, February 24, 2015 ● 7:30 a.m. - 12:00 p.m.
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Moderators: Rudrani Banik, MD & Timothy McCulley, MD – after break

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Tuesday, February 24, 7:30 - 7:45 a.m.

Improvements in Binocular Summation after Strabismus Surgery

Stacy L Pineles[1], Joseph L Demer[1], Sherwin J Isenberg[1], Eileen E Birch[2], Federico Velez[1]

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Introduction:
Binocular summation (BiS), or improvement in vision using binocular vision compared to the better eye alone, is diminished in patients with strabismus. However, it is still not known how strabismus surgery affects BiS.

Methods:
Ninety-seven subjects recruited within one month before undergoing strabismus surgery underwent high and low contrast visual acuity testing binocularly and monocularly at pre-operative and two month post-operative visits. BiS was calculated for high contrast ETDRS and Sloan low contrast acuity (LCA) charts at 2.5% and 1.25% levels as the difference between the binocular score and that of the better eye. Pre-operative and post-operative values were compared.

Results:
There was a significant improvement in BiS at the two low contrast levels for all subjects, and for all contrast levels in the 75 patients in whom surgery successfully restored binocular alignment. For LCA, the proportion of subjects with BiS >5 letters post-operatively was almost twice that pre-operatively (16% to 30% and 11% to 21% for 2.5% and 1.25% contrast, respectively). Similarly, the proportion of subjects with binocular inhibition (binocular score worse by at least 5 letters than better eye score) was decreased post-operatively at all contrast levels (from 19% to 9% for 1.25% contrast). Twenty-eight percent of subjects experienced improvement in BiS scores post-operatively at the lowest contrast level.

Conclusions:
BiS scores improved post-operatively in most subjects undergoing strabismus surgery. This occurred most frequently at the lowest contrast level. Improved BiS represents a newly recognized functional benefit from surgical correction of strabismus, which is especially important in adults who were previously thought to achieve only psychosocial benefits.

References:
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Keywords: Binocular Summation, Strabismus, Strabismus Surgery, Binocularity

Financial Disclosures: The authors had no disclosures.

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Tuesday, February 24, 7:45 - 8:00 a.m.

A Novel Diagnostic Tool for Myasthenia Gravis: Ocular Vestibular Evoked Myogenic Potentials (oVEMP)

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Introduction:
Diagnosis of myasthenia gravis (MG) can be challenging, especially in patients with isolated ocular involvement, negative autoantibodies and absence of the characteristic decrement in repetitive nerve stimulation. Ocular vestibular evoked myogenic potentials (oVEMP) are a recently developed, non-invasive test that allows electromyographic registration of extraocular muscle activity. Originally, the test was designed to assess vestibular function. We adapted oVEMP to detect the decrement in extraocular muscles of MG patients.

Methods:
26 MG patients and 17 healthy controls participated. We applied vibration stimuli to the forehead and recorded activity of the inferior oblique eye muscle with two surface electrodes placed beneath the eyes. To identify the oVEMP parameters with the highest sensitivity and specificity, we evaluated the decrement over 10 stimulus repetitions at three different repetition rates (3Hz, 10Hz, 20Hz).

Results:
Mean age of MG patients and controls was 57±18 and 40±17 years, respectively. Mean disease duration was 43±57 months. All MG patients had ocular symptoms, including ptosis (n=26) and diplopia (n=20). Twelve patients (46%) had isolated ocular symptoms, 4 (15%) had additional bulbar weakness and 10 (39%) generalized muscle weakness. Repetitive stimulation at 20Hz appeared to yield the best differentiation between MG patients and controls. Specifically, we found a bilateral decrement of >15% between the 2nd and 9th stimulus in 15 MG patients (58%) but in none of the controls ($p<0.001$). Among the 12 patients with isolated ocular MG, 11 (92%) showed a decrement (7 (58%) bilaterally, 4 (33%) unilaterally).

Conclusions:
Preliminary data of our study suggest that the presence of an oVEMP decrement is sensitive for MG, especially for its isolated ocular form. Thus, oVEMP should be considered a promising, additional diagnostic tool in MG. This simple, non-invasive test can be implemented in any neuromuscular clinic.

References: None.

Keywords: Myasthenia Gravis, Ocular Vestibular Evoked Myogenic Potentials (oVEMP), Electromyography, Eye Muscle, Decrement

Financial Disclosures: The authors had no disclosures.

Grant Support: Forschungskredit of the University of Zurich.

Tuesday, February 24, 8:00 - 8:15 a.m.

Compartmentalization of Superior Oblique (SO) Muscle Function Has Implications for Superior Oblique Palsy

Joseph L. Demer[1,2,3,4], Robert A. Clark[1,2], Alan Le[1], Sun Y. Shin[1,5]

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Introduction:
Intramuscular innervation of horizontal rectus extraocular muscles is divided into inferior and superior divisions innervating non-overlapping compartments of parallel-oriented muscle and tendon fibers. Functional magnetic resonance imaging (MRI) has demonstrated differential contractile function of horizontal rectus compartments during vertical duction, convergence, and ocular counter-rolling, as well as selective neurogenic atrophy in superior compartment lateral rectus palsy. We sought evidence of compartmental specialization in the SO, suspecting that selective damage to one or the other compartment might underlie some of the variation in clinical presentations of SO palsy.

Methods:
Gross dissections and 3-dimensional reconstructions of the intramuscular trochlear nerve were performed in humans, monkeys, cows, and rabbits. Multipositional, surface coil MRI was performed in 14 normal volunteers during 1° prism-induced vertical fusional vergence, and in central gaze in 19 patients with SO palsy, evaluating contractility by quantitative analysis of differential compartmental volume changes.

Results:
External to the SO belly, the trochlear nerve bifurcates into medial and lateral divisions innervating non-overlapping groups of muscle fibers. Gross dissection demonstrates that the inferolateral SO compartment inserts posteriorly on the sclera for mainly vertical action, while the superomedial portion inserts anteriorly for mainly torsional action. Traction on muscle fibers in one cadaveric compartment was transmitted selectively to the corresponding region of the scleral insertion. In normal volunteers, these compartments contracted differently during vertical fusional vergence. Eight of 19 patients with SO palsy exhibited elongated SO cross sections on MRI suggestive of neurogenic atrophy thinning only one compartment, and exhibited strabismus patterns differing from those with generalized SO atrophy.

Conclusions:
The SO functions as two parallel muscles specialized for vertical vs. torsional effects, and having separate peripheral innervation differentially susceptible to trochlear nerve pathology. Variable patterns of differential compartmental impairment contribute to the wide spectrum variations in patterns of cyclovertical incomitance in SO palsy.

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Keywords: Superior Oblique Palsy, Extraocular Muscle, Hypertropia, Trochlear Nerve, Functional MRI of Etraocular Muscle

Financial Disclosures: The authors had no disclosures.

Grant Support: NIH grant EY08313.

Tuesday, February 24, 8:15 - 8:30 a.m.

Development of Audiovisual Integration in Children and Adults with Amblyopia

Agnes M.F. Wong[1,2,3], Cindy M. Narinesingh[1], Rana A. Raashid[1], Herbert C. Goltz[1,3]

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Introduction:
The McGurk effect is an audiovisual illusion that involves the concurrent presentation of a phoneme (auditory syllable) and an incongruent viseme (visual syllable). Adults with amblyopia show less susceptibility to this illusion than visually normal controls, suggesting a deficit in audiovisual integration. The present study investigated the developmental trajectory of audiovisual integration in both adults and children with amblyopia using the McGurk effect.

Methods:
Sixty-two participants with amblyopia (22 adults, 12 older children, 28 younger children) and 66 visually normal controls (25 adults, 17 older children, 24 younger children) viewed videos that combined phonemes and visemes, and were asked to report what they heard. Videos with both congruent (auditory and visual matching) and incongruent (auditory and visual not matching) stimuli were presented. Incorrect responses on incongruent trials correspond to a strong McGurk effect, indicating that the viseme influenced the phoneme (i.e., strong audiovisual integration).

Results:
Participants with amblyopia demonstrated a weaker McGurk effect than visually normal controls across all age groups. Effect strength increased with age for both amblyopic participants and controls. Both groups showed a similar response pattern to different speakers and syllables, but amblyopic participants consistently demonstrated a weaker effect.

Conclusions:
Amblyopia is associated with deficits in audiovisual integration in both children and adults. Our findings indicate that the deficits are not simply a delay in development of audiovisual integration in children with amblyopia; rather they represent permanent deficits that persist into adulthood.

References: None.

Keywords: Pediatric Neuro-Ophthalmology, Multisensory Integration, Amblyopia

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, February 24, 8:30 - 8:45 a.m.

Pitfalls in the Use of Stereopsis For the Diagnosis of Non-Organic Visual Loss

Kevin R. Sitko[1], Jason H. Peragallo[1,5], Samuel S. Bidot[1], Valerie Biousse[1,2], Nancy J. Newman[1,2,3], Beau B. Bruce[1,2,4]

Introduction:
Polarized vectogram stereoacuity testing is used to estimate visual acuity (VA) in the diagnosis of non-organic visual loss (NOVL),[1] but only predicts mean VA and doesn't account for normal inter-subject variability. These predictions were derived from optical degradation of VA in normal subjects and may not account for the variability seen in patients with neuro-ophthalmic pathologies included in the differential diagnosis of NOVL.[2,3]

Methods:
All patients presenting to our service between 4/25/2014 and 6/26/2014 underwent routine neuro-ophthalmic examination, including polarized vectogram stereoacuity measurements (Titmus). A compound Bayesian logit-lognormal model accounting for heteroskedasticity was used to determine 95% and 99% prediction intervals of the worse eye's near visual acuity (VA) based on stereoacuity. LogMAR acuity and log stereoacuity were analyzed.

Results:
Of 405 patients, 16 were excluded for missing stereoacuity or VA measurements, 3 for cognitive issues, 3 for suspected NOVL, and 92 for heterotropia or history of strabismus/amblyopia. Patients who correctly identified zero circles (34) were also excluded from the calculation. 257 subjects were analyzed [median age: 45-yo (range: 11-91); 184(72%) women; median worse-eye VA 20/25; median: 7 circles correct]. Stereoacuity was positively associated with VA: 9 circles correct (40 seconds of arc) indicated VA of at least 20/39 with 95% confidence and 20/79 with 99% confidence; 6 circles correct (80 seconds of arc): 20/61 and 20/178; and 4 circles correct (140 seconds of arc): 20/103 and 20/544, respectively.

Conclusions:
When fully accounting for individual variation and the full spectrum of neuro-ophthalmic diseases affecting VA, stereoacuity remains associated with VA, but commonly-used VA estimates based on stereoacuity overestimate VA. Our results more accurately predict minimum VA from polarized vectogram stereoacuity and should be preferentially used when evaluating patients with suspected non-organic visual loss. We demonstrate that polarized vectogram stereoacuity cannot establish definitively normal VA, and therefore can only suggest, but not establish, the diagnosis of NOVL.

References:
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2. Levy NS, and Glick EB. Stereoscopic perception and Snellen VA. Am J Ophthalmol 1974; 78: 722-724
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Keywords: Stereopsis, Non-organic, polarized stereogram, vectogram

Tuesday, February 24, 8:45 - 9:00 a.m.

Natural History of Ocular Myasthenia Gravis in 101 cases: Towards a Risk of Generalization ('ROG') Score.

Sui H. Wong[1,2,3], Aviva Petrie[4], Gordon T. Plant[1,2,3]

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Introduction:
There is currently no prognostic test to individualize prediction of Generalized Myasthenia Gravis (GMG) risk in patients who first present with ocular disease. Most studies that report risk factors are flawed by the mix of patients on immunosuppression. We aimed to create a prognostic score to predict the risk of GMG.

Methods:
Multi-centre retrospective cohort study of patients with OMG for minimum 3months, untreated with immunosuppression for minimum 2years or until GMG onset. Data analyzed by logistic regression to develop the predictive score for GMG at 2years.

Results:
101(57F) patients were included, with mean follow-up 8.4y(2-42) from disease onset. 31 developed GMG at median 1.31y(3.5mo-20.2y); 19 occurred within 2years. Univariable logistic regression analysis produced three significant predictors($p<0.10$); adjusted ORs in a multivariable logistic model (Chi-square $p=0.001$): seropositivity 5.63(95%CI,1.42-22.33); presence of one or more comorbidity 5.56(95%CI,0.66-46.62); thymic hyperplasia 6.66(95%CI,0.45-98.01). Prognostic score derived from the coefficients of the logistic model: sum of the points (one point for presence of each of the above predictive factors); classified 'low risk' if ≤1, 'high risk' if ≥2. Predicted probabilities: 0.07(SD 0.03) for 'low risk', 0.39(SD 0.09) for 'high risk'. Negative predictive value(NPV) 91%(95%CI,79-98), Positive Predictive Value 38%(95%CI,23-54), Sensitivity 79%(95%CI,54-94), Specificity 63%(95%CI,50-74), area under Receiver Operating Characteristic curve 0.74(95%CI,0.64-0.85).

Conclusions:
We present one of the few natural history studies on OMG and describe risk factors for GMG not previously reported (thymic hyperplasia, presence of comorbidities), but do not show association with others (age, sex, autoimmunity). We created the first predictive score to prognosticate the risk of GMG. The high NPV is useful in identifying low risk patients, and can complement decision-making and counsel patients at diagnosis. This approach of risk stratification moves us towards addressing the question of modifying GMG risk in high-risk patients. Furthermore the effect of comorbidities is novel and demands further elucidation.

References: None.

Keywords: Myasthenia Gravis, Ocular Myasthenia Gravis, Prognosis

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Tuesday, February 24, 9:00 - 9:15 a.m.

Cortical Control of Vertical Versus Horizontal Saccades in Parkinsonian Syndromes: An fMRI study

Joao Lemos[1], Daniela Pereira[2,3], Luciano Almendra[1], Diliana Rebelo[3], Joao Castelhano[3], Gil Cunha[2,3], Cristina Januario[1,4], Luis Cunha[1,4], Antonio F Goncalves[1,4], Miguel Castelo-Branco[3,4]

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Introduction:
Examination of saccades has gained overwhelming acceptance as a clinical tool in evaluation of parkinsonian syndromes. While Parkinson's disease patients usually evidence hypometric self-paced saccades, patients with progressive supranuclear palsy characteristically show small and slow saccades, especially in the vertical direction. Although the brainstem structures responsible for the control of saccades have been thoroughly studied, the cortical saccadic circuitry, particularly for vertical saccades is far less known. We sought to compare functional Magnetic Resonance Imaging (fMRI) activation between two parkinsonian syndromes during the execution of vertical and horizontal saccades.

Methods:
In this ongoing study, we measured perisaccadic blood oxygenation-level dependent (BOLD) activation in Parkinson's disease (PD) patients (n=19), progressive supranuclear palsy (PSP) patients (n=4) and controls (CTs; n=17) while performing a block-design task, consisting of two runs (prosaccades, PS; antisaccades, AS) of 6 blocks each (3 vertical, V; 3 horizontal, H).

Results:
In V>H (PS) within groups effects analysis, CTs showed no significant differences between vertical and horizontal prosaccades. In contrast, PD and PSP patients showed greater activations, particularly in the latter group: left intraparietal sulcus (IPS) in PD patients and left dorsolateral prefrontal cortex and anterior and posterior cingulated girus in PSP patients. Regarding V>H (AS) within groups effects analysis, an opposite phenomenon was noted across groups, again particularly marked in PSP patients: several hypoactivations were found, including in bilateral occipital cortex in CTs, left ventral striatum in PD patients, and bilateral orbitofrontal cortex, ventral striatum, thalamus and left fusiform gyrus in PSP patients.

Conclusions:
Greater cortical activations during vertical prosaccades in parkinsonian patients may reflect a compensatory mechanism in an attempt to overcome specific saccadic deficits in these syndromes. Marked hipoactivations during vertical antisaccades in progressive supranuclear palsy patients possibly indicate additional cortical and sub-cortical impairment in response to a cognitively demanding task such as antisaccades, especially in the vertical direction.

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Keywords: Ocular Motility, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: A grant from Portuguese Brain Imaging Network supported this study.

Tuesday, February 24, 10:00 - 10:15 a.m.

Long Distance Homonymous Hemi-Macular Retrograde Degeneration of the Visual Pathway: A Comparison of Anterior and Posterior Visual Pathway Lesions

Y. Joyce Liao[1], Alekya Rajanala, Mohammad A. Shariati
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Introduction:
Trans-synaptic degeneration of the visual pathway following ablation of the striate cortex is well established in non-human primates and involves parvocellular retino-geniculate connections.[1-3] In humans, trans-synaptic degeneration is more controversial but has been described recently.[4-9] In this study, we used optical coherence tomography (OCT) to examine the severity and timing of retrograde degeneration in human anterior (optic tract, lateral geniculate nucleus) and posterior (occipital) visual pathway lesions.

Methods:
We performed retrospective chart review of over 70 patients with homonymous visual field loss with confirm lesions of the visual pathways on brain imaging studies. We analyzed the high quality OCT studies and correlated the findings with visual field loss and MRI. Statistical significance was determined using Mann-Whitney U test.

Results:
There was significant homonymous, hemi-macular thinning of the ganglion cell complex (ganglion cell layer + inner plexiform layer) in patients with anterior (N = 11, P = 0.0001) and posterior (N = 19, P = 0.006) visual pathway lesions, and the pattern of thinning correlated with that of visual field loss. Anterior lesions led to rapid, severe hemi-macular thinning within months (P <0.0001), while posterior lesions were associated with relatively more modest and much slower thinning over years (anterior: 54.9 ± 2.3 μm, N = 11; posterior: 64.0 ± 2.5 μm; N = 18: P <0.02). Within one-year, many cases of occipital lesions showed no thinning, even when the lesion was large. OCT studies performed 1-3 years after onset revealed progressive thinning over time. Patients with congenital or incidentally noted homonymous hemifield defects often exhibited hemi-macular thinning, presumably because the thinning has had years to develop.

Conclusions:
Retrograde, homonymous, hemi-macular thinning occurred in the human visual pathway over long distance, even trans-synaptically. There was more rapid and more severe thinning in anterior visual pathway lesions (optic tract, LGN) compared with that of occipital lobe lesions.

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Keywords: Trans-Synaptic Degeneration, Hemi-Macular Thinning, Visual Fields, Optical Coherence Tomography, Stroke

Financial Disclosures: The authors had no disclosures.

Grant Support: Burroughs Welcome Foundation Career Award in Biomedical Studies

Tuesday, February 24, 10:15 - 10:30 a.m.

Astronaut Preflight Cardiovascular Health is Highly Correlated with Postflight Eye Outcome Measures in the Visual Impairment Intracranial Pressure (VIIP) Risk following Long Duration Spaceflight

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Introduction:
Seventy percent of tested ISS astronauts demonstrate changes in ocular structure and function; 32% with disc edema, and five with elevated CSF pressure. Increased vascular compliance may predispose astronauts to VIIP. The purpose of this study was to determine if astronauts with higher preflight cardiovascular risk profiles demonstrated worse post flight eye outcomes.

Methods:
A preflight "cardiovascular profile" for 31 ISS astronauts was compiled using twelve parameters: systolic blood pressure, pulse pressure, body mass index, percentage fat, LDL, HDL, triglycerides, anti-lipid medication use, fasting glucose, maximal oxygen uptake, age, and salt intake. This profile was compared with seven postflight eye outcome variables: globe axial length; optic nerve sheath diameter, optic nerve diameter, optic nerve to sheath ratio, intraocular pressure, change in manifest refraction, and circumpapillary retinal nerve fiber layer. Twenty-two percent of the eye outcome data were missing; consequently, a multivariate multiple imputation technique with predictive mean matching methods was employed. Rubin's rules for collapsing the statistical results across the multiply imputed data sets was applied to assess the canonical correlation.

Results:
A highly significant canonical correlation of .97 ($p<.00001$) indicated a strong association between preflight cardiovascular health and postflight eye outcomes. The "joint test" revealed a significant difference in cardiovascular profile between male and female astronauts (Prob > F = 0.00001); female astronauts demonstrating a healthier cardiovascular profile.

Conclusions:
The presence of multiple cardiovascular risk factors is a known independent predictor of decreased vascular compliance[1]. Preflight cardiovascular profile was strongly associated with VIIP eye outcome. Female astronauts had a significantly healthier cardiovascular profile than the males. No female astronaut has developed optic disc edema. We speculate that astronauts with poorer cardiovascular health have decreased vascular compliance resulting in: a higher 24 hour mean central venous pressure, cerebral venous congestion, decreased CSF resorption, and elevated ICP in space.

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Keywords: Visual Impairment, Vascular Compliance, Intracranial Pressure, Spaceflight

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, February 24, 10:30 - 10:45 a.m.

Natural History of Conversion of Patients with LHON

Tiffany J Hwang[1], Edward R Chu[3], Andrew Pouw[1], Milton M Filho[2], Solange R Salomao[2], Adriana Berezovsky[2], Rubens Belford Jr[2], Filipe Chicani[2], Rustum Karanjia[3], Alfredo Sadun[3]

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Introduction:
Leber Hereditary Optic Neuropathy (LHON) is a maternally inherited disorder that presents as subacute asynchronous bilateral loss of vision in young adult males. While fundus changes have been described around time of conversion, no published studies include changes preceding conversion, as based on standard clinical criteria. We report the natural history of conversion of 6 patients whose funduscopic and clinical changes were recorded for more than 1 year pre- and post- conversion.

Methods:
A retrospective database initiated in 2001 of a 336 member seven-generation pedigree of 11778 mtDNA mutation, homoplasmic J-haplogroup LHON was reviewed for carriers who converted to affected status, resulting in twelve eyes from 6 patients included in this study. Medical records were reviewed 1 year pre- and post- conversion for: mean deviation, -logMAR, and RNFL thickness. Data from all 12 eyes were sorted, averaged, and analyzed within 2 month time periods.

Results:
Decrease in mean deviation occurred as early as 2 – 4 months preceding the date of conversion, after which values dropped precipitously until plateau at a complete loss of vision around 6 – 8 months. Decreased visual acuity as demonstrated by -logMAR was noted up to 2 months preceding the date of conversion, after which values continued to decrease at a fairly constant rate. Average RNFL thickness began increasing immediately at conversion, followed by a sharp decrease around 2 months post-conversion with a steady decline to plateau around 8 – 10 months.

Conclusions:
Early funduscopic changes in mean deviation suggest that structural changes precede functional conversion in LHON patients by up to 8 months. In addition, sub-clinical losses of vision were noted to precede the clinical date of conversion. RNFL changes support the suggested pathophysiology of initial RNFL swelling at conversion followed by dramatic atrophy. The criteria for establishing the date of conversion has not yet been objectively defined.

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Keywords: Optic Neuropathy, Diagnostic Tests, Genetic Disease, RNFL, OCT

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, February 24, 10:45 - 11:00 a.m.

The Association of Intraocular Pressure on Visual Function in Papilledema from Idiopathic Intracranial Hypertension

Gary L. Yau[1], Martin W. ten Hove

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Introduction:
Idiopathic intracranial hypertension (IIH) frequently manifests as papilledema associated with visual loss. Recent studies suggest that higher intraocular pressure (IOP) may counteract the effect of elevated intracranial pressure (ICP) at the level of the lamina cribosa, possibly mitigating the damage to axonal transport and subsequent visual function. The current study aimed to test the hypothesis that eyes with higher IOP are associated with superior visual function in those with papilledema secondary to IIH.

Methods:
A retrospective, cross-sectional, paired-eye, comparison study was conducted on a consecutive series of newly diagnosed patients with IIH from a single Neuro-ophthalmology specialist practice between January 2006 and January 2014. Included subjects had baseline bilateral IOP measurements obtained by applanation tonometry and concurrent automated perimetry. Patients were divided into two groups for analysis. The first group had symmetric IOPs bilaterally (within 1 mmHg) whereas the second group had asymmetric IOPs (of 2 mmHg or greater) between eyes. The primary outcome was Mean Deviation (MD) as measured by perimetry.

Results:
Fourty-four patients were analyzed, with 31 in the symmetric group and 13 in the asymmetric group. Baseline demographic characteristics were similar between both groups. When comparing MD between eyes, there was no difference in the symmetric group ($p = 0.89$), whereas a significant difference was observed in the asymmetric group ($p = 0.007$). Specifically, in the asymmetric group, the eye with the higher IOP (mean, 15.77 SD 2.52 mmHg) had less visual loss (MD: -5.72 SD 7.13 dB) compared to their fellow eye (MD: -7.04 SD 7.66 dB) with lower IOP (mean, 12.77 SD 2.92 mmHg).

Conclusions:
Patients presenting with papilledema from IIH with asymmetric IOP's display better visual function in the eye with higher IOP. This novel observation suggests that IOP may play an important role in visual loss from IIH. Further investigation into this relationship is warranted.

References: None.

Keywords: Pseudotumor Cerebri, High intracranial Pressure/Headache

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Tuesday, February 24, 11:00 - 11:15 a.m.

Dramatic Fixation Instability in Peripheral Vestibulopathies without Visual Feedback Compared with Central Vestibulopathies

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Introduction:
Eye movement abnormalities are common in central and peripheral vestibulopathies, and characterization of eye movements using infrared oculography can help teach us important ways to localize the lesion. In this study, we compare and contrast eye movement findings of patients with peripheral vestibulopathies with that of central pathway lesions.

Methods:
We performed 60-Hz 3D infrared oculography with and without a fixation target and analyzed fixation instabilities and waveform characteristics in 10 patients with peripheral and 10 patients with central vestibulopathies. Fixation target at distance in the light is displayed by a custom-made LED board. Fixation target in the dark is seen within the infrared recording goggle and turned on and off to assess changes in eye position. All patients had relatively mild or no dizziness at the time of recording.

Results:
In patients with peripheral vestibulopathies, such as acoustic neuromas or vestibular neuronitis, visual fixation at a distant target is typically good when the patient is relatively asymptomatic, with rare, small amplitude square wave jerks. Without visual feedback, patients can rapidly decompensate, exhibiting rapid deviations of eye positions, often in square wave jerk waveform with rapid on and off set and may be accompanied by a torsional nystagmus. In contrast, patients with central vestibular pathway lesions, such as Wallenberg syndrome or brainstem cavernous malformations, typically exhibit uni- or multi-directional oscillations initiated by a slow phase. Without visual feedback, patients with central vestibulopathies have less prominent changes in eye movement waveform.

Conclusions:
A useful test to distinguish peripheral and central vestibulopathies is to observe patient eye movement behavior during fixation with and without visual feedback, since peripheral vestibular patients are more likely to exhibit dramatic and rapid fixation instability without visual feedback.

References: None.

Keywords: Nystagmus, Eye Movement Abnormality, Peripheral Vestibulopathy, Central Vestibulopathy, Dizziness

Financial Disclosures: The authors had no disclosures.

Grant Support: Burroughs Wellcome Foundation Career Award in Biomedical Sciences

Tuesday, February 24, 11:15 - 11:30 a.m.

A Radiographic Target Sign for Abnormal Vertebral Artery Fflow in Stroke Patients with Acute Vestibular Syndrome

Jorge C Kattah[1] , John H Pula[1], Jeffrey DeSanto[1], Ali S Teharni[1], David E Newman Toker[2]

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Introduction:
Stroke involving the brainstem and cerebellum may present with isolated acute vestibular syndrome (AVS). Vertebral artery (VA) thrombo-embolism or dissection is a potential cause, and may be noted as a VA flow abnormality seen as V4 segment hyper-intensity or asymmetry on axial T2 MRI.

Methods:
Retrospective study of 223 AVS patients presenting over 15 years to a single stroke referral center. Of these, 145 had available T2 MRI scan (160 scans). Axial T2 MRIs were reviewed by a blinded neuro-radiologist and a non-blinded clinician for presence of V4 segment hyper-intensity or asymmetry (target sign). Disagreements were adjudicated. We report percentages for presence of target sign in each group, odds ratio, target sign and lesion laterality, presence of target sign in stroke patients with negative initial DWI MRI, and Kappa for inter-rater reliability.

Results:
Of the 145 AVS patients with available axial T2 MRI scans, 71 had stroke, and 74 were diagnosed with vestibular neuritis (VN). VA V4 segment hyper-intensity was seen in 42.2% of stroke patients (30/71), and 8.1% of patients with VN (6/74). Odds ratio of stroke in patients with a “target sign” was 8.29 (95% CI 3.18-21.6). With the exception of one stroke patient, all found target signs were ipsilateral to the side of final stroke. Among stroke patients with negative initial DWI MRI, 41.7 % (5/12) had a VA V4 segment hyper-intensity. Cohen’s kappa for inter-rater reliability was 0.78.

Conclusions:
The VA V4 segment hyper-intensity or “target sign” identified pathologic VA abnormalities in a nearly half of stroke patients presenting with AVS. In VN, the target sign was uncommon. The VA target sign may precede restricted diffusion, and may help distinguish stroke from VN in selected acute presentations. When present, it should prompt clinicians to repeat DWI MRI to confirm a potentially missed ischemic cerebrovascular syndrome.

References: None.

Keywords: Vertigo, Vestibular Neuritis, Stroke, Vertebral Artery Stenosis, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: No grant support

Tuesday, February 24, 11:30 - 11:45 a.m.

20/40 or Better Visual Acuity After Optic Neuritis: Not as Good as We Once Thought

Rachel C. Nolan[1], Kristin M. Galetta[2], Kannan Narayana[1], James A. Wilson[2], Peter A. Calabresi[3], Elliot M. Frohman[4], Steven L. Galetta[1], Laura J. Balcer[1]

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Introduction:
It has been reported that patients with acute optic neuritis (ON) have good visual recovery, with return of high-contrast visual acuity (VA) to 20/40 or better in 95% of affected eyes. Vision-specific quality of life (QOL), however, is reduced among overall cohorts of patients with history of ON, even years following the acute event. We examined vision-specific QOL scores in a cohort of multiple sclerosis (MS) patients among the specific sub-group of subjects with history of ON and high-contrast VA of 20/40 or better in both eyes.

Methods:
Participants in an ongoing collaborative study of MS visual outcomes completed 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) and 10-Item Neuro-Ophthalmic Supplement, as well as VA and low-contrast letter acuity (LCLA) testing. Spectral-domain optical coherence tomography (SD-OCT) was performed to determine peripapillary retinal nerve fiber layer thickness (RNFL) and macular ganglion cell+inner plexiform layer thickness (GCL+IPL).

Results:
Analyses of data from 247 patients with MS (age 47.1±11.6 years) showed that among those with a history of ON (n=128), vision-specific QOL scores were reduced compared to disease-free controls even among the sub-group with VA 20/40 or better in both eyes (n=106, $p<0.001$ for NEI-VFQ-25 composite and 10-Item Supplement, linear regression, accounting for age). Specifically, NEI-VFQ-25 scores were 83.6±14.7 (compared to 98.4±1.8 for controls), with Supplement scores 73.8±17.9 (vs. 96.8±4.9 for controls). Those with greater binocular LCLA had better QOL scores (2.5%: $p=0.02$; 1.25%: $p=0.006$, accounting for age). Eyes in this sub-group had significant thinning of the RNFL (79.8 vs. 93.0 microns for controls, $p<0.001$) and GCL+IPL (69.7 vs. 80.4 microns, $p<0.001$, accounting for age and within-patient, inter-eye correlations).

Conclusions:
Even when VA is 20/40 or better, patients with history of acute ON are left with clinically meaningful reductions in vision-specific QOL, and manifest significant degrees of retinal axonal and neuronal loss.

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Keywords: Optic Neuritis, Quality of Life, Multiple Sclerosis, Binocular Vision, Optical Coherence Tomography

Financial Disclosures: The authors had no disclosures.

Grant Support: National MS Society

Tuesday, February 24, 11:45 a.m. - 12:00 p.m.

Chronic Optic Neuropathy Causes Decreases in Both Inner Retinal Blood Flow and Prelaminar Optic Nerve Blood Flow

Enrique J. Rivera[1], Susan Anderson[1,2], Matthew Thurtell[1,2], Michael Wall[1,2], Robert Mallery[1], Randy Kardon[1,2]

[1]University of Iowa Department of Ophthalmology and Visual Sciences, Iowa City, IA, USA, [2]Iowa City VA Medical Center, Iowa City, IA, USA

Introduction:
Our purpose was to determine if optic neuropathy results in an obligatory decrease in blood flow to the inner retina and optic nerve due to decreased metabolic demand from non-functioning neurons. Visual stimulation causes transient hyperemia, but it is unknown if decreases in neuron activity cause reduced blood flow.

Methods:
Laser speckle blood flowgraphy imaging (LSFG-NAVI; Softcare Ltd, Fukuoka, Japan) was performed on a 25x20 degree area of the fundus incorporating the optic nerve head. Blurring of the laser speckle pattern by moving particles in the image plane was used to simultaneously measure blood flow in the major circumpapillary retinal arteries and veins, and below the surface of the optic nerve head. Blood flow was determined in each eye of 19 patients with unilateral optic neuropathy (ischemic=13, compressive=5, inflammatory=1) in the chronic state. Inner retinal blood flow and optic nerve head blood flow were compared between affected and unaffected eyes. Retinal nerve fiber layer (RNFL) and retinal ganglion cell layer complex (GCL) were compared to retinal and optic nerve blood flow.

Results:
There was a significant decrease in inner retinal blood flow in eyes with optic neuropathy compared to the fellow normal eye ($P=0.002$; mean=69±17% of fellow eye). A significant decrease in optic nerve head blood flow deep to the superficial retinal capillaries was also present ($P<0.001$; mean=65±22% of fellow eye). There was also significant decrease in both RNFL ($P=0.02$; mean=83±32% of fellow eye) and GCL thickness ($P<0.001$; mean=71±11% of fellow eye), but no significant correlation between the inter-ocular asymmetry of retinal or optic nerve blood flow and RNFL or GCL thickness.

Conclusions:
Chronic optic neuropathy results in decreased retinal and optic nerve head blood flow, likely due to reduced metabolic demand. Laser speckle blood flowgraphy allows non-invasive simultaneous measurement of retinal, choroidal, and optic nerve head blood flow.

References: None.

Keywords: Optic Neuropathy, Vascular Disorders, Diagnostic Tests

Financial Disclosures: Novartis steering committee OCTiMS - Randy Kardon consulting

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Poster Presentations

Tuesday, February 24, 2015 • 6:00 p.m. – 9:30 p.m.
Authors will be standing by their posters during the following hours:
Odd-Numbered Posters: 6:45 p.m. – 7:30 p.m.
Even-Numbered Posters: 7:30 p.m. – 8:15 p.m.

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Category: Anterior Afferent Visual Pathway (Optic Neuropathy and Chiasm)		
1	Normal Tension Glaucoma (NTG) is it a Type of Glaucoma or an Entity of a Compressive Optic Neuropathy (CON)?	Mohammed Areesh
2	Anterior Ischemic Optic Neuropathy Due to Biopsy-Proven Giant Cell Arteritis in Thai Patients	Taweevat Attaseth
3	Visual Outcomes Following Perioperative Vision Loss	Jasmina Bajric
4	Pituitary Apoplexy in Pregnancy	Matthew J. Benage
5	Bilateral, Sequential Anterior then Posterior Ischemic Optic Neuropathy in a Young Migraineur	Damian E. Berezovsky
6	Traumatic Optic Neuropathy. Our Experience	Mariana de Virgiliis
7	Sensitivity of Magnetic Resonance Imaging in Acute Demyelinating Optic Neuritis	Lulu LCD Bursztyn
8	Characterization of Leber's Hereditary Optic Neuropathy Patients Treated with Idebenone	Jasdeep S. Chahal
9	Gliosarcoma of the Optic Nerves 15 years After Radiation Treatment for Hypophyseal Adenoma	Ayse I. Colpak
10	Optic Nerve Compression by an Anomalous Internal Carotid Artery	Valerie I. Elmalem
11	Identifying Risk Factors for the Development of Radiation Optic Neuropathy at "Safe" Doses: A Review of Cases Seen 1994-2014	Pavle Doroslovački
12	Optic Neuritis After Refractive Surgery: Causal or Coincidence?	Shlomo Dotan
13	Long Term Treatment of Lebers Hereditary Optic Neuropathy with Idebenone	Jennifer I. Doyle
14	Macular Star Formation in Diabetic Patients with Non-Arteritic Anterior Ischemic Optic Neuropathy (NA-AION)	Alberto Galvez-Ruiz
15	Seasonal Influence on the Incidence of Biopsy-Proven Giant Cell Arteritis: The University of California Davis Institutional Experience	Kimberly K. Gokoffski
16	Possible Revatio (Sildenafil) Induced Optic Neuropathy in Mice	Nitza Goldenberg-Cohen
17	Cyclosporine Induced Papilledema without Elevated Intracranial Pressure	Poorav J. Patel
18	Asymptomatic Leukemic Optic Nerve Infiltration as Presentation of Acute Lymphoblastic Leukemia Relapse	Florin Grigorian
19	Progressive Visual Loss: An Unusual Presenting Symptom in Giant Cell Arteritis	Parima Hirunwiwatkul
20	Demyelinating Disorder with Optic Neuropathies in a Patient with Monoclonal Gammopathy: Case Report and Literature Review	Whitney B. Hough
21	Retrospective Review of Ophthalmic and Systemic Associations of Optic Nerve Hypoplasia	Imran Jivraj
22	Optic Nerve Morphology as Marker for Disease Severity in Cerebral Palsy of Perinatal Origin	Sachin Kedar

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24	Methanol Causes Highly Selective Retinal Ganglion Cell Layer Loss and Inner Nuclear Layer Microcysts	Kendra A. Klein
25	Parsing the Differences Between LHON Affected: Genetic Vs Environmental Triggered Disease	Valerio Carelli
26	Changes in Macular OCT Retinal Sublayers of Patients and Carriers in the Natural History Phase of the Leber Hereditary Optic Neuropathy G11778A Gene Therapy Clinical Trial	Byron L. Lam
27	Low Grade Glioma of the Pituitary Stalk, Case Report with Review of the Literature	Su Ann Lim
28	Visualisation of Nerve Fibre Orientation in the Human Optic Chiasm Using Photomicrographic Image Analysis	Neeranjali Jain
29	Optic Neuropathy in Chronic Lymphocytic Leukemia	Amina I. Malik
30	How is Eye Fixation Affected by Optic Neuropathy? Diagnostic Value of Precise Recording of Retina Movement During an OCT Scan	Robert M. Mallery
31	A Novel OPA1 Mutation in Autosomal Dominant Optic Atrophy (ADOA)	Jordan A. Margo
32	The Vegetative Aspects of Neuroprotective Action of High Corticosteroid Doses in Compressive Traumatic Optic Neuropathies (TON)	Yulya T. Maslyak
33	Optic Atrophy in a Large Specialist Hospital	Joyce N. Mbekeani
34	Neurofibromatosis 1 with Large Suprasellar and Bilateral Optic Nerve Pilomyxoid Astrocytoma	Joyce N. Mbekeani
35	Optic Neuropathy in Wolfram's Syndrome Imaged with High-Definition Spectral Domain OCT	Dan Milea
36	Retinal Oximetry (Oxygen Saturation) and Peripapillary Vascular Diameters in Normal Eyes and in Non-Arteritic Ischemic Optic Neuropathy (NAION)	Ashwin Mohan
37	Is Ishihara Color Plate Testing as Reliable on iPod/iPhone and iPad as on Paper Format?	Katherine Boudreault
38	Multifactorial Optic Neuropathy - When it isn't Always Glaucoma	Deborah C. Parish
39	Cobalt-Chromium Metallosis with Normal ERG	Huy V. Nguyen
40	Nonarteritic Anterior Ischemic Optic Neuropathy (NAION): A Misnomer. A Non-Ischemic Papillopathy Caused by Vitreous Separation	Cameron F. Parsa
41	Visual and Oculomotor Outcomes in Children with Posterior Fossa Tumors	Crandall E. Peeler
42	Radiation Optic Neuropathy and Retinopathy from Low Dose (20Gy) Radiation Treatment	Crandall E. Peeler
43	Bilateral Optic Neuropathy in Superficial Intracranial Siderosis	Thong D. Pham
44	Binocular Acuity Summation (BAS) in Multiple Sclerosis (MS): Relation to Retinal Architecture and Visual System Neurophysiology	Sara S. Qureshi
45	Nutritional Optic Neuropathy after Bariatric Surgery	Yuna Rapoport
46	Lyme Disease Mimicking Giant Cell Arteritis	Nailyn Rasool
47	Structural Analyses of the Anterior Visual Pathway in Compressive Neuropathy	Won Hyung A. Ryu

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Category: Anterior Afferent Visual Pathway (Optic Neuropathy and Chiasm) *continued*		
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49	A First Case Report of Chordoid Glioma Invading Optic Nerve	Nicolae Sanda
50	Clinical Spectrum of Optic Neuritis in Indian Children at a Tertiary Care Centre	Swati Phuljhele
51	Prognosticating Factors in Nonarteritic Ischaemic Optic Neuropathy	Swati Phuljhele
52	Sweep My Blindness Away!	Salwa Abdel Aziz
53	Progressive Non-Arteritic Optic Neuropathy as the First Presentation of Anti-Phospholipid Antibody Syndrome	Tarek A. Shazly
54	Anterior Visual Pathway(AVP) Meningiomas: A Dosimetric Comparison of IMRT to Pencil-beam Proton Therapy	Scott L. Stafford
55	A Case of Lyme Neuroretinitis- An Elusive Entity	Padmaja Sudhakar
56	50% of Non-Arteritic Anterior Ischemic Optic Neuropathy Occurs Between 40-55 Years Old	Ming-Hui Sun
57	Evaluation of Retinal Nerve Fiber Layer and Ganglion Cell Complex in a Cohort of Chinese with Optic Neuritis or Neuromyelitis Optica Spectrum Disorders Using SD-OCT	Guohong Tian
58	Transient Monocular Vision Loss Upon Awakening: A Benign Phenomenon	Marc A. Bouffard
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Poster 1

Normal Tension Glaucoma (NTG) is it a Type of Glaucoma or an Entity of a Compressive Optic Neuropathy (CON)?

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Introduction:
NTG is known to be a special type of glaucoma which is still a matter of dispute in its etiologic, diagnostic, therapeutic aspects and its terminology(1).A lot of studies have been carried out, that indicated difference of POAG vs NTG such as:1. Optic nerve head localized affection in NTG vs POAG. (2) 2.overally VF defect is less affected in NTG and both central and paracentral defect were seen vs PAOG.(2,3)3. Genetic differences.(4)4. Optic nerve head blood flow.(5) 5. The NTG patients were more younger.(1)In this study we propose that labeling these patients as NTG could be a misinterpretation and NTG could be really an entity of a CON.

Methods:
Total of 27 patient's eyes (10men and 17 women) were included in this study, and Best corrected visual acuity(BCVA), IOP, vertical c/d ratio, VF test, Ishihara Red/Green test, Gonioscopy, Relative afferent pupillary defect were established on all cases.

Results:
Total of 20(6 men and 14 women) patient's eye from 27 patient's eye were included in this study so the results are as below:1.BCVA was achieved and 20/20 in all cases.2. The mean IOP measured so no IOP greater than 21mmHg was recorded.3. The vertical c/d ratio was measured and significantly different in each patients.4. The Humphrey VF study indicates central relative or absolutely defects.5. Ishihara revealed relative Red-Green deficiency in both eyes according to plate's response were detected.6.detectable RAPD recorded in the eye with larger c/d ratio in all patients.

Conclusions:
All these signs coincide with the compression of the optic nerve. So the authors of this article have come to the conclusion that NTG be considered under category of optic neuropathy. In fact we think that it may be a type other than glaucoma and maybe misnamed. According to this study all the clinical signs are in favor of the CON.

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Keywords: Normal Tension Glaucoma, Compressive Optic Neuropathy, Primary Open Angle Glaucoma, Visual Field Defect, Red-Green Deficiency

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Poster 2

Anterior Ischemic Optic Neuropathy Due To Biopsy-Proven Giant Cell Arteritis In Thai Patients

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Introduction:
Giant cell arteritis (GCA) is a vasculitis of medium- to large-sized artery which can interfere with arterial flow to the optic nerve head causing arteritic anterior ischemic optic neuropathy(AION). Little data has been published regarding arteritic AION in Asians, including Thais probably due to its rarity.

Methods:
The records of 236 patients with AION, seen during January 2005 to October 2014 at a tertiary care center in Bangkok, Thailand were reviewed. Only 6 patients with arteritic AION due to biopsy-proven giant cell arteritis were included in this study.

Results:
Of 6 patients, 4 (67%) were male and 2 (33%) were female. Mean age at onset was 72.5 years, ranged from 63 to 81 years. Two patients had bilateral simultaneous involvement and 4 patients had unilateral involvement. In unilateral AION, 2 patients developed contralateral visual loss from cilioretinal artery occlusion 2 weeks before the onset of AION. All eyes had severe visual loss (20/200 or worse) at initial presentation including 3 eyes with no light perception. Fluorescein angiography showed choroidal filling delays in 4 eyes. All patients had an elevated erythrocyte sedimentation rate (mean 95 mm/hr). High dose intravenous methylprednisolone and subsequent long-term oral corticosteroid were given in all cases. Final visual acuity remained unchanged in most of patients (5 eyes, 63%). Three eyes (37%) showed improvement of their visual acuity and 2 eyes achieved a final visual acuity of 20/50.

Conclusions:
Arteritic AION in GCA is a rare disease and represents 2.5 % of AION patients in a tertiary neuro-ophthalmologic service in Thailand. The clinical features and visual outcome in Thai patients are not different to those describe in white patients.

References: None.

Keywords: Neuro-Ophth & Systemic Disease (Eg. MS, MG, Thyroid), Optic Neuropathy, Vascular Disorders, Retina, Orbit/Ocular Pathology

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Poster 3

Visual Outcomes Following Perioperative Vision Loss

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Introduction:
The aim of this study was to determine visual acuity outcomes following perioperative vision loss due to ischemic optic neuropathy, retinal artery or vein occlusion, and cortical blindness.

Methods:
In this retrospective chart review, all surgical procedures performed on adults and requiring general anesthetic between 2003 and 2012 at the Mayo Clinic were screened for visual complications. Patients who had new-onset vision loss within 30 days of surgery and a complete ophthalmic exam were included. Patients with surgery on the visual pathways or whose diagnosis was not related to surgery were excluded. Outcomes were determined up to 1 year after surgery.

Results:
A total of 41 cases of perioperative vision loss were identified after screening 352, 717 general anesthetic procedures (risk of 0.012%). Visual acuity was 20/490 for all patients at baseline and improved to 20/295 at 3 months ($p = 0.27$), 20/132 at 6 months ($p = 0.001$) and 20/53 at 1 year ($p = 0.02$). A similar pattern of visual acuity improvement was seen in 14 patients who had complete 1-year follow-up: 20/289 at baseline, 20/118 at 3 months ($p = 0.004$), 20/100 at 6 months ($p = 0.006$), and 20/53 at 1 year ($p = 0.02$). Visual field deficits were 73% at baseline and 83% at 1 year ($p = 0.56$). Color vision deficits were 57% at baseline and 79% at 1 year ($p = 0.63$). Ischemic optic neuropathy was the most common cause (57%), followed by retinal artery occlusion (19%), retinal vein occlusion (12%) and cortical blindness (12%).

Conclusions:
The risk of perioperative vision is low. Visual acuity improves throughout the first year following perioperative. Visual field and color vision deficits remain similar to baseline at one year following vision loss.

References: None.

Keywords: Optic Neuropathy, Vascular Disorders, Visual Fields

Financial Disclosures: The authors had no disclosures.

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Poster 4

Pituitary Apoplexy in Pregnancy

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Introduction:
We present a case of pituitary apoplexy of a pregnant female with an initial presentation of mild headache and bitemporal hemianopia.

Methods:
This is a descriptive case report based on clinical records, patient observation and analysis of diagnostic studies.

Results:
An 18 year old G1P0 woman presented at 26 weeks gestation (Di/Di twins) with new onset visual disturbance and a mild headache. She described the headache as dull and diffuse. She noted trouble seeing peripherally to her right. On initial exam, she displayed visually significant temporal field loss to confrontation OD. Dilated fundoscopic exam was normal OU. Within 12 hours, the patient noted worsening of visual disturbance and new field loss temporally to confrontation was noted OS. Due to the bitemporal field loss as evident on CVF, she underwent an MRI brain for possible pituitary pathology. The MRI displayed a T2 and FLAIR rounded hyperintense focus measuring 7 x 11 x 6 mm located in the pituitary. GRE and flare sequences were notable for a fluid-filled level within the structure representing pituitary apoplexy. The patient was admitted for initial work-up. She was scheduled for follow-up MRI and visual field testing in four weeks. The clinical course is ongoing at this time.

Conclusions:
This is a case of pituitary apoplexy in a pregnant woman with mild headache and bitemporal visual disturbances. Pituitary apoplexy is a rare diagnosis, especially in pregnancy. Management of apoplexy includes urgent corticosteroid replacement if indicated with continuous monitoring of electrolytes. In life-threatening cases, trans-sphenoidal decompression may be indicated. Pituitary apoplexy in pregnancy is best managed by a multidisciplinary team including endocrinologists, obstetricians, ophthalmologists, and neurosurgeons.

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Keywords:

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 5

Bilateral, Sequential Anterior then Posterior Ischemic Optic Neuropathy in a Young Migraineur

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Introduction:
Non-arteritic anterior (NAION) and posterior (PION) ischemic optic neuropathy infrequently affect patients under 50; the two largest case series suggest that this group represents up to 23% of NAION patients.[1,2] Within this group of young NAION patients, 41-43% had eventual bilateral involvement. Risk factors in this population included crowded discs (82-88%), hyperlipidemia (23-47%), hypertension (32-35%), smoking (27-29%) and migraines (20%). Sequential NAION followed by PION in a young patient has not been previously reported.

Methods:
Case report and review of the literature.

Results:
A 37 year old female with frequent, severe headaches associated with photophobia and nausea noted the acute onset of right-sided painless visual loss upon awakening. Visual acuity was 20/70 in the right eye and 20/30 in the left eye, with an afferent pupillary defect (APD) on the right, disc edema on the right, and normal fundus on the left except for a small cup: disc ratio of 0.1. Visual field testing revealed an inferior altitudinal defect on the right. Contrasted brain MRI, lumbar puncture, inflammatory markers, ANA screen, and hypercoagulation panel were unremarkable. She was given intravitreal triamcinolone without improvement, and superior optic nerve pallor was observed at two-month follow-up. At this visit, she reported the recent sudden onset of blurry vision in her left eye, with unchanged visual acuity, no APD, and no disc edema. VF testing revealed a new superior and inferior nasal defect on the left, and a repeat contrasted brain MRI was normal.

Conclusions:
This is a unique case of sequential, anterior then posterior ischemic optic neuropathy occurring in a young patient with frequent migraines and small cup: disc ratio bilaterally. This case, as well as previous case series, highlights the frequent association between migraine headaches and ischemic optic neuropathy.[1-3]This suggests that vasospasm may play a role in ischemic optic neuropathy, especially in young patients.

References:
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Keywords: Optic Neuropathy, Headache, Visual Fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 6

Traumatic Optic Neuropathy. Our experience.

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Introduction:
Traumatic Optic Neuropathy (TON) is the optic nerve damage related with encephalo-cranial traumatism. Usually affects young people with potential severe visual loss. There is no proven effective treatment.

Methods:
Retrospective review of medical histories of patients treated in ophtalmology hospital between January 2012 and March 2014, selected those patients diagnosed with TON.

Results:
There were 52 patients with TON. 79% males younger than 39 years old (73%), only 3,8% were over 60 years. Ninety five percent of the TON were unilateral and all cases were indirect traumatic optic neuropathies, due to blunt head trauma Among the causes, Traffic collisions were the most frequent (46%), 67% had a motorcycle involvement (mostly without helmet); followed by direct blunt trauma 35% and due to falls from height 19%. Regarding the initial trauma: 60% of patients had loss of consciousness; 68% were hospitalized, 56% had abnormal neuroimagen and 19% required neuro surgical treatment. The first neuro ophthalmology visit, was within two months in 52 % of patients, but only 9% within first week from initial trauma. Initial Visual Acuity (VA) was worst than 0.1 en 57% of patients, 13,4 % had No light Perception. First Month control (23 patients): 63% visual acuity improvement. Last control (32 patients): 58% improvement in visual acuity; meanwhile only 15% had better color test result Initial ophthalmoscopic findings was: Difuse optic disc pallor 31% Normal optic nerve 29%, Temporal Pallor 25%, Optic nerve cupping 14%. All types of visual field defects were found, none of which were prevalent. OCT main findings was diffuse decreased retinal nerve fiber layer (RNFL).

Conclusions:
NOT is a significant cause of severe visual loss in young men, mainly related with motorcycle accidents without helmet protection and associated with other life threatening conditions secondary to head injuries. Consistent with other reports, spontaneous visual acuity improvement was seen.

References:
1. Yu-Wai-Man P, Griffiths PG. Steroids for traumatic optic neuropathy. Cochrane Database Syst Rev. CD006032. 2013. Warner, Eggenberger . Traumatic optic neuropathy: a review of the current literatura. Current Opinion in Ophthalmology, 21:459 – 462. 2010
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Keywords: Optic Nerve Trauma And Treatment, Trauma, Optic Neuropathy, Neuroimaging, Visual Fields6

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Poster 7

Sensitivity of Magnetic Resonance Imaging in Acute Demyelinating Optic Neuritis

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Introduction:
Magnetic resonance imaging (MRI) of the orbits is often used to confirm a diagnosis of optic neuritis when clinical findings are uncertain. The sensitivity of MRI in optic neuritis (ON) has not been well studied but has been estimated to be approximately 80-90%.[1,2] The aim of this study was to determine the sensitivity of MRI findings in acute demyelinating ON.

Methods:
We retrospectively reviewed the charts of all patients with ON diagnosed using ONTT criteria seen for a first or follow-up visit in the last 2 years in a single neuro-ophthalmology practice. Data abstracted included: age at diagnosis, sex, initial and final Snellen visual acuity, visual field mean deviation, optic disc edema, optic nerve abnormalities on MRI (none, high T2 signal, post-contrast enhancement, or enlargement), presence of 1 or more high T2-signal lesions on brain MRI and diagnosis of multiple sclerosis during the follow-up period. Descriptive statistics were used to describe the distribution of all variables and calculate the sensitivity of orbital MRI findings individually and in aggregate for ON.

Results:
Thirty patients met all inclusion criteria and 22 (73%) had at least one MRI feature consistent with ON. There was no difference in age, visual function, optic disc edema, or delay from symptom onset to MRI in patients with and without findings on MRI. Patients with MRI features of ON were more likely to have white matter lesions on MRI (55% vs 25%) and have an eventual diagnosis of multiple sclerosis (27% vs 0%) over a mean follow-up period of 3.1 years (range 0.4 to 8.7 years).

Conclusions:
The sensitivity of MRI in acute optic neuritis (73%) is lower than estimated. Optic neuritis without MRI features consistent with ON may have a lower risk of MS. We are reviewing additional cases to confirm these results.

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Keywords: Optic Neuropathy, Neuroimaging, Demyelinating Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 8

Characterization of Leber's Hereditary Optic Neuropathy Patients Treated with Idebenone

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Introduction:
There is conflicting data regarding the efficacy of Idebenone as a treatment for Leber's Hereditary Optic Neuropathy (LHON) [1, 2]. Klopstock et al. did not find a significant increase in recovery of BCVA in patients treated with Idebenone while Carelli et al. did (from off-chart (<20/400) to on-chart), specifically in the mutation 11778. Our aim was to determine if there was an improvement in vision even if patients stayed off-chart.

Methods:
A retrospective chart review was done looking at all patients who visited a tertiary care eye clinic from 2009 until June 2014 and were diagnosed with LHON. Duration of disease, visual acuity (VA) and mean deviation (MD) were recorded for each visit. Counting fingers was estimated in decimal acuity by calculating the numbers of minutes of arc subtended by 3 fingers, which would represent the letter E. VA was assessed to be off-chart at the beginning of therapy, 6 months of therapy, 1 year, and at the end of therapy.

Results:
70 patients were identified with LHON--16 of these were treated with Idebenone for greater than a year and seen within 3 months of start of treatment (12 with 11778, 3 with 14484, 1 with 3460). Patients with 11778 showed a significant improvement in VA at the end of therapy, however this effect took longer than 1 year to manifest. There was no significant difference in VA and MD between right and left eyes at 1 year past conversion. VA improved from 20/1676 ± 2105 to 20/829 ± 920 ($p=0.04$, $n=24$ eyes) at end of therapy. 11/24 eyes were off-chart at the beginning of therapy, 13/24 eyes at 6 months, 14/24 eyes at 1 year and 16/24 eyes were off-chart at the end of therapy.

Conclusions:
Idebenone therapy can improve VA in mutation 11778, even if VA remains off-chart.

References:
1. Carelli, V., et al., Idebenone treatment in Leber's hereditary optic neuropathy. Brain, 2011. 134(Pt 9): p. e188.
2. Klopstock, T., et al., A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. Brain, 2011. 134(Pt 9): p. 2677-86.

Keywords: Genetic Disease, Optic Neuropathy, Visual Fields, Diagnostic Tests

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 9

Gliosarcoma of the Optic Nerves 15 years After Radiation Treatment For Hypophyseal Adenoma

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Introduction:
Gliosarcoma is a very rare mixed tumor in the central nervous system, consisting of glial and malignant mesenchymal elements. Gliosarcoma is considered a subtype of glioblastoma and termed as primary gliosarcoma. Secondary gliosarcoma is detected at subsequent surgery for previously resected and irradiated glioblastoma multiforme. We describe an unusual case with vision loss due to gliosarcoma, probably radiotheraphy-induced,15 years after radiation treatment for hypophyseal adenoma.

Methods:
Single case report

Results:
A 56 year old woman with a past history of pituitary adenoma and thyroid micropapillary carcinoma presented with bilateral progressive loss of vision over a year. She had undergone surgical resection of the hypophyseal adenoma followed by fractionated external beam radiation with a total dose of under 50 Gy, 15 years prior to her presentation. At the time of her first symptom visual acuities were 20/20 OD and counting fingers OS. Fundoscopy demonstrated an optic atrophy of OS with a normal fundus OD. Brain MRI revealed T2 hyperintensity, mild thickening with enhancement of the chiasm and left optic nerve. The patient was considered to have radiation induced optic neuropathy and underwent hyperbaric oxygen therapy, systemic corticosteroids and intravenous bevacizumab. Over the following months her vision is deteriorated to NLP OU. Repeated MRI showed progressive T2 hyperintensity and severely enlarged optic nerves, chiasm and optic tracts with patchy enhancement, suggestive of a high grade optic pathway glioma. Histopathological examination following excisional biopsy and debulking of the tumor revealed pleomorphic spindle cells with negative staining for glial fibrillary acidic protein (GFAP) and S-100 with GFAP and S-100 positive atypical cells consistent with gliosarcoma.

Conclusions:
Radiation induced gliosarcomas are very rare and to our knowledge this is the first report of gliosarcoma of the optic pathways. This case provides an insight for the carcinogenic effect of radiation therapy on intracranial tumors.

References: None.

Keywords: Optic Neuropathy, Radiation Injury, Gliosarcoma, Optic Pathway Glioma

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Poster 10

Optic Nerve Compression by an Anomalous Internal Carotid Artery

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Introduction:
Although there are several etiologies for optic atrophy, compression by intracranial masses or aneurysms is of particular concern. One infrequently reported cause of compressive optic neuropathy (CON) is compression of the intracranial portion of the optic nerve by an anomalous or ectatic internal carotid artery (ICA).

Methods:
Here we report three cases of CON caused by an anomalous ICA identified by magnetic resonance imaging (MRI).

Results:
The three patients presented in this series range in age from 27 to 71. All patients initially presented with decreased vision, a relative afferent pupillary defect (RAPD), and visual field deficits. Dilated funduscopic examination (DFE) revealed asymmetric cupping of the optic nerve with pallor in excess of cupping in the affected eye of all patients. Visual field deficits in the affected eye included constriction with a small central island, junctional scotoma, and arcuate defects. Two of the three patients were being treated for presumed glaucoma. Laboratory evaluation for other etiologies of optic neuropathy was negative. MRI brain and orbits was significant for close apposition with displacement or compression of the optic nerve by the intracranial portion of the ICA. The youngest of the three patients had progressive profound visual loss with chiasmal involvement and has been referred for neurosurgical evaluation.

Conclusions:
These cases add to the small number of reported patients with optic atrophy caused by close apposition/compression of the optic nerve by the internal carotid artery. Though a seemingly rare occurrence, this is an important, potentially treatable cause of optic atrophy. Often mistakenly presumed to have progressive glaucoma, this diagnosis should be considered in patients with marked asymmetry or in patients with progression of visual dysfunction despite adequate treatment with medications to lower the intraocular pressure. Although controversial, surgical decompression may be considered in selected cases.

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Keywords: Optic Neuropathy, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 11

Identifying Risk Factors for the Development of Radiation Optic Neuropathy at "Safe" Doses: A Review of Cases Seen 1994-2014

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Introduction:
Radiation optic neuropathy (RON) is an uncommon but often visually devastating complication caused by radiation therapy to structures near the anterior visual pathways. Published reports have identified a radiation dose of less than 55-60 Gy,[1,2] or 8 Gy for stereotactic radiosurgery,[3] below which RON is unlikely to occur. Having observed multiple cases of RON occurring at doses below these thresholds, we attempted to identify potential risk factors for the development of RON in these patients.

Methods:
Retrospective chart review of patients with the diagnosis of radiation optic neuropathy seen between 1994 and 2014.

Results:
Thirteen patients with 18 affected eyes were included in the study. The radiation modalities included external beam radiation (N=5), whole brain radiation (N=2), stereotactic radiosurgery (N=2), proton beam (N=3), and unknown (N=1). For patients with known target tissue doses (N=10), the mean dose (±standard deviation) was 50.2±13 Gy, with only 2/10 patients receiving ≥55 Gy. For eyes with available follow up (mean follow up: 15 months), 4/14 were NLP (29%), 6/14 (43%) were 20/200-HM, 2/14 (14%) were 20/50-20/200, and 2/14 (14%) were 20/40 or better, at the last visit. Of the patients who received a target tissue dose of <55 Gy, 6/8 had vasculopathic risk factors, such as a past history of heavy smoking, hypertension, and hyperlipidemia. Multiple treatment modalities were attempted, including steroids, anticoagulation, hyperbaric oxygen, bevacizumab, and blood viscosity reduction, with no improvement in vision in the majority of eyes (10/14), although a minority showed relative stability in visual acuity (4/14).

Conclusions:
RON can occur with different radiation modalities and can also occur at target tissue doses often thought to be within "safe" levels (<55 Gy). Vasculopathic risk factors may increase the risk of RON, leading to occurrence at lower doses. Prognosis continues to be poor, with no clearly effective treatment modality.

References:
1. Mayo C, et al. Radiation dose–volume effects of optic nerves and chiasm. Int J Radiation Oncology Biol Physics. 2010; 76(3): S28-S35.
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Keywords: Chemotherapy And Radiation Injury, Optic Neuropathy, Neuro-Ophth & Systemic Disease

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Poster 12

Optic Neuritis After Refractive Surgery: Causal Or Coincidence?

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Introduction:
Although the number of laser-assisted in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) procedures performed is growing steadily, there are no reports in the literature on associated optic neuritis.

Methods:
In this retrospective observational case series, we report three patients who developed acute visual loss following refractive surgery. All three underwent complete eye examinations with detailed evaluation of the optic nerve, Humphrey 24-2 SITA visual field testing, retinal nerve fiber layer thickness using optical coherence tomography (OCT) instrument, serologic evaluation, and magnetic resonance imaging of the brain and orbits.

Results:
Two patients underwent LASIK and one PRK. All had clinical evidence of optic neuritis, manifested by a subjective decrease in visual acuity and visual field abnormality, and relative afferent pupillary defect. Two had normal-appearing optic discs and one had optic disc edema initially. Two of the patients had remarkable recovery of visual function within two weeks, while one showed no signs of recovery and developed optic atrophy in the affected eye.

Conclusions:
Optic neuropathy has been previously reported after LASIK surgery due to barotrauma or ischemia, related to extreme elevation of intraocular pressure that occurs during a portion of the procedure. There are no reports in the literature on other etiologies for optic nerve disorders associated with LASIK and PRK. Anxiety could be considered a plausible trigger of optic neuritis after refractive surgery.

References:
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2. Ackerman, Heyman, Rabin, Anderson, Houck et al.: Stressful life events precede exacerbations of multiple sclerosis. Psychosomatic Medicine,64, 916, 2002.

Keywords: Optic Neuritis, Visual Field Testing, Diagnostic Tests, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 13

Long Term Treatment of Lebers Hereditary Optic Neuropathy With Idebenone.

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Introduction:
Lebers hereditary optic neuropathy (LHON) has classically been viewed as a non-treatable disease. However, recently there have been several publications, including case reports, retrospective and prospective studies, which document visual improvement with the use of Idebenone. We report a case of Lebers heredity optic neuropathy treated with Idebenone that showed significant visual recovery.

Methods:
A case report.

Results:
A 47 year old white male presented with visual loss of unknown etiology that was determined to be LHON mutation 11778. Vision on presentation was 20/400 OD and HM OS. Color vision was 4/8 OD and 0/8 OS. He was placed on 900mg of Idebenone QD in September 2012 and followed. At recent visit in October 2014, his best corrected vision had improved to 20/25 OD and 20/200 OS with 7.5/8 color vision OU. His VEP shows improvement consistent with exam.

Conclusions:
This case supports the treatment of long term Idebenone alone for LHON and documents VEP improvement in this setting. The retrospective case series on Idebedone treatment had variable treatment protocols. The prospective case series studied patients on treatment for only six months. Another case report shows concomitant use of Idebenone with IV steroids and oral co-enyzme Q. Our patient received only oral Idebenone after diagnosis and has been on it for 24 months with significant improvement.

References:
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2. Klopstock T1, Yu-Wai-Man P, Dimitriadis K, et al.
A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. Brain. 2011 Sep;134(Pt 9):2677-86
3. La Morgia C1, Carbonelli M2, Barboni P3, Sadun AA4, Carelli V1.
Medical management of hereditary optic neuropathies. Front Neurol. 2014 Jul 31;5:141

Keywords: Genetic Disease, Visual Fields, Diagnostic Testing

Financial Disclosures: The authors had no disclosures.

Grant Support: The Eye Sight Foundation of Birmingam, AL

Poster 14

Macular star formation in diabetic patients with non-arteritic anterior ischemic optic neuropathy (NA-AION)

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Introduction:
NA-AION is a condition that exhibits a number of unique characteristics in diabetics compared with the rest of the population. In some diabetic patients with NA-AION, lipid deposits can be observed around the macula forming an incomplete macular star.

Methods:
We describe 12 case studies of patients with NA-AION observing the development of lipid deposits around the macula forming an incomplete macular star.

Results:
All our patients developed some level of lipid deposits around the macula in the form of a macular hemistar in the course of their illness.

Conclusions:
Some authors have suggested that the macular star is formed by transudation from capillaries deep in the optic disc through the intermediary tissue of Kuhnt, which is located between the retina and the anterior portion of the lamina retinalis. However, the development of the macular star is currently understood not as a simple transudation but as a multifactorial process involving the presence of vascular damage around the optic disc, which is considered one of the most important factors leading to its occurrence. Although some studies mention the presence of a macular star in patients with NA-AION, we believe that this phenomenon may be significantly more common than the current literature suggests.

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3. Lee MS, Grossman D, Arnold AC, Sloan FA. Incidence of nonarteritic anterior ischemic optic neuropathy: increased risk among diabetic patients. Ophthalmology. 2011 May;118(5):959-63.
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Keywords: Lipid Deposits, Neuroretinitis, Non-Arteritic Anterior Ischemic Optic Neuropathy, Macular Hemistar, Diabetes Mellitus

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 15

Seasonal Influence on the Incidence of Biopsy-Proven Giant Cell Arteritis: the University of California Davis Institutional Experience

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Introduction:
Giant cell arteritis (GCA) is a vasculitis that affects large and medium sized arteries. The etiology of GCA is unknown and numerous risk factors have been proposed. We and other investigators have perceived an increased incidence over the summer months and hypothesized that this may represent an unrecognized risk factor for the disease.

Methods:
We performed a retrospective review based on billing codes of temporal artery biopsies performed at the University of California, Davis from January 2000 to June 2014. We recorded patient demographics, onset and nature of presenting symptoms, date of biopsy and, when possible, visual acuity and lab values.

Results:
We identified 175 biopsies (119 female, 56 male) during our time period. Of these, 21 positive biopsies were female while 9 were male. Although twice as many biopsies were performed on women, women were three times more likely to have a positive biopsy. Positive biopsies were significantly more likely to occur in the summer months (June through August) than the rest of the year ($p=0.039$). Patients with a positive biopsy averaged 76 ± 9 years of age.

Conclusions:
Our retrospective study is the first report of the seasonal incidence of biopsy-proven GCA in California. Our data suggests that increased age, female gender and summer months are risk factors for developing biopsy-proven GCA in our region. One plausible hypothesis to explain this finding is that GCA may be due to an infectious agent, such as CMV, parvovirus or Mycoplasma. Our data support this hypothesis, however, to date no infectious agents have consistently been isolated from positive biopsies.

References: None.

Keywords: Giant Cell Arteritis, Seasonal Incidence, Biopsy-Proven, California

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Poster 16

Possible Revatio (Sildenafil) Induced Optic Neuropathy in Mice

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Introduction:
Purpose: To investigate possible Revatio (sildenafil) induced optic neuropathy in mice.

Methods:
Right optic nerve crush (ONC) was induced in 53 out of 134 mice used. Revatio was administered with and without ONC. In the ONC group, 27/53 received intravitreal (IVT) injection of Revatio (0.24µg/3µl) immediately before ONC induction and 26/53 mice received no treatment (saline). The left eyes served as a control. In remaining 81 mice without ONC induction, 21/81 were injected IVT and 60/81 intraperitoneally (IP, 24µg/300µl). FA was performed (day 0). Quantitative real-time PCR was used to quantify optic nerve apoptosis-related, oxidative-stress and ischemic-related gene expression on days 1 and 3. Retinal and optic nerve histology was examined on days 14 and 21 using flat mount, H&E, 2,3,5-Triphenyltetrazolium chloride (TTC) and luxol fast blue (LFB).

Results:
Maximal retinal vessels dilatation and increased choroidal effusion were detected by FA immediately after IVT Revatio injection, and 30 minutes after IP injection. At 21 days following ONC and IVT Revatio, RGCs were protected relative to ONC without treatment. In the Revatio injected mice without ONC induction, IVT produced no RGC loss on histology, or optic nerve stroke, at 14 or 21 days from the injection (n=10). However, molecular studies revealed 2 stroke candidates nerves (2/11) and increased Bcl-2 on day 1 which reverted to baseline at day 3. Following IP Revatio (n=40) 6 animals showed RGC loss and associated optic nerve damage histologically. All genes measured in the IP group without ONC (n=20), relating to apoptosis and oxidative-stress, decreased (<0.5 fold) on both days 1 and 3.

Conclusions:
Revatio increased choroidal perfusion and mildly dilated retinal vessels. Injection immediately before ONC, revealed a possible neuroprotective effect. Without ONC induction, possible occurrence of optic nerve stroke was observed, This might be associated with vessel dilatation and reperfusion, affecting optic nerve autoregulation.

References: None.

Keywords: Revatio (Sildenafil), Optic Neuropathy, Optic Nerve Crush, Mouse Model, Optic Nerve Stroke

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Poster 17

Cyclosporine Induced Papilledema without Elevated Intracranial Pressure

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Introduction:
Cyclosporine (CsA) is an immunosuppressant used to prevent renal transplant rejection. CsA has documented central nervous system toxicities including pseudotumor cerebri syndrome. We present a patient taking CsA for 20 years found to have papilledema without increased intracranial pressure, which resolved after discontinuation.

Methods:
Case report and literature review including data query of the World Health Organization Uppsala Monitoring Centre's medication related ocular toxicities.

Results:
A 48 year-old male with history of cadaveric kidney transplant August 26, 1991 due to chronic glomerulonephritis, was found to have papilledema on routine eye exam for blurred vision at near only. He denied transient visual obscurations, diplopia, pulse synchronous tinnitus, snoring, or weight change. Medications included azathioprine 150 mg daily and cyclosporine 175 mg twice daily. Neuro-ophthalmic examination revealed distance visual acuity without correction right eye 20/20-1, left eye pinhole 20/25+2. The remainder of his neuro-ophthalmic examination was normal with exception of bilaterally enlarged blind spots with superior arcuate depression both eyes and severe Frisén grade V papilledema.MRI brain was normal. Lumbar puncture found an opening pressure of 15 cm H2O and normal cerebral spinal fluid. Renal function, blood pressure and BMI were normal. Cyclosporine was discontinued with improved vision left eye and gradual resolution of bilateral disc edema over the subsequent 9 months .Query of the WHO database found 59 cases of papilledema with mean onset of 255 days and max of 4 years.

Conclusions:
Cyclosporine is a neutral, lipophilic, cyclic undecapeptide derived from the fungus Trichoderma polysporin, primarily used as an immunosuppressant metabolized by the hepatic cytochrome P-450 enzymes. Current research suggests that cyclosporine modifies mitochondrial structure and function through reactive oxygen species (ROS) which can induce obstructed axoplasmic transport and pseudo-papilledema . We present a rare case of papilledema without increased intracranial pressure due to CsA use after 20 yrs

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Keywords: Cyclosporine, Toxicity, Papilledema, Pseudotumor Cerebri, Immunosuppresion

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Poster 18

Asymptomatic Leukemic Optic Nerve Infiltration as Presentation of Acute Lymphoblastic Leukemia Relapse

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Introduction:
We present a 4 year old boy with history of CNS acute lymphoblastic leukemia (ALL) in remission, diagnosed with leukemic optic neuropathy at a routine eye exam.

Methods:
Vision was equal in both eyes, measuring 20/30 by Allen, considered normal given the age limitations. Color vision (HRR) was normal and equal in both eyes and pupils were equally reactive to light and accommodation without relative afferent papillary defect (RAPD). Fundus examination was normal in the right eye and revealed a white mass covering the left optic disk, completely obscuring it and peripapillar vascular sheathing. The rest of the fundus was normal.

Results:
The MRI showed no enhancement of the optic nerves or brain tissue. There was a questionable diffusion restriction of the left optic nerve head. The peripheral blood smear showed 1% blasts (5% diagnostic for relapse) and the CSF revealed rare cells suspicious of blasts. Chemotherapy was started (Methotrexate and Vincristine). No ocular radiation was performed due to the asymptomatic nature of the condition. At 3 weeks follow up the vision exam was the same and the mass covering the left optic nerve was replaced by mild gliosis with good visualization of the optic nerve head. The fluorescein angiography did not demonstrate any defects. The CSF pathology later revealed blasts as the dominant cells and the bone marrow biopsy revealed hypercellularity confirming the relapse.

Conclusions:
Tumoral optic nerve infiltration may be the first sign of ALL relapse. In our case the vision, color vision and pupillary reflexes were normal and maintained throughout the evolution of the disease.Of note, the absence of enhancement on MRI does not exclude neoplastic infiltration.We recommend routine ophthalmological exam for all patients with history of ALL to exclude optic nerve involvement without systemic symptoms or signs.

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Keywords: Infiltrative Neuropathy, Leukemia

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Grant Support: None

Poster 19

Progressive Visual Loss: An Unusual Presenting Symptom In Giant Cell Arteritis

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Introduction:
Arteritic anterior ischemic optic neuropathy (AAION) due to Giant cell arteritis (GCA) is a rare cause of visual loss in Asian people. However, there are a few AAION cases in Asian that have been reported. In general, patient with AAION usually presented with acute severe visual loss with disc edema and systemic presentation of GCA.

Methods:
Case report

Results:
We herein report a case of 77-year-old Thai man who presented with gradual painless visual loss in his right eye for 2 weeks. His vision progressively deteriorated from 20/40 to counting finger. Fundus examination revealed chalky disc swelling at the same time as when the visual loss started. His associated systemic symptoms were weight loss and limb claudication without scalp tenderness or jaw claudication. On examination, a cord-like lesion of right temporal artery with absence of pulsation was found. An extensive investigation for a definite diagnosis was attempted. The diagnosis of GCA was finally made due to the pathognomonic histopathology result of the temporal artery biopsy. After treatment, his vision slightly improved and stabilized. Limb claudication also improved.

Conclusions:
Due to the unusual presentation, a misdiagnosis may be made in this case. The differences between Caucasian and Asian AAION was reviewed. The temporal artery pulsation, disc character and elevated levels of inflammatory markers are the clues for the diagnosis of GCA. The temporal artery biopsy was the definite investigation for his diagnosis.

References: None.

Keywords: Optic Neuropathy, Giant Cell Arteritis, Temporal Arteritis, Progressive Visual Loss, Ischemic Optic Neuropathy

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Poster 20

Demyelinating Disorder with Optic Neuropathies in a Patient with Monoclonal Gammopathy: Case Report and Literature Review

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Introduction:
Neurologic involvement in monoclonal gammopathy typically consists of demyelinating/axonal peripheral neuropathies with many features in common with chronic inflammatory polyneuritis. Evidence of CNS involvement is occasionally present. Clinical findings reported include nystagmus, ataxia, dysarthria, and extensor plantar responses. MRI scans typically show multiple white matter lesions, similar findings are reported in Chronic Inflammatory Demyelinating Polyneuropathy (CIPD), and similar to MS (1). CSF findings are generally acellular with occasionally elevated protein, oligoclonal bands are typically absent (2).

Methods:
A 55 yo woman complained of blurred vision, slurred speech and unsteadiness with falling over several months. PMH was remarkable only for Benign Positional Vertigo, obesity and hypertension. Examination showed corrected VA of 20/30, 20/50; HRR 4/6 OU, mild disc head pallor on fundoscopy, binocular arcuate defects on Humphrey's 24.2 visual fields collaborated by spectral OCT scans. Neurologic revealed generalized hyperreflexia, wide based unsteady gait, positive Romberg with substandard limb coordination but preserved primary sensory modalities.

Results:
CBC and metabolic panels, VDRL, ACE and B12/folate levels unremarkable. ESR elevated at 68mm. MRI brain showed multiple subcortical white matter lesions; CSF analysis demonstrated acellular fluid, normal chemistries, but elevated monoclonal gamma spike matched by elevated IgM kappa light chain in serum. Oligoclonal bands were absent.

Conclusions:
In this case symptoms, signs, and MRI scans were consistent with CNS demyelination, as reported in other cases of monoclonal gammopathies. The absence of oligoclonal bands (present in 98.5% of MS patients) and matching monoclonal spikes in serum and in CNS suggest the gammopathy is causal. Monoclonal gammopathy should be added to the list of uncommon causes of afferent visual pathway defects.

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Keywords: Optic Neuropathy, Monoclonal Gammopathy Of Undetermined Significance (MGUS), CNS Demyelination

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Poster 21

Retrospective Review of Ophthalmic and Systemic Associations of Optic Nerve Hypoplasia

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Introduction:
Optic Nerve Hypoplasia (ONH) is a leading cause of childhood blindness and visual impairment. ONH is characterized by an abnormally small or cupped optic disc with a subnormal number of axonal fibers. We sought to describe the prevalence of ophthalmic and non-ophthalmic associations of ONH in our practice.

Methods:
A retrospective review of an electronic database which spanned twenty years of a pediatric neuro-ophthalmologist's practice was completed and patients with ONH were identified. Charts were reviewed for sex, symmetry of ONH, coexisting ophthalmological and non-ophthalmological features, and neuroimaging findings.

Results:
Of the 340 patients with ONH, 46% were female and 54% were male. ONH was graded as mild (40%), moderate (31%), or severe (29%). ONH was bilateral and symmetrical in 43%, bilateral and asymmetrical in 33%, and unilateral in 24%. Atypical features of the optic nerve head were identified in 12.1% of patients which included cupping (5.3%), segmental truncation (2.9%), and a dysplastic appearance (3.8%). Other ophthalmological features included strabismus (68%) and nystagmus (51%). Coexisting ophthalmological conditions were identified, including cortical visual impairment (18.5%), high myopia (5.2%), and anisometropia (4.7%). Hypopituitarism was identified in 12.6% of patients. The most frequently identified structural brain abnormalities were absence of the septum pellucidum (15.3%), obstructive hydrocephalus (8.2%), and hypoplasia/aplasia of the corpus callosum (6.5%). There was a high prevalence of neurodevelopmental issues including developmental delay (66.8%), seizure disorder (23.2%), and cerebral palsy (19.1%). Genetic syndromes were identified in 12.1% of patients.

Conclusions:
While retrospective in nature, our study includes one of the largest groups of patients with ONH. Hypopituitarism was identified in 12.6% of cases of ONH which is lower than most reports [1, 2]. We identified a significant prevalence of strabismus, nystagmus, cortical visual impairment, and developmental delay among patients with ONH.

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Keywords: Optic Nerve Hypoplasia, Neuro-Ophth & Systyemic Disease, Pediatric Neuro-Ophthalmology

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Poster 22

Optic Nerve Morphology as Marker for Disease Severity in Cerebral Palsy of Perinatal Origin

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Introduction:
Due to neuroplasticity, it is difficult to prognosticate the eventual neurologic outcome and ambulatory status from perinatal neurological insult till age 2-5 years. The objective of this study is to correlate ONH morphology (disc pallor and cupping) with period of gestation (POG) and severity of neurological damage in children with perinatal onset static encephalopathy (POSE).

Methods:
54 consecutive patients with POSE were enrolled. Exclusion criteria included genetic, metabolic or congenital structural brain abnormalities not related to perinatal complications; intraocular disease (ROP/glaucoma/cataract) and hydrocephalus. ONH morphology (pallor and cup to disc ratio-CDR) was assessed independently by 2 fellowship trained ophthalmologists by dilated direct and indirect ophthalmoscopic examination. ONH were labeled as pale or large cup (cup/disc ratio≥0.5) only if the 2 ophthalmologists agreed. Inter-rater reliability was >0.8 for all parameters. The pediatric neurologist determined eligibility, age of onset of POSE, neurological deficit and reviewed available neuroimaging.

Results:
Mean age was 11.88±6.53years; period of gestation: 33.26±4.78weeks. 33/54 (61%) showed ONH pallor or cupping. Of 17/54 patients with ONH pallor, 88% were quadriplegic and 82% non-ambulatory. Mean CDR was 0.45±0.22; 27/54 (50%) patients had large cup. Multivariate logistic regression models showed that disc pallor was significantly associated with non-ambulatory status (OR: 12.5; p=0.03) and quadriplegia (OR: 21.7; p=0.0025) and large cup was associated with age at examination (OR 1.15; p=0.025). CDR and age at exam showed positive correlation (r=0.42; p=0.002). ONH parameters were not associated with POG.

Conclusions:
ONH changes are common in POSE and are not associated with POG as previously hypothesized. Optic disc pallor, a bedside clinical finding, can serve as a prognostic indicator for severe neurological insult in high risk children with perinatal complications that should prompt early referral for rehabilitation. Recognition of association of cupping with POSE will prevent unnecessary glaucoma examinations under anesthesia.

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Keywords: Optic Disc Pallor, Cerebral Palsy, Optic Neuropathy, Pediatric Neuro-Ophthalmology

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Poster 23

Clinical Characteristics of Optic Neuritis Associated with Viral Infection

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Introduction:
Viral infection is well known to be associated with pediatric optic neuritis (ON) and some of adult ON. The optic neuritis study group reported that 26.1% of ON patients have a viral syndrome preceding visual loss. This study was conducted to characterize optic neuritis associated with viral infection.

Methods:
A retrospective chart review was performed on 124 patients with ON over 15 years old who visited a tertiary referral center in Korea from 2004 to 2014. Demographics, symptoms, signs and laboratory results were reviewed. Magnetic resonance images (MRI) and cerebrospinal fluid findings were also analyzed.

Results:
Seventeen out of 124 ON patients had medical history related to viral infection. There were 9 males (52.9%) and mean (±SD, range) age of onset was 36.07 (±12.82, 18-64) years. Ten (76.9%) patients initially presented with poor visual acuity, which was defined by equal or worse than counting finger. Ocular pain or headache was accompanied in 82.4% of cases. Optic disc swelling was observed in 41.2% of the patients. Good visual outcome, equal or better than 20/40, was observed in 84.6%. Three patients had bilateral optic neuritis and thee patients had recurrent optic neuritis. CSF analysis was evaluated in 12 patients and all patients had normal features. Antinuclear antibody was positive in 3 out of 12 patients. Among six patients who tested aquaporin-4 (AQP4) antibody, 2 patients showed positive result. Central scotoma was observed in 7 patients, and other variable field defects was also observed. Optic nerve enhancement in MRI was observed in 8 out of 15 cases.

Conclusions:
Optic neuritis associated with viral infection has distinct clinical profile compared with idiopathic optic neuritis.

References: None.

Keywords: Demyelinating Disease, Neuro-Ophth & Infectious Disease, Optic Neuropathy

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Poster 24

Methanol causes highly selective retinal ganglion cell layer loss and inner nuclear layer microcysts

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Introduction:
Methanol in adulterated liquor can cause devastating metabolic acidosis, acute neurologic dysfunction, and vision loss by interfering with the mitochondrial respiratory chain.[1,2,3,6] Methanol differentially affects the small caliber axons of the papillomacular bundle.[11]

Methods:
A 19-year-old student developed severe systemic methanol toxicity and relatively mild optic neuropathy. Optical coherence tomography (OCT) showed unique changes.

Results:
A previously healthy woman developed ataxia, confusion, and difficulty breathing hours after drinking homemade alcohol in Indonesia. She was found to have a serum pH of 6.79 and elevated blood methanol which was treated with intravenous ethanol, solumedrol, and sodium bicarbonate. When she awoke she had blurred vision, photophobia, and central scotomas in both eyes.Her visual acuities were 20/30-1 OD and 20/15-1 OS. She had mild central depression on Humphrey visual field (HVF) testing and mild temporal pallor of the optic disc OS. OCT of the retinal nerve fiber layer (RNFL) was normal, but ganglion cell layer (GCL) analysis showed highly selective loss of the nasal fibers OU. Further, OCT of the maculas demonstrated inner nuclear layer (INL) microcysts OU in the corresponding areas of GCL loss.

Conclusions:
Selective involvement of the papillomacular bundle is common in toxic optic neuropathy. Prior OCT studies in methanol toxicity have shown diffuse RNFL thinning, typical of the widespread destruction of axons.[5,12,6,7] Retinal ganglion cell loss may be an early indicator of optic neuropathy.[8] The relative sparing of the optic nerve in this case shows the evolution of methanol toxicity with early segmental GCL involvement and preservation of the RNFL. INL microcysts have been observed in a variety of diseases, but have not been described in methanol optic neuropathy.[4,9,10] These findings support that INL microcysts are non-specific and may signify preferential loss off small caliber axons of the papillomacular bundle rich in mitochondria, which are most vulnerable in energy-depleted states.

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Keywords: Methanol Toxicity, Microcysts, Ganglion Cell Layer, Optical Coherence Tomography, Papillomacular Bundle

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Poster 25

Parsing the differences between LHON affected: genetic vs environmental triggered disease

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Introduction:
We aim to demonstrate that “purely genetic” and “tobacco-triggered” LHON may be different diseases.

Methods:
We present three LHON affected brothers: two cases strikingly resembled “tobacco-alcohol amblyopia”, with late-onset after decades of heavy smoking and strict temporal loss of fibers, whereas the third brother had classic severe LHON presentation in adolescence. In two cases (classic LHON and tobacco-related) we studied postmortem optic nerve cross-sections. We also retrieved the information on age of onset and environmental exposure in a large cohort of Italian LHON patients (n=134) and unaffected mutation carriers (n=126) and analyzed the data as in Kirkman et al., (Brain 2009).

Results:
At histology a devastating loss of axons involved the entire optic nerve with some peripheral sparing in the young-onset case, whereas the late-onset, tobacco-related case had a selective loss of temporal axons. In the Italian cohort, 2/3 of the affected individuals were smokers, compared with 1/2 of the unaffected carriers. Purely genetic cases (non-smokers) had a median age of onset of 16 yrs with a tight distribution, whereas smokers had a broader distribution with a median age of onset of 29 yrs. Gender stratification further highlighted tighter distribution of age of onset in males. The Kaplan-Meyer curve corroborated the existence of two distinct subpopulations in affected individuals, related to age of onset and tobacco exposure.

Conclusions:
LHON can be distinguished in a “classic” early-onset form (15-30 years), with a prevalent genetic predisposition. A second late-onset form (>40 years) is strongly associated with long-term (decades) heavy smoking and most of these patients remained unaffected if avoided smoking. This distinction is crucial for identification of nuclear genetic modifiers of LHON penetrance. In fact, the genes most important for conversion in pure genetic cases may not be the same genes critical in tobacco-induced LHON.

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Keywords: Genetic Disease, Optic Neuropathy

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Poster 26

Changes in Macular OCT Retinal Sublayers of Patients and Carriers in the Natural History Phase of the Leber Hereditary Optic Neuropathy G11778A Gene Therapy Clinical Trial

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Introduction:
We determined macular retinal sublayer changes of patients and carriers with G11778A Leber hereditary optic neuropathy (LHON) by utilizing data from the natural history phase of the gene therapy trial where subjects underwent visual examination every 6 months from 2008 to 2013.

Methods:
Spectral-domain Cirrus OCT 512x128 macular cube scans were segmented for the baseline examination. Segmented retinal sublayers were the RNFL, GCL-IPL, INL-OPL, ONL-IS, and OS. Poor quality scans that cannot be segmented accurately were excluded. The thickness of the retinal sublayers of the LHON subjects and carriers were compared to a normal group.

Results:
Segmented macular OCT data were available from 20 LHON subjects (age 31$\pm$14 years, range 10-61), 31 LHON carriers (age 38$\pm$18, 9-65), and 14 normal subjects (age 39$\pm$13, 23-61). In general, parameters were not significantly correlated with age in any of the groups. There were no differences between carriers and normals for any sublayers but some layers were thinner or thicker in LHON subjects. Layers showing the most striking differences between LHON and the other two groups included the RNFL, GCL-IPL, and OS (p-values from 0.046 to <0.001). LHON RNFL and GCL-IPL were thinner than carriers and normals while LHON OS was thicker than carriers and normals. Differences between groups were not significant in the INL+OPL. The ONL+IS layer of the temporal and inferior quadrants (inner and outer macular annular rings) was thicker in LHON ($0.041 \geq p \geq 0.009$).

Conclusions:
LHON patients, compared to normal subjects, have thickened photoreceptor outer segment layer and some thickening of the ONL-IS in spite of having thinner RNFL and GCL-IPL layers. LHON carriers have retinal sublayer thickness similar to normal subjects. The findings indicate optic nerve degeneration in LHON also has an effect on the morphology of the outer retina.

References: None.

Keywords: Leber Hereditary Optic Neuropathy, OCT, Photoreceptor Outer Segment

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Poster 27

Low Grade Glioma of the Pituitary Stalk, Case Report with Review of the Literature.

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Introduction:
In adults, thickening of the pituitary stalk can be the result of primary or secondary tumours, inflammatory or vascular lesions.[1] Glioma of the pituitary stalk is rare. Only two other cases have been reported in the English literature.[2,3]. Clinical, imaging and pathological features of this rare tumour will be presented.

Methods:
Case report

Results:
A 39 year old female presented with diabetes indipidus (DI) and amenorrhea. Investigations revealed panhypopituitarism and as well as thickening of the pituitary stalk. She was followed up for a year during which the lesion enlarged causing visual field loss. Initial biopsy was inconclusive. Subsequent stereotactic biopsy revealed features compatible with a low grade glioma.

Conclusions:
To our knowledge, only two other cases of glioma affecting the pituitary stalk have been published. Although rare, this tumour should be considered, especially in cases presenting with DI and pituitary stalk thickening. Other glial tumours in this region, namely pituicytoma, spindle cell oncocytoma and granular cell tumour, do not usually presently with DI, prolactinemia or galactorrhoea. These tumours usually present with visual disturbance and headache.[4] Stereotactic biopsy increases the accuracy of targeting the lesion and obtaining diagnostic yield[2].

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Keywords: Pituitary Stalk Enlargement, Glioma, Diabetes Insipidus, Tumors, Visual Fields

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Poster 28

Visualisation of nerve fibre orientation in the human optic chiasm using photomicrographic image analysis

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Introduction:
Compression of the optic chiasm typically gives rise to bitemporal hemianopia due to selective damage to the decussating nasal fibres. It is unclear why nasal fibres are particularly vulnerable to the extent of generating a sharp vertical cut-off in the visual fields. One theory suggests that this is due to the geometry of individual fibres within the chiasm.[1] Unfortunately, detailed anatomical information about the precise arrangement and crossing of nerve fibres in the chiasm is limited. This study aimed to clarify the microscopic anatomy of the chiasm, looking particularly at nerve fibre distribution and the location of nerve fibre crossings.

Methods:
A human optic chiasm obtained at autopsy was stained *en bloc* with silver stain and sectioned in the axial plane at 5 µm intervals. Photomicrographs were digitized and subdivided into smaller regions of interest (ROIs). Fibre orientation distribution data for each ROI were obtained and processed using *ImageJ* software and custom-written MATLAB code. The orientation data and crossing angles were then represented graphically.

Results:
The central portion of the chiasm was found to contain fibres travelling predominantly in parallel in a medio-lateral direction. Nerve fibre crossings were located in the antero-inferior and supero-posterior portions of the para-central parts of the chiasm.

Conclusions:
This study suggests that nerve fibre crossings are not located centrally in the chiasm but in the paracentral regions. The data from the study will be used to inform models of the optic chiasm which, in turn, will generate further insight into the pathophysiology of bitemporal hemianopia.

References:
1. McIlwaine GG, Carrim ZI, Lueck CJ, Chrisp TM. A mechanical theory to account for bitemporal hemianopia from chiasmal compression. Journal of Neuro-Ophthalmology. 25(1), 40-3, 2005

Keywords: Optic Chiasm, Histology, Bitemporal Hemianopia, Photomicrographs

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Poster 29

Optic Neuropathy in Chronic Lymphocytic Leukemia

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Introduction:
Central nervous system involvement in chronic lymphocytic leukemia(CLL) is rare. It may manifest with cognitive dysfunction, cerebellar signs, or cranial nerve palsies (1,5,6) . Optic neuropathy (ON) in CLL is extremely rare with few previous reports described. Diagnosis is typically made from CSF analysis. Previous case studies have reported successful treatment with radiation or intrathecal methotrexate. We report an unusual case of CLL optic neuropathy.

Methods:
A case report is described.

Results:
A 42 year old African American male with history of CLL in remission presented with subacute onset of right sided blurry vision. Visual acuity was 20/30 OD, 20/20 OS with right afferent pupillary defect. Fundoscopy revealed 2+ disc edema OD, 1+ disc edema OS. MRI brain and orbits showed bilateral diffuse optic nerve enlargement. The patient underwent lumbar puncture (LP), which revealed 13 wbcs/microL (95% lymphocytes)with negative cytology and flow cytometry Patient's disc edema was re-evaluated at 1 month, and had increased to 3+ OD, 2+ OS. Biopsy of the tissue adjacent to the right optic nerve was performed, which revealed abnormal B cell lymphocytic proliferation. Repeat LP revealed 13 wbcs/microL (100% lymphocytes) with cytology and flow cytometry showing clonal B cells co-expressing CD5 with kappa light chain restriction. This patient was treated with intrathecal methotrexate and chemotherapy (ibrutinib). At 3 month follow-up, his disc edema had improved to 1+ and visual acuity to 20/25 OD.

Conclusions:
We report an unusual case of CLL ON, diagnosed by peri-optic nerve biopsy after negative initial CSF cytology, suggesting that multiple LPs may be necessary to diagnose CNS involvement in CLL. While previous reports have described ON development during hematologic relapse, this patient's symptoms developed while in remission. Additionally, this case describes successful use of intrathecal methotrexate with chemotherapy, without need for orbital radiation, in a patient with CLL ON.

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Keywords: Chronic Lymphocytic Leukemia, Optic Neuropathy, Disc Edema

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Poster 30

How is Eye Fixation Affected by Optic Neuropathy? Diagnostic Value of Precise Recording of Retina Movement During an OCT Scan

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Introduction:
Instability of fixation and emergence of alternate preferred retinal loci (PRL) for fixation are well described in macular disease, but have not been well characterized in optic neuropathy. We evaluated the extent of retinal movements recorded during a standard OCT macular volume scan and explored its diagnostic utility.

Methods:
19 patients with central visual field loss from optic neuropathy (14 unilateral, 5 bilateral) and 11 normal subjects underwent OCT scanning with eye tracking (Spectralis, Heidelberg Engineering). Subjects fixated on an internal central blue target during OCT volume scans acquired with SLO eye tracking, lasting approximately 30 seconds. The distribution of fixation points on the retina with respect to the anatomic fovea during the OCT scan was quantified using Kernel Density Estimation (KDE). Each patient underwent EDTRS visual acuity testing and perimetry (Goldmann or Humphrey 24-2 SITA) to confirm central visual field loss.

Results:
Stability of fixation, measured by the area enclosed by the 68% isoline of the KDE of retina position, was significantly worse in the 22 eyes with optic neuropathy (mean=0.7 deg^2) compared with the 33 unaffected eyes (mean=0.062 deg^2) (two-sample t-test, p=0.005). Multiple PRL of fixation were identified in 8/22 eyes with optic neuropathy, and the degree of extra-foveal fixation was greater in eyes with optic neuropathy (two-sampled t-test, p=0.001). In patients with unilateral optic neuropathy, ANOVA identified a difference in fixation stability (p=0.013) and eccentricity of fixation (p=0.043) between the eyes with optic neuropathy and their paired, unaffected eyes.

Conclusions:
We introduce a readily accessible method of eye tracking recorded during OCT to provide an objective measure of fixation, which was significantly impaired in patients with optic neuropathy who have central visual field loss. Fixation stability assessed during standard OCT may help differentiate causes and severity of vision loss and facilitate monitoring of optic nerve function.

References: None.

Keywords: Optic Neuropathy, Fixational Eye Movements, Diagnostic Tests, Optic Coherence Tomography, Scanning Laser Ophthalmoscope

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Poster 31

A Novel OPA1 Mutation in Autosomal Dominant Optic Atrophy (ADOA)

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Introduction:
Autosomal dominant optic atrophy (ADOA), or Kjer's disease, often overlaps clinically with other forms of optic atrophy making diagnosis challenging. Considering the potential for ADOA to cause significant visual impairment and its high degree of penetrance, it is important to make the correct diagnosis for both the individual patient and the family members.

Methods:
Here we describe a case of ADOA in a 61-year-old West African male who presented after several years of symptoms. Our investigation resulted in the detection of a novel mutation in OPA1 that had not been previously classified.

Results:
The patient presented with complaints of bilateral visual decline, beginning in his 30s, progressing over 10-15 years and then stabilizing. Examination was significant for the following findings: visual acuity of 20/100 OD, 20/80 OS and abnormal Ishihara testing in both eyes without APD. Fundoscopic examination revealed temporal disc pallor and thinning was confirmed on OCT. Previous testing showed reduced amplitudes and prolonged latencies on VEP and bilateral nasal visual field defect on microperimetry. Multifocal and full field electroretinography was normal and pedigree revealed similarly affected family members. Closer consideration of test results helped identify ADOA as the most likely cause of vision loss. Genetic testing identified a novel pathologic mutation in OPA1, variant c.748 (isoform 8) G>A; p.A1a250/Thr.

Conclusions:
Our patient was diagnosed with a rare cause of optic atrophy, years after symptom onset and fragmented care at multiple institutions. Genetic testing in concert with his clinical presentation revealed ADOA as the most likely diagnosis. This case helps further characterize ADOA by introducing a novel mutation and demonstrating its clinical significance. It also serves as a reminder that selective genetic testing can and should be performed after patient counseling and following initial laboratory and imaging work-up for progressive bilateral vision loss.

References: None.

Keywords: Genetic Disease, Optic Neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 32

The vegetative aspects of neuroprotective action of high corticosteroid doses in compressive traumatic optic neuropathies (TON).

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Introduction:
Approaches to traumatic optic neuropathy treatment vary from country to country. High doses of corticosteroids is considered to be standard modality of management in many countries. However, there are several issues related to the possible side effects of this treatment option. The other limitation is inability to use this treatment modality in the first 48 years of the condition.

Methods:
Damage to right optic nerve in surgical setting has been modeled in 22 rabbits. 11 rabbits have been administered methylprednisolone subcutaneously (30mg per 1 kg) starting from the second day for three days. The dose was decreased after the third day of treatment. Control group consisted of 11 rabbits. Heartbeats and amplitude of pupil reaction (2 weeks and one month after trauma) have been measured in all 22 rabbits.

Results:
Methylprednisolone administration resulted in statistically significant elevation of heartbeat to 219$\pm$31 bpm one month post trauma in study group and 182$\pm$23 bpm in control group that proves normalization of the vegetative system functioning. Amplitude of pupil reaction on the affected side has increased from 0mm without treatment to 1$\pm$0.5mm one month after treatment. This proves functional capability recovery of the optic nerve's afferent portion. Furthermore, this means beginning of optic nerve regeneration.

Conclusions:
Use of high doses of corticosteroids facilitates improved function of vegetative system. Therefore, it has neuroprotective action on neural tissue in compressive traumatic damage of the optic nerve in experiment.

References: None.

Keywords: Traumatic Optic Neuropathy, Pupil, Heartbeat, Corticosteroids, Rabbit

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 33

Optic Atrophy in a Large Specialist Hospital

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Introduction:
Optic atrophy is a frequent presentation in our clinics. It is not a diagnosis but represents permanent retinal ganglion cell loss that warrants investigations to establish etiology. Often the result of ischemic insult or neuritis in developed nations, we have noticed many other causes especially the effects of intracranial tumors. Our purpose was to elucidate the demographics and distribution of causes within our population.

Methods:
A prospective, descriptive study of patients presenting with optic atrophy was conducted with institutional IRB approval. Diagnosis was made based on visual acuities, ophthalmoscopic features and ancillary tests. Patient demographics, data from clinical exams and, where possible, VF, OCT, VEP and neuro-radiologic findings were tabulated. Decimal visual acuities were used to facilitate calculations. Sub-populations were compared and correlations determined by Chi-square, Mann-Whitney and Kruskal-Wallis tests. Atrophy secondary to glaucoma and primary retinal causes were excluded.

Results:
353 eyes of 204 patients were diagnosed with optic atrophy over nine months. The mean age was 30.8years (range 0.25-77) with a median of 27years (IQR=27). There were 111 (54.4%) females and 93 (45.6%) males. With statistical significance set at $p=0.05$, there was no difference in age of presentation between the genders. 155 cases (76%) were bilateral whilst 49 (24%) were unilateral. The commonest cause, intracranial tumors, accounted for 123 (60.3%) with the next cause, autoimmune diseases, accounting for 24 (11.8%). Neoplasia was more likely to cause bilateral atrophy than the other causes combined ($p=0.007$) and occurred more in adults than pediatric (<20years) patients when compared to other causes ($p=0.019$). There was no significant correlation between gender or visual acuity and the etiology of optic atrophy.

Conclusions:
Neoplasia was the most common cause of optic atrophy. Although this may have resulted from mostly complicated, advanced case-referrals to a specialist hospital, it may also represent a high incidence of aggressive tumors and low awareness resulting in late presentations in the studied population.

References: None.

Keywords: Optic Nerves, Optic Atrophy, Neoplasia, Intracranial

Financial Disclosures: The authors had no disclosures.

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Poster 34

Neurofibromatosis 1 with Large Suprasellar and Bilateral Optic Nerve Pilomyxoid Astrocytoma

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Introduction:
Bilateral optic nerve gliomas are suggestive of NF1 and typically are low grade (WHO Grade I) pilocytic astrocytoma (PA). Pilomyxoid astrocytoma (PMA) is a newly characterized, aggressive glioma (WHO grade II) with a propensity for the hypothalamic-chiasmal axis. It occurs in a younger age group and has a higher recurrence and lower survival rate. There are few reports associating PMA with NF1.

Methods:
We present a patient with genetically determined NF1 who presented with a large hypothalamic PMA extending to both optic nerves. Clinical, neuro-radiologic and histopathologic findings will be presented.

Results:
A previously healthy 2 year old girl with NF1 was noticed to have limited eye movements, strabismus and decreasing body mass. MRI revealed a large heterogeneous suprasellar and hypothalamic mass, involving the chiasm and extending into both optic nerves. Surgical debulking was performed and pathology revealed spindle-shaped, piloid astrocytes within a rich myxoid matrix. Classified as pilomyxoid astrocytoma, chemotherapy was given but radiation was avoided to avert inducing secondary tumors common in NF1. She has been followed regularly by ophthalmology, neurosurgery and pediatric neurology. On recent exam at 10years of age, she had multiple café au lait spots and axillary freckling. Visions were NPL OD and 20/200 OS. EOMs were full with a large angle right exotropia. Pupils were sluggishly reactive, anterior segments revealed few iris Lisch nodules but were otherwise normal and ophthalmoscopy revealed bilateral optic atrophy with severe loss of arcuate fibres. Recent MRI revealed post-operative changes but no evidence of residual tumor or recurrence.

Conclusions:
Although NF1 typically presents with pilocytic astrocytoma, the clinically and histopathologically distinct pilomyxoid astrocytoma should be considered. PMA is a more aggressive tumor occurring in a younger age group, and typically has a heterogenous MRI pattern. Its manifestation in this setting likely represents the wide phenotypic spectrum of NF1.

References: None.

Keywords: Neurofibromatosis 1, Optic Nerve Glioma, Pilomyxoid Astrocytoma, Optic Atrophy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 35

Optic neuropathy in Wolfram's syndrome imaged with high-definition spectral domain OCT

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Introduction:
Optic neuropathy is a cardinal finding in Wolfram syndrome (WS), which typically also associates at least one of the following findings: diabetes mellitus, diabetes insipidus and deafness. The aim of this study was to describe genetic, clinical and high definition OCT (HD-OCT) findings in patients with an optic neuropathy associated with genetically confirmed Wolfram syndrome.

Methods:
This cross-sectional study included 19 patients with an optic neuropathy and genetically confirmed WS due to mutations in the *WFS1* gene, including three previously unreported mutations (c.1525_1539del15, c.1153G>T and c.1592_1593dup) and 39 age-matched healthy controls. Routine ophthalmic examinations, including HD-OCT (Cirrus, software version 6.0, Carl Zeiss Meditec, Dublin, CA), with segmentation of the peripapillary retinal nerve fiber layer (RNFL) and of the perifoveal retinal ganglion cell-inner plexiform layer (GC-IPL).

Results:
The mean age at onset of optic neuropathy was 15.9 years (SD=14), significantly younger in patients with compound heterozygous mutations (n=13, mean age=9.1) than in patients with single allele mutations (n=6, mean age=33.3, p=0.001). HD-OCT imaging disclosed diffuse thinning of RNFL and IP-GCL in WS patients, most severely in the inferotemporal parapapillary region (54.15%, p=0.001). GC-IPL thinning was correlated with age in WS patients, in the inferior quadrant (r = -0.611, B = -0.4, p = 0.009) and in the temporal quadrant (r = -0.537, B = -0.412, p = 0.026). RNFL thickness in the temporal quadrant was significantly correlated with visual acuity (r = 0.644, B = 13.01, p = 0.004). Patients with WS had statistically significant larger vertical cup disc ratios, compared to controls (0.62 vs 0.43, p=0.001) and smaller rim areas (1.06 vs 1.45 mm, p=0.001).

Conclusions:
Optic neuropathy in Wolfram's syndrome may present at later ages than previously reported, when associated with single allele mutations in the *WFS1* gene. HD-OCT allows anatomical phenotyping of the optic neuropathy, disclosing diffuse thinning of the retinal nerve fiber layers, with a predominant inferotemporal RNFL loss and associated optic disc cupping.

References: None.

Keywords: Wolfram Syndrome, Hereditary Optic Neuropathy, Optic Neuropathy, OCT, Genetics

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 36

Retinal oximetry (oxygen saturation) and peripapillary vascular diameters in normal eyes and in non-arteritic ischemic optic neuropathy (NAION)

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Introduction:
Retinal oximetry is a non-invasive dual wavelength photo-spectrometric imaging of the retina which gives the oxygen saturation in the retinal vessels. Non-arteritic ischemic optic neuropathy results due to ischemia in the circulation of the optic nerve head. The central retinal artery enters the eye through the optic nerve. The disc swelling may directly affect the arterioles and venules, or the same pathology affecting the optic nerve head circulation may also affect the retinal circulation. We aim to study these alterations in the retinal vessels in cases of non-arteritic ischemic optic neuropathy

Methods:
Fifteen eyes diagnosed to have non-arteritic ischemic optic neuropathy on clinical examination underwent retinal oximetry(Oxymap T1, Oxymap hf, Iceland) to determine the oxygen saturation in the retinal vessels and their diameters. The values obtained from the affected eyes were compared to the other eye and 50 age matched normals.

Results:
Arteriolar diameters were reduced and venous diameters were increased in the affected eyes. Arteriolar saturations were increased, venous saturations were decreased and arterio-venous saturation difference (AVSD) was increased as compared to the other groups. The fellow eye showed alterations in oxygen saturation as compared to the age-matched normal, however the changes were subtle and not statistically significant.

Conclusions:
Decreased arteriolar diameters and increased venous diameters suggest stasis possibly due to the increased pressure due to optic nerve head edema. This may result in increased arterio-venous transit time thus allowing more time for oxygen exchange. This could possibly explain the increased arterio-venous saturation difference. Alterations in the fellow eye need to be confirmed with a larger case series, where favorable results imply that oximetry may be useful in the screening and prevention of ischemic optic neuropathy in patients with disk at risk or systemic diseases like diabetes mellitus or hypertension that place them at risk for NAION and possibly predict NAION in the fellow eye.

References: None.

Keywords: Oximetry, Optic Neuropathy, Ischemia

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 37

Is Ishihara Color Plate Testing As Reliable On IPod/IPhone and IPad as on paper format?

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Introduction:
Ishihara testing is frequently used to evaluate dyschromatopsia in patients with optic nerve disease. Several electronic versions are available nowadays. We compared results on the electronic versus paper formats in patients with dyschromatopsia.

Methods:
Our study was comprised of 3 groups. Group 1 included 20 normal patients, group 2 had 20 patients with unilateral optic neuropathy and group 3, 21 patients with unilateral maculopathy. All patients performed 3 Ishihara tests (same color plates on paper, iPod and iPad) in an aleatory order. Results were reported on a total of 13. For each patient, the scores of the different versions were compared to verify if a systematic difference was detectable.

Results:
Compared with the normal group, patients in groups 2 and 3 had weaker performances with both paper and electronic formats ($p<0.0001$). Patients in the three groups had more difficulty with the electronic versions ($p<0.0001$). The iPod gave inferior results compared with the iPad ($p<0.0001$). When comparing both normal eyes, in group 1, results were constant for each eye, regardless of the testing version used ($p=0.42$). In groups 2 and 3, the difference between both eyes (normal versus diseased eye) was less pronounced with the paper format and the difference was worse with the iPod than with the iPad ($p=0.002$).

Conclusions:
Our study shows that Ishihara electronic versions are more difficult to perform than the paper format in all groups. Results were different even between electronic devices (iPod/iPad). Considering that other factors can influence the results, such as the versions of color vision tests on the Internet and the type of electronic devices used, we cannot extrapolate on the reliability of the electronic formats compared to the gold standard paper test. However, this study highlights the importance of not comparing results between different formats and even between different electronic devices.

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Keywords: Ishihara Color Plate Testing, Ipod/Iphone/Ipad, Optic Neuropathy, Dyschromatopsia

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Poster 38

Multifactorial Optic Neuropathy - When it isn't always glaucoma.

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Introduction:
We present a case of a rare HLA-B27 associated optic neuropathy masquerading as glaucomatous progression.

Methods:
A 38-year-old male with a history of HLA-B27 positive uveitis presented with an elevated intraocular pressure (IOP) of 60mmHg OD / 30mm Hg OS. He had a past ocular history of bilateral Retisert implants for persistent macular edema after cataract surgery. The patient subsequently underwent glaucoma device implant (GDI) placement and was started on topical therapy. Despite adequate IOP control, the patients vision in his right eye remained LP but the vision had deteriorated from 20/40 to 20/400 OS. Given the patients progressive vision loss and pain, despite adequate IOP, a neuro-ophthalmology consult was obtained. At the time of our exam, the patients vision had decreased to 20/800 OS and the patient was unable to perceive control Ishihara or contrast sensitivity plates. There was a right RAPD and an irregular surgical pupil OS. Ocular alignment revealed a sensory XT in primary gaze with normal motility. DFE revealed bilateral pallor of the optic nerves with C/D ratios of 0.99 OD and 0.5 OS.

Results:
MRI revealed an abnormal T2 signal with enhancement of the optic nerve and retrobulbar tissues. Goldmann visual fields were significant for generalized depression of the visual field sparing an sland of vision nasally OD and global restriction OS. OCT and HRT were not consistent with glaucomatous damage. An extensive workup for suspected optic neuropathy included inflammatory, infectious, autoimmune and neoplastic etiologies. After all testing returned normal, the patient was admitted for IV steroids. Within 3 days of treatment, the patients had subjective improvement of his pain and his vision had improved to 20/80.

Conclusions:
Inflammatory optic neuropathy may initially be difficult to distinguish from glaucomatous damage, however, this case illustrates the importance of a thorough workup and evaluation in cases that masquerade themselves as pure glaucoma.

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Keywords: Glaucoma, Optic Neuropathy, Hla-B27, Uveitis

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Poster 39

Cobalt-Chromium Metallosis with Normal ERG

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Introduction:
Patients with a failed ceramic hip implant replaced by a cobalt-chromium implant may experience wear of the metallic implant from ceramic debris, resulting in elevations in serum cobalt and chromium. Within a year, patients may develop visual loss, sensory-neural hearing loss, hypothyroidism and cardiomyopathy. The visual loss has been assumed to be a toxic optic neuropathy. A previous case of cobalt/chromium toxicity suggests retinal involvement, with photopic ERG showing delayed and reduced amplitude and scotopic ERG showing reduced amplitude with an electronegative waveform.[1] Here, we present a patient with early cobalt/chromium metallosis.

Methods:
Case Report

Results:
A 66 year-old man with amblyopia OD presents with a two-month history of decreased color and acuity OU, difficulty hearing, cold intolerance, and cognitive decline. Seven months prior, he underwent a left cobalt-chromium head replacement for a failed ceramic hip. At time of presentation, the patient's serum cobalt was 1,076 ug/L (normal <0.9 ug/L) and his chromium level was 57 ug/L (normal <0.3 ug/L). On examination, his visual acuity was 20/30 OS and 20/80 OD with no RAPD. He saw 0/6 color plates OU. Fundi were normal. Humphrey 24-2 and 10-2 VF revealed central depressions OU. Multifocal VEP showed regions of central depressions consistent with defects seen on visual fields. OCT revealed retinal layers within normal limits, including the nerve fiber layer thickness OU. ISCEV Standard full-field ERG showed a normal latency and normal amplitude in both photopic and scotopic responses.

Conclusions:
Previous studies are divided as to whether cobalt/chromium toxicity causes damage to the retina or optic nerve.[1-4] Here, in our early case of cobalt-chromium metallosis, the results are not consistent with a retinal origin.

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Keywords: Optic Neuropathy, Neuro-Ophth & Systemic Disease, Diagnostic Tests, Visual Fields

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Poster 40

Nonarteritic Anterior Ischemic Optic Neuropathy (NAION): A Misnomer. A Non-Ischemic Papillopathy Caused By Vitreous Separation

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Introduction:
The fact that vascular abnormalities such as disc hemorrhages and swelling are present at the time of visual loss in NAION, followed by peripapillary vascular narrowing and ensuing disc pallor is enticing, but not etiologically conclusive for ischemia. There is both optic disc as well as retinal evidence that whiteness with disc swelling is indicative of axoplasmic stasis (cotton wool spots) that may also occur simply from anatomic distortion of axons rather than occlusion of vessels.[1] It may also occur from mechanical stretching and fracture of the axonal cytoskeleton [2] and frank membrane disruption with axoplasmic "leakage."

Methods:
Thirty-three patients with new-onset NAION and controls were examined for vitreous separation. Patients underwent OCT scanning to assess vitreous attachment to the peripapillary area. If no attachments were noted by OCT or by ophthalmoscopy, dynamic B-scan ultrasonography was performed to assess for total vitreous detachment.

Results:
Vitreous was fully detached from the optic disc in 40% of affected eyes while in the remaining 60% there was complete parapapillary detachment and only partial residual attachment to the disc. Findings were consistent with those reported in NAION showing complete peripapillary vitreous separation in all cases and elevated percentages of complete vitreous detachment from the disc (35-65%). [3,4] Teleangectatic vessels on the disc surface in 10% correlated with visual field sparing and corresponded to areas of unseparated vitreous under tension. In age-matched individuals, only 10% had complete PVD, 70% partial PVD, and 20%, no PVD.

Conclusions:
Where ILM is absent over the disc and peripapillary retina and, most notably in cupless discs, vitreous adhesions are strongest, vitreous separation may momentarily stretch and elongate axons, breaking the cytoskeleton in more aged and less distensible axons,[5] leading to immediate axoplasmic accumulation and axonal atrophy in the prelaminar sites of separation. Ischemic pathophysiology need not be invoked in so-called NAION.

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Keywords: NAION, Optic Neuropathy, Diagnostic Tests, Vitreous Separation, Axonal Cytoskeleton Fracture

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Poster 41

Visual and Oculomotor Outcomes in Children with Posterior Fossa Tumors

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Introduction:
As the survival rate from childhood tumors continues to improve, visual morbidity from childhood cancer is significant. Data are limited regarding visual and oculomotor outcomes in pediatric patients with posterior fossa tumors. We present these detailed outcomes in the largest pediatric cohort yet reported.

Methods:
A six year retrospective chart review of all patients with posterior fossa tumors was performed in the ophthalmology departments of two children's hospitals. Data including clinical presentation, tumor diagnosis and treatment, and ophthalmic findings from the most recent eye exam were recorded.

Results:
We identified 139 patients (42.4% female) with posterior fossa neoplasms. Mean age at diagnosis was 6.74 years, and mean ophthalmologic follow-up after tumor diagnosis was 20.5 months. Common ophthalmic signs and symptoms at presentation included esotropia (26.4%), diplopia (13.8%), and nystagmus (9.2%). The most frequent diagnoses were medulloblastoma in 65 patients (46.8%), juvenile pilocytic astrocytoma (JPA) in 45 patients (32.4%), and ependymoma in 14 patients (10.1%). Surgical resection occurred in 125 patients (89.9%) and 96 (69.0%) underwent radiation and/or chemotherapy. Visual outcomes were "good" (bilateral acuity of 20/20-20/40) in 101 patients (72.7%), "fair" (<20/40-20/200 in one or both eyes) in 12 patients (8.6%), and "poor" (<20/200 in one or both eyes) in 9 patients (6.5%). Medulloblastoma was the tumor type most commonly associated with optic nerve atrophy and a poor visual outcome. Thirty-two patients (23%) developed nystagmus and 59 (42.4%) developed strabismus after tumor resection, among whom 24 underwent eye muscle surgery for persistent diplopia.

Conclusions:
Although the majority of the patients in our cohort had good visual outcomes, 15.1% demonstrated significantly decreased visual acuity in one or both eyes, a finding most often associated with medulloblastoma. In addition, 17.3% of patients underwent eye muscle surgery to correct persistent diplopia as a result of their tumor or secondary to treatment.

References: None.

Keywords: Tumors, Nystagmus, Ocular Motility, Pediatric Neuro-Ophthalmology, Chemotherapy And Radiation Injury

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Poster 42

Radiation Optic Neuropathy and Retinopathy from Low Dose (20Gy) Radiation Treatment.

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Introduction:
The risk of optic neuropathy is thought to be low in patients receiving radiation to the anterior visual pathway in cumulative doses less than 50 Gy. We report a case of radiation optic neuropathy (RON) in a patient who received a total dose of 20 Gy, administered in two fractions.

Methods:
Case report.

Results:
A 44-year-old woman with a history of non-small cell lung cancer (NSCLC) presented with a three day history of painless vision loss OS. Visual acuity was 20/20 OD and 20/40 OS. There was dyschromatopsia and an afferent pupillary defect OS. Dilated fundus exam revealed swelling of the left optic nerve with adjacent nerve fiber layer hemorrhage. There was also a chorioretinal scar in the superior macula and scattered dot-blot retinal hemorrhages. MRI of the brain and orbits with gadolinium demonstrated enhancement of the left optic nerve but was otherwise normal. Five weeks following initial presentation, she developed sudden worsening of her vision OS and was noted to have neovascularization of the disc and a dense vitreous hemorrhage. Eighteen months prior to presentation, the patient underwent proton beam radiotherapy OS to treat a uveal metastasis of her NSCLC. The total radiation dose was 20 Gy, delivered in two 10 Gy fractions. Since that time, she had also been on maintenance chemotherapy for her underlying malignancy.

Conclusions:
Though radiation doses to the anterior visual pathway of less than 50 Gy are generally thought to be safe, the risk of RON increases when treatments are administered in fractions larger than 1.9 Gy[1-2]. Chemotherapy can also potentiate the effects of radiation[3]. Our patient developed radiation optic neuropathy, retinopathy, and neovascularization of the disc (a rare finding) following a relatively low total dose of proton beam radiation. This suggests that even low doses of radiation should be delivered in multiple, small fractions.

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Keywords: Chemotherapy And Radiation Injury, Optic Neuropathy, Tumors

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Poster 43

Bilateral Optic Neuropathy in Superficial Intracranial Siderosis.

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Introduction:
Superficial intracranial siderosis (SIS) results from chronic subarachnoid hemorrhage. It can cause anosomia, sensorineural hearing loss, cerebellar dysfunction, pyramidal signs and dementia. Optic neuropathy is a rare complication of this disorder.

Methods:
A 60 year old man with hypertension and past alcohol and heroin abuse presented with three years of worsening bilateral visual and hearing loss, falls and cognitive problems. There was no history of severe headache or acute symptomatology. Examination showed acuities of 20/30 OD and 20/50 OS with flat, atrophic discs. There was moderate bilateral limb and gait ataxia and evidence of mild dementia.

Results:
Automated perimetry showed inferior altitudinal loss with superior arcuate scotoma OU (mean deviations: -8.31 db OD, -22.81 db OS). OCT demonstrated bilateral superior-predominant peripapillary RNFL loss (mean thickness: 77 microns OD, 58 microns OS). MRI showed evidence of over 30 cerebral and brainstem cavernomas, the largest of which abutted the right frontal horn. Extensive leptomeningeal hypodensity was seen on gradient echo (GrE) imaging, including the basilar cisterns, perichiasmatic region and optic nerve sheaths. Both intracranial optic nerves also showed hypodensity on GrE, implying intraparenchymal hemosiderin deposition. Ventricles were mildly enlarged. Lumbar picture showed acellular CSF with mildly elevated protein and a normal opening pressure of 11 cm H_2O.

Conclusions:
We attributed our patient's optic neuropathy to SIS from recurrent intraventricular and subarachnoid hemorrhage due to periventricular cavernoma. It is important to suspect this diagnosis and order imaging accordingly in patients with an appropriate history.

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Keywords: Optic Neuropathy, Diagnostic Tests (OCT), Visual Fields, Neuroimaging, Vascular Disorders

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Poster 44

Binocular Acuity Summation (BAS) in Multiple Sclerosis (MS): Relation to Retinal Architecture and Visual System Neurophysiology

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Introduction:
The afferent visual pathway (AVP) is commonly involved in MS and neuromyelitis optica (NMO). Patients with/without history of acute optic neuritis (ON) can have inter-ocular differences (IOD) in visual acuity (VA), especially at low-contrast levels, which interfere with BAS. BAS is defined as the degree to which binocular vision is greater than VA of the better eye. Reductions in binocular visual functioning may impair depth/motion perception with important quality of life ramifications.[1,2,3] We determined the relation of BAS to scores for structural, functional and electrophysiological measures of the AVP in an MS/NMO cohort.

Methods:
High and low-contrast letter acuities (LCLA) were assessed binocularly and monocularly in MS/NMO patients and disease-free controls. Clinically significant BAS was defined as ≥ 7 letters (level beyond test-retest variability) improvement upon binocular versus monocular assessment. Spectral domain optical coherence tomography (OCT) and scanning laser polarimetry (GDx) were performed along with visual evoked potentials (VEP) and multifocal VEP (mfVEP).

Results:
Analyses at low-contrast levels (1.25% and 2.5%) in the MS and combined (MS+NMO+control) groups showed greater ability to summate with lower IOD in VA, retinal nerve fiber layer (RNFL) thickness as measured by OCT and GDx, and mfVEPP1 ($p<0.05$ using logistic regression models accounting for age; *p=0.06 for GDx in MS group at 1.25%*). Frequencies of BAS were 4.8% for high-contrast, 38.7% for 2.5%LCLA and 56.5% for 1.25%LCLA. Among 'summators' maximum IOD for RNFL thickness was 8 µm for high-contrast, 12 µm for 2.5%LCLA, and 34 µm for 1.25%LCLA.

Conclusions:
BAS, under low contrast conditions, occurs more frequently and despite greater IOD of RNFL thickness. This may reflect the superior sensitivity of LCLA compared to high-contrast VA to detect perceived visual disability among patients with unilateral ON. Conversely, this may suggest that under low contrast conditions binocular visual function is less sensitive to inter- eye differences.

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Keywords: Binocular Acuity Summation, Low Contrast Visual Acuity, Optical Coherence Tomography, Scanning Laser Polarimetry, Visual Evoked Potentials

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Poster 45

Nutritional Optic Neuropathy after Bariatric Surgery

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Introduction:
We present a case of a patient with nutritional optic neuropathy attributed to copper deficiency as a result of bariatric surgery.

Methods:
Retrospective case report.

Results:
A 47-year-old woman developed progressive blurred central vision. Four weeks after onset of decreased vision, she developed formed, nonthreatening visual hallucinations. Her husband also noticed that she had mild cognitive dysfunction and some falls for 2 months prior to presentation. Her past surgical history was significant for vertical banded gastroplasty 24 years prior, Rouy-en-Y gastric bypass 4 years prior, and a recent C6-7 fusion complicated by pneumonia requiring intubation. Her exam was significant for visual acuity of 20/400 each eye, impaired color vision (Ishihara plates OD: 3/14, OS: 1/14), bilateral central scotomas, and mild temporal pallor of each optic disc. Optical coherence tomography was significant for thinning of the temporal retina bilaterally. Blood tests for vitamin B1, B6, and B12, methylmalonic acid, and red cell folate were sent. The B12 level was elevated but she had an elevated methylmalonic acid level, and a low serum copper level, confirming a nutritional optic neuropathy. Five weeks after beginning copper tablets and B12 injections, the patient reported improvement in her vision and five months after beginning treatment her best corrected visual acuity was 20/25 with each eye. We briefly review a differential diagnosis for bilateral blurred vision with central scotomas including other toxic and nutritional optic neuropathies to put this copper deficiency case in perspective.

Conclusions:
Gradual, progressive, painless, bilaterally symmetric visual loss in a patient with a history of a gastric bypass procedure should prompt evaluation for nutritional optic neuropathy to prevent permanent severe optic atrophy. The visual hallucinations likely were a variant of the Charles Bonnet syndrome as a result of relative visual deprivation.

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Keywords: Optic Neuropathy, Visual Fields, Higher Visual Functions, Neuro-Ophth & Systyemic Disease

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Poster 46

Lyme Disease Mimicking Giant Cell Arteritis

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Introduction:
Steere et al first described a patient who went blind from severe panophthalmitis from Borrelia burgdorferi in 1985[1]. Since then, a spectrum of afferent and efferent manifestations have been reported secondary to Lyme borreliosis including optic neuritis, peri-neuritis and cranial nerve palsies that have expanded our understanding of the neuro-ophthalmic manifestations of this treatable disease.

Methods:
Case Report

Results:
We report a case of a 74 year old Caucasian woman who developed severe headaches over the left forehead and temporal region. As part of her work up at an outside hospital, her brain MRI without contrast was normal. Two weeks later she developed a lower motor neuron facial palsy in association with scalp tenderness, shoulder and neck pain. ESR and CRP were reported to be elevated and she was started on prednisone 70mg/day for presumed GCA. A temporal artery biopsy was negative and prednisone was discontinued. One month later, she developed jaw claudication and an inferior altitudinal defect. ESR was 73mm/hr and CRP was 48.6 and prednisone was restarted for presumed GCA with complete resolution of her systemic symptoms. Two months later while taking prednisone 35mg/day, she developed iritis OS and a swollen optic nerve with an inferior altitudinal defect OD. MRI orbit/brain with gadolinium was normal. ESR was 34mm/hr and CRP 2. Blood work for Lyme disease showed 9/10 positive bands IgG and 3/3 positive bands IgM. CSF had 8 WBCs with normal protein and glucose. CSF Lyme IgM and IgG were positive.

Conclusions:
Ocular manifestations of Lyme disease can involve any ocular structure. Neuro-ophthalmologists often include Lyme disease in the differential diagnosis of optic neuritis and perineuritis in endemic regions. This case demonstrates that this infection can mimic the signs and symptoms of GCA and helps to broaden the clinical spectrum of neuro-ophthalmic manifestations of Lyme disease.

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Keywords: Lyme Disease, Giant Cell Arteritis, Optic Neuritis, Headache

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Poster 47

Structural analyses of the anterior visual pathway in compressive neuropathy

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Introduction:
Pituitary tumors are one of the most common types of brain tumors that can cause progressive blindness. Due to the indolent nature of the vision loss, these patients are often misdiagnosed which can turn a reversible cause of visual dysfunction into a permanent life-altering disability. Adding to the difficulty in treating patients with pituitary tumors is the lack of validated preoperative predictors of visual outcome. The purpose of this study was to determine whether structural changes in the anterior visual pathway differ in patients with good versus poor visual recovery.

Methods:
25 patients (15F: 10M) with radiographic diagnosis of pituitary macroadenomas underwent a neuro-ophthalmic evaluation and spectral-domain optical coherence tomography (OCT) testing pre-operatively and 6-months after surgery. Pre-operative retinal nerve fiber layer thickness (RNFLT) and macular volume (MV) were compared between patients with normalized visual function versus persistent visual deficits after surgery (visual acuity ≤ 20/40; visual field mean deviation ≤ -5.0 decibels).

Results:
There was a significant difference in pre-operative MV (9.9 vs 9.4mm3; p = 0.018) when comparing patients with good versus poor visual outcome. Even after complete surgical decompression of the pituitary tumor, patients with persistent visual deficits had significantly greater thinning of the RNFL at 6 months follow-up (-1.9 vs -7.9μm; p = 0.0002).

Conclusions:
Structural changes seen in the anterior visual pathway may provide new predictive measures of visual outcomes after surgical resection of pituitary tumor. Specifically, visual recovery may be dependent on whether surgical decompression occurs before a critical threshold is reached in patients with compressive neuropathy.

References: None.

Keywords: Tumors, Neuroimaging, Diagnostic Tests, Visual fields

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Poster 48

Changes In Thickness Of Retinal Segments In The Early Course Of Non-Arteritic Ischaemic Optic Neuropathy

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Introduction:
Purpose: To characterise changes of the retinal layers in patients with anterior ischaemic optic neuropathy (AION) aiming to identify imaging markers for predicting the residual visual function

Methods:
Retrospective review of consecutive patients with unilateral AION from January 2010 to December 2013. Case-control analysis of affected eyes at baseline and 1 month later, and fellow eyes. Algorithmic segmentation in layers and division in ETDRS quadrants of optical coherence tomography images of the macula. Regression analysis of retinal layer thickness and best corrected visual acuity (BCVA) in logMAR units and mean deviation of the visual field (VF)

Results:
20 eyes from 20 patients were included in the case-control analysis. At baseline we found significant thickening of the retinal nerve fibre layer (RNFL) at 42.2µm compared to 37.9µm in control eyes ($p=0.002$). The outer nuclear layer (ONL) was also significantly thickened at 96.6µm compared to 90.8µm in the fellow eye ($p<0.001$). After 1 month the RNFL and the ganglion cell layer (GCL) were thinned 17.7% (to 31.2µm, $p<0.001$) and 19.3% (to 66.5µm, $p<0.001$) compared to the contralateral eye. Additionally, the ONL remained thickened at 96.7µm ($p<0.001$). At baseline, we found a significant correlation between the ONL thickness and the VF ($r= -0.482$, $p=0.005$) and the BCVA at discharge ($r= 0.552$, $p<0.001$), as well as between the GCL thickness and the BCVA at discharge ($r=0.411$, $p=0.02$). At the 1 month time point the GCL thinning was correlated with both the VF ($r=0.471$, $p=0.005$) and the BCVA ($r=-0.456$, $p=0.007$)

Conclusions:
Changes in thickness of different layer of the retina occur early in the course of AION and evolve in time resulting in the atrophy of the GCL and RNFL. Very early thickening of the OPL is the earliest predictor of residual visual dysfunction. Thinning of the GCL after 1 month correlates with poorer final outcomes.

References: None.

Keywords: Retinal Ganglion Cell, Ganglion Cell Layer, Ischemic Optic Neuropathy, Optical Coherence Tomography, Visual Fields

Financial Disclosures: The authors had no disclosures.

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Poster 49

A First Case Report Of Chordoid Glioma Invading Optic Nerve

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Introduction:
Chordoid glioma of the third 3rd is a rare, grade II glial tumor, that usually presents a poor outcome due to it's vicinity to hypothalamus and visual pathways. It is considered non-invasive.

Methods:
Case report.

Results:
A 39 yo male with unnoticeable medical history, presented with bi-temporal visual field defects, headache and sleep disorder. Right eye (RE) visual acuity was 1, left eye (LE) visual acuity 0.9; intraocular pressure was in normal range and pupils were isochoric. He had a right relative afferent pupillary defect and bilateral optic disc pallor. Humphrey perimetry showed bi-temporal hemianopia, more extensive in the RE. Except for a slightly diminished prolactine level and thyreotrop insufficiency all hypothalamic and pituitary hormones were in normal range. MRI revealed relatively homogenous mass developed in the anterior part of the 3rd ventricle with MRI signal, T1 isointense/ T2 hyperintense, exhibiting strong and uniform gadolinium enhancement that seemed to invade the right optic nerve. One T2*GRE slice presented a hypointense spot suggestive of micro-hemorrhage or calcification. There was no sign of hydrocephalus.Surgery revealed a tumor inserted into the anterior part of the 3rd ventricle floor and adherent to the lateral walls of the 3rd ventricle and to anterior cerebral arteries. It invaded the chiasm and the right optic nerve dividing its fibers up to the lateral aspect. Excision was subtotal. The tumor exhibited typical features of chordoid glioma; GFAP, CD34 were highly positive, NF was negative and Ki67 was 2-3%. No other oncological treatment was delivered. Thyroid hormones deficit aggravated after surgery and the patient developed cortisonic deficiency requiring substitution.Residual tumor remained stable and visual field improved over a period of 18 months of follow-up.

Conclusions:
This is a first case report of a chordoid glioma invading optic nerve.

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Keywords: Chordoid Glioma, Optic Nerve

Financial Disclosures: The authors had no disclosures.

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Poster 50

Clinical spectrum of optic neuritis in Indian children at a tertiary care centre

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Introduction:
To study the clinical spectrum of pediatric optic neuritis in Indian children

Methods:
A prospective study of patients diagnosed as optic neuritis below 20 yrs of age at a tertiary care centre. 28 cases (44 eyes) were reviewed. The ophthalmological examination findings, Goldmann perimetry, electrophysiological tests and MRI were analysed.

Results:
The study patients had a mean age of 12.64 ± 4.95 yrs and were followed up for a mean period of 6.38± 4.99 months. 32.1% were females (F: M – 0.47). Six patients (20.7%) had a viral prodrome and 12 (42.9%) complained of painful ocular movements. The mean baseline visual acuity was 1.80 ± 0.6 logMAR units and the last best visual acuity was 0.43 ± 0.4 log units. Thirty six eyes (81.8%) had a visual acuity of 3/60 or lower and 40 eyes (90.9%) had 6/60 or lower of the snellen chart at the time of presentation. Sixteen patients (57.1%) had a bilateral presentation and 20 (71.4%) had papillitis. All patients were given intravenous steroid treatment. At one wk, 21 out of 44 eyes (47.7%) had a visual acuity ≥ 6/18 of the snellen chart. Three patients showed demyelination changes on MR imaging of brain. Those below 10 yrs of age presented more commonly with papillitis (p value = 0.01).

Conclusions:
Pediatric optic neuritis patients have poorer initial visual acuity, but are associated with a faster recovery and a better visual outcome. There are no gender differences in either the presentation or the visual recovery. Papillitis was more often seen in children below 10 yrs of age.

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Keywords: Optic Neuritis, Multiple Sclerosis, Vision, Papillitis, Dexamethasone

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Poster 51

Prognosticating factors in nonarteritic ischaemic optic neuropathy

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Introduction:
To review prognosticating factors in non arteritic ischaemic optic neuropathy (NAION)

Methods:
A prospective observational study of 27 NAION patients and 20 controls. Visual acuity, colour vision, contrast sensitivity, slitlamp biomicroscopy, visual evoked potential, Goldmann visual fields, optical coherence tomography, and fundus flourescien angiography, were done and repeated at 1 and 3 months.

Results:
There were 16 males (59.3%) and 11 females (40.7%) with a mean age of 52.9 +/- 8.4 years. The right eye was affected in 20 (74.1%) patients and five patients (18.5%) had bilateral NAION. The mean presenting visual acuity was 1.5 ± 01 logMAR units with 14 patients (51.8%) above 50 years of age. 11 patients (40.7%) had no systemic associations. The remaining had diabetes (14.8%), hypertension (18.5%), both (18.5%) and hyperlipidemia (7.5 %). Visual parameters improved significantly at 1 month follow up (pvalue 0.002,0.01and 0.01 respectively) with no further improvement at 3 months (pvalue 0.08,1.0 and 0.2 respectively). Thirteen patients (48.2%) showed spontaneous visual recovery on follow up. Mean baseline visual parameters were similar in patients with or without systemic disease (P value= 0.2), but the latter improved more on follow up (P value 0.03). Patients with a central scotoma had poorer vision (p value 0.01) and a larger number improved (P value 0.09). Presenting visual acuity and age did not affect the final visual outcome (pvalue 0.2 and 0.7 respectively). There was no significant difference in the VER and optic nerve head parameters at presentation or on follow up between the patients with and without visual recovery.

Conclusions:
NAION patients in Asia are younger with maximum visual recovery in the first month. Spontaneous visual improvement is seen in about half of the patients. Patients with systemic disease and central scotoma have a poorer visual prognosis. Presenting visual acuity, age and gender do not affect visual outcome.

References: None.

Keywords: Optic Neuropathy, NAION, Prognosticating, Systemic Disease

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Poster 52

Sweep My Blindness Away!

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Introduction:
Optic neuropathy secondary to Antiphospholipid antibody syndrome (APS) can result in severe vision loss.

Methods:
Case report.

Results:
A 61-year-old female presented to our neuro-ophthalmology clinic with bilateral subacute painless vision loss. Best corrected acuity was 20/30 bilaterally with normal color vision and papillary examination. Fundus examination revealed normal optic nerves. Humphrey visual fields revealed bilateral central scotomas. Brain MRI with contrast was normal. Serologies revealed positive antiphospholipid antibodies which remained positive on repeat testing. Hematology started 81mg aspirin. Three months later, her acuity worsened to 20/40 bilaterally with inferior nasal field loss OS. CSF was normal and she received IV methylprednisolone for 3 days. Two weeks later she developed inferior nasal field loss in the right eye. Within 3 months her visual fields deteriorated, with bilateral dense inferior altitudinal field loss with central vision of 20/50 bilaterally. Hematology started Plasmapheresis. Her visual fields continued to worsen with peripheral constriction in both eyes with relative sparing of the central 10 degrees. Given her deteriorating vision, Hematology started IVIG despite the absence of systemic involvement of APS. Despite 3 IVIG infusions, central vision worsened to 20/70 bilaterally. Coumadin was contraindicated for the concern of fall risk with her poor vision. In spite of the progressive worsening of vision, no signs of optic nerve examination remained normal and Optical coherence Tomography revealed no RNFL, macular or ganglion cell thinning. Given the discrepancy between her visual testing and physical findings we obtained sweep and pattern Visual evoked potentials (VEPs). Pattern VEP was normal bilaterally and SVEP measured visual acuity of 20/16 OD and 20/17 OS.

Conclusions:
Early diagnosis of confounding functional visual loss allows proper patient management and avoidance of unnecessary and potentially harmful treatments. VEPs offer a means of objectively estimating acuity and therefore could assist with early and accurate diagnosis.

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Keywords: VEP, Sweep, Antiphospholipid, Optic Neuropathy

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Grant Support: None.

Poster 53

Progressive Non-Arteritic Optic Neuropathy As The First Presentation Of Anti-Phospholipid Antibody Syndrome

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Introduction:
To report the clinical presentation and visual outcomes of non-arteritic anterior ischemic optic neuropathy (NAION) with anti-phospholipid antibody syndrome (APS).

Methods:
A non-comparative consecutive case series. Electronic medical records were retrospectively reviewed for all patients with NAION seen at our institution with progressive vision loss with positive APS antibodies between 2001 and 2014. The corresponding clinical records were then reviewed to evaluate the clinical features, laboratory results and visual outcomes.

Results:
Four patients were identified, two of the patients were females and 2 males with a mean age of 63.3 +/- 7.9 years. All patients initially presented with classic altitudinal visual field loss above or below the horizontal midline, with swelling and hemorrhage of the corresponding portion of the optic nerve typical of NAION. Presenting Snellen visual acuity in the affected eye at the time of the first episode of NAION ranged from 20/20 to 20/30, while visual acuity at the time of the second episode ranged from 20/20 to counting fingers. Examination at the time of the second episode revealed ipsilateral visual field loss in their previously unaffected hemi-field, with new, acute optic nerve hemorrhages and disk edema corresponding to the new visual field loss. The interval between the first and the second episodes in the same eye ranged from 15 to 71 days (mean 37 days, SD 25.37 days).

Conclusions:
Patients with NAION, particularly in the setting of progressive or recurrent vision loss, should be tested for APS and promptly treated to avoid progressive severe vision loss. NAION secondary to APS leads to severe progressive vision loss and requires close monitoring and prompt control vs treatment of the underlying hematological disorder.

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Keywords: Antiphospholipid, Optic, Neuropathy, NAION, Visual

Financial Disclosures: The authors had no disclosures.

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Poster 54

Anterior Visual Pathway(AVP) Meningiomas: A Dosimetric comparison of IMRT to Pencil-beam Proton Therapy

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Introduction:
Introduction: Intensity Modulated Radiation Therapy (IMRT) is therapy is the standard technique to minimize dose to nearby organs at risk (OAR) when treating tumors involving or abutting the Optic Nerve. Proton therapy may further decrease the dose to OAR while maintaining primary target coverage. A dosimetry study compared IMRT photons to pencil-beam protons to evaluate the utility of protons in these tumors.Methods: Four representative tumors involving the AVP, treated with IMRT were planned with pencil-beam proton planning. Equivalent target coverage and OAR dose- volume restrictions were applied to both modalities, and dosimetric outcomes compared. Patient 1: large orbital schwannoma. Patients 2,3,4: orbital optic nerve sheath, clinoid, and cavernous sinus meningiomas.Results: Patient 1: ipsilateral retina V20, and mean dose were significantly less with protons. Chiasm dose was substantially less with protons. Pituitary mean dose was substantially less with protons Patient 2 and 3: Ipsilateral retina, pituitary doses, and brain V5Gy, all received significantly less dose with protons. Chiasm dose was no different in patient 2 (due to proximity to target volume), but markedly reduced in patient 3. Pt four: Chiasm V40Gy, Pituitary mean and maximum dose, and ON V40 are all less with proton therapy. Brain V5 was less for protons (50%-70%) in all patients. Conclusions: Pencil beam protons decrease dose to OAR in all but small apical tumors. OAR 1cm to 5cm distant to target volumes receive substantially less dose with protons but clinically relevant differences with IMRT is variable with cavernous sinus and para-clinoid tumors benefiting for more OAR. Brain dose is much less with protons (V5Gy). Protons should be considered for large benign tumors involving the AVP where OAR dose differences impact long term toxicity risk. Small apical tumors can be treated with IMRT photons. Reduced brain dose theoretically may reduce second malignancies.

References: None.

Keywords: IMRT, Proton Therapy, Dosimetric Comparisons, Toxcity, AVP Tumors

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Poster 55

A Case Of Lyme Neuroretinitis- An Elusive Entity

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Introduction:
Lyme disease is a multi-organ systemic infectious disease caused by Borrelia burgdorferi. Neuro-ophthalmic manifestations include papilledema, papillitis, retrobulbar neuritis and neuroretinitis. Using strict diagnostic criteria modified from the CDC surveillance criteria, there are very few cases of “Lyme” optic neuropathy (other than papilledema) in literature. We present the clinical, serological and radiological characteristics of a patient with Lyme neuroretinitis.

Methods:
Single case report and review of literature

Results:
A 10-year-old boy presented with bilateral progressive loss of vision. 2 months prior to presentation, he had suffered multiple tick bites that resulted in several “ring” rashes on his body. 1 month later he developed headaches, vomiting, neck stiffness, bilateral blurred vision and binocular horizontal diplopia. At presentation, exam revealed visual acuity of 20/200 in both eyes, left 6th nerve palsy and bilateral disc edema with macular exudation. He had constricted visual fields and central scotoma on confrontation testing. Contrast enhanced MRI orbit showed bilateral prominent focal nodular enhancement of the optic discs. CSF opening pressure was > 55mm Hg; he had lymphocytic pleocytosis (17 cells) with normal glucose and protein. Western blot of CSF and serum confirmed Lyme. Testing for all other infections including serum and CSF RPR were negative. He received a course of ceftriaxone with acetazolamide following which his visual acuity and fundus exam improved but developed bilateral disc pallor.

Conclusions:
Our patient met Category II criteria (Sibony et al) for optic neuropathy from Lyme’s disease. Using these criteria, only 11 cases of Lyme optic neuropathy were reported in a recent review on the topic (Traisk et al). This patient likely suffered from papilledema secondary to meningitis as well as neuroretinitis, both resulting from Lyme disease. Focal nodular optic disc enhancement on MRI orbits was suggestive of optic disc inflammation

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Keywords: Lyme Disease, Neuroretinitis, Encephalitis, Papillledema

Financial Disclosures: The authors had no disclosures.

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Poster 56

50% of Non-Arteritic Anterior Ischemic Optic Neuropathy Occurs between 40-55 Years Old

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Introduction:
Non-arteritic ischemic optic neuropathy (NAION) is the most common acute optic neuropathy in those older than 50.[1-2] and young onset NAION has been reported in 4-23% of patients.[1-4] Aging is a risk factor for NAION, and the normal rate of retinal ganglion cell axonal loss triples after 50.[5] The aim of our study is to investigate the age of onset of NAION and correlation with risk factors.

Methods:
We performed a retrospective review at a single institution of patients with NAION (2009-2014) and analyzed patient characteristics, visual field, and optical coherence tomography (OCT).

Results:
We studied 57 NAION eyes in 30 patients (32 male, 8 female). NAION led to significant visual field loss (mean deviation AION: -14.1±1.5 dB; control: -1.6±0.5 dB; P<0.001, Mann-Whitney) and thinning of OCT mean retinal nerve fiber layer (AION 63±2 µm; control: 88±5 µm, P<0.001) and ganglion cell complex (AION: 61±2 µm; control: 80±4 µm; P<0.001). Although 50 is commonly considered the cut-off for young onset AION, 50% patients had their first event between age 40-55, with onset at ≤50 in 11 (33.7%) and >50 in 19 (66.3%). We examined the NAION risk factors and found that optic disc drusen was associated with earlier onset by 2 decades (N=2). Optic disc-at-risk was common in all ages (mean optic disc diameter 1.60± 0.04 mm, N = 45 eyes). Analysis of many risk factors revealed that the ≤50 and >50 groups were indistinguishable. Obstructive sleep apnea was the most common risk factor (≤50: 82%, >50: 79%), and vascular risk factors are common in all age groups. Younger patients did have better prognosis, with final visual acuity better than 20/40 in 75% of those ≤50 vs. 21% in >50 group.

Conclusions:
Since 50% of NAION patients had onset at 40-55, >50 should not be considered the common presentation of NAION.

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Keywords: NAION, Age, Risk Factors, OCT, Visual Field

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Poster 57

Evaluation of Retinal Nerve Fiber Layer and Ganglion Cell Complex in a Cohort of Chinese with Optic Neuritis or Neuromyelitis Optica Spectrum Disorders Using SD-OCT

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Introduction:
To evaluate the retinal nerve fiber layer (RNFL) in eyes of patients with typical multiple sclerosis related optic neuritis (MS-ON), relapsing optic neuritis(R-ON) or neuromyelitis optica spectrum disorders (NMO-SD) using SD-OCT.

Methods:
Retrospective and prospective cross sectional study. Patients diagnosed of optic neuritis were recruited between May 2013 and July 2014 in neuro-ophthalmology division. Demographics and clinical features as well as optic disc SD-OCT at least 3 months after the acute attack were analyzed.

Results:
Fifty-seven patients with 79 eyes were evaluated. Three groups included MS-ON (32 cases, 39 eyes), R-ON (8 cases, 13 eyes) and NMO-SD (17 cases, 27 eyes). The mean age in three groups was 32.97±13.8y、44.00±13.37y and 42.41±12.64y, p=0.026 between groups. The RNFL in three groups showed *p*=0.019 between groups. The age was unrelated with the RNFL thickness. The GCC volume in MS-ON group was about 5μm and 10μm thicker than R-ON and NMO-SD group respectively.

Conclusions:
OCT retinal nerve fiber layer and GCC measurement will be helpful in distinguishing NMO spectrum disorders from other forms of MS disease.

References: None.

Keywords: Optic Neuritis, Optic Neuritis, Optical Coherence Tomography, Retinal Nerve Fiber Layer, Retinal Nerve Fiber Layer

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Poster 58

Transient Monocular Vision Loss Upon Awakening: a Benign Phenomenon

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Introduction:
Transient monocular vision loss is often an alarming symptom, as the differential diagnosis includes thromboembolism and giant cell arteritis in the right age group. However, when patients describe waking up with dim or blurred vision in one eye, which resolves quickly, we found workup to be uniformly negative.

Methods:
We describe a group of 16 patients who were referred for transient monocular vision loss upon awakening and review patient characteristics and results of their workup.

Results:
Medical records of 16 patients (14 women and 2 men), ages 20 to 67, who had been seen in the Neuroophthalmology Clinic for transient monocular vision loss upon awakening were reviewed. All except 3 patients had workup. 11 patients had imaging studies and various combinations of carotid dopplers, echocardiograms and hypercaogulable studies. Workup uniformly failed to explain the patients' symptom.

Conclusions:
While transient monocular vision loss is an alarming symptom in most patients, waking up with blurred or dim vision in one eye with subsequent improvement in minutes seems to be an exception. Literature search did not find any description of this phenomenon. The majority of our patients underwent extensive testing for their episodes of visual disturbance. To our knowledge, this is the first report describing a uniformly negative workup in patients presenting with this symptom.

References: None.

Keywords: Transient Vision Loss

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Poster 59

Autosomal Dominant Optic Atrophy In Singapore: Multiethnic Involvement And Report Of A New Gene Mutation Causing Optic Atrophy And Deafness

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Introduction:
Autosomal dominant optic atrophy (ADOA) is a ubiquitous condition causing bilateral visual loss, most commonly related to mutations in the *OPA1* gene, mapped on the chromosome 3q28-q29. Recent data suggests a minimum prevalence of 4.07/100 000 in northern England while ADOA is more rarely reported in Asia. Our study aimed to detect patients with genetically confirmed ADOA in Singapore.

Methods:
We conducted a preliminary cross-sectional study at our institution, testing patients (using direct sequencing of the *OPA1* gene) who had a clinical picture compatible with ADOA, seen at our neuro-ophthalmology clinics between January and August 2013.

Results:
We tested 6 patients after ruling out other causes of bilateral optic neuropathy including glaucoma, Leber's hereditary optic neuropathy, compressive, nutritional and toxic causes. We found 4 patients with genetically confirmed ADOA on exons 8, and 9 and 17: c.869G>A (p.Arg290Glu), c.871-1G>A, and c.892A>G (p.Ser298Gly) and c.1669C>T (p.Arg557X). Each patient belonged to a different family and 3 different ethnic groups were represented, namely Chinese, Malay and Indian. All patients had bilateral visual loss associated with paracentral scotomas, color vision loss and optic atrophy. A positive family history of visual loss was found in only one of the patients. One proband harboured a novel heterozygous *OPA1* pathogenic variant c.892A>G (p.Ser298Gly) that has not been previously catalogued in the eOPA1 database, causing optic atrophy and deafness in early childhood.

Conclusions:
We report the first 4 families with genetically confirmed ADOA in Singapore, belonging to the three main ethnic groups of the country. Among them, we report a new, previously undescribed mutation causing "dominant optic atrophy plus", adding deafness to the classical phenotype of optic atrophy. Further epidemiological studies are needed in order to determine the prevalence of ADOA in Singapore.

References: None.

Keywords: Genetic Disease, Optic Neuropathy

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Poster 60

Optic Nerve Head and Macular Choroidal Vascularization in Patients Affected by Normal Tension Glaucoma and Non-Arteritic Ischemic Optic Neuropathy: What do they share? What is different?

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Introduction:
To compare peripapillary and macular choroidal vascularization in patients affected by Normal Tension Glaucoma (NTG) and Non-Arteritic Ischemic Optic Neuropathy (N-AION).

Methods:
Two consecutive series of patients affected by chronic optic neuropathy due to NTG and N-AION, as well as a cohort of healthy subjects, underwent complete ophthalmological examination, Humphrey Visual Field (HVF), Enhanced Depth Imaging Optical Coherence Tomography (EDI OCT). Peripapillary choroidal thickness has been measured on peripapillary circular scans at 3, 6, 9, 12 clocks' hours. Macular choroidal thickness was evaluated on line scans below the subfoveal region (SF), and at 750- and 1000-μm intervals, nasally, inferiorly, temporally and superiorly to the fovea. Ganglion Cell Complex (GCC) thickness was also considered in the study. T-test and ANOVA were used to perform statistical analysis.

Results:
Twelve and 17 patients diagnosed with chronic optic neuropathy due to NTG and monolateral N-AION, respectively, and 14 healthy subjects were enrolled in the analysis. Non statistically significant difference was found in the macular choroidal thickness of N-AION group compared with controls, neither between N-AION affected eyes and the fellow ones. Statistically significant difference was found in the macular choroidal thickness of NTG group in the SF region ($p<0.01$), at the all 750-μm intervals ($p<0.01$), and at superior ($p<0.01$), nasal, and inferior ($p=0.01$) 1500-μm intervals from the fovea. Non statistically significant difference was found in the peripapillary choroidal thickness among the 2 groups of patients, compared with healthy subjects. Statistically significant GCC thickness' reduction was also found in both NTG and N-AION groups ($p<0.01$), compared with controls.

Conclusions:
The present study demonstrates no changes in the peripapillary choroidal vascularization in patients affected by NTG and N-AION. Interestingly, macular choroidal vascularization resulted markedly affected in NTG patients, but apparently unmodified in both N-AION affected and fellow eyes.

References: None.

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Poster 61

Multifocal ERG Shows Pre-Ganglion Cells Dysfunction in Dominant Optic Atrophy: Genotype-Phenotype Correlation.

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Introduction:
To assess the macular function by means multifocal electroretinogram (mfERG) in patients with dominant optic atrophy (DOA) stratified by *OPA1* mutation type.

Methods:
A consecutive series of DOA patients, and a group of healthy controls, underwent complete ophthalmological examination and mfERG. Patient's eyes were stratified by *OPA1* mutation type. Two types of analysis have been performed on the mfERG responses: (i) "rings analysis" consisted on analyzing the averaged response obtained from 5 concentric rings centered on the fovea; (ii) "sectors analysis" considered the averaged response obtained from 4 sectors: temporal-superior (TS), temporal-inferior (TI), nasal-superior (NS), and nasal-inferior (NI). For each obtained averaged response we evaluated the response amplitude densities (RAD) between the first negative peak - N1 - and the first positive peak - P1 - (N1-P1 RAD, expressed in nanoVolt/degree^2).

Results:
Eighteen patients from 14 pedigrees with DOA harboring heterozygous mutations in the *OPA1* gene (12 patients with OPA1 missense mutations (DOA-M) and 6 patients with haploinsufficiency mutations (DOA-H), providing 11 eyes), and 29 age-matched healthy subjects were enrolled in the study. "Rings analysis": DOA-M Group showed Ring 1, Ring 2, Ring 3 and Ring 4 N1-P1 RADs values significantly reduced ($p<0.01$) compared to controls. In DOA-H Group, only the Ring 1 N1-P1 RADs values were significantly reduced ($p<0.01$) compared to controls. "Sectors analysis": DOA-M Group showed a significant reduction ($p<0.01$) of N1-P1 RADs values observed in TI, NS, and NI sectors, compared to controls. In DOA-H Group, the N1-P1 RADs values detected in all sectors (TS, TI, NS, NI) were not significantly different ($p>0.01$) compared to controls.

Conclusions:
A clear genotype/phenotype correlation emerged stratifying mfERG responses by *OPA1* mutation type, being missense mutations the most severe. In addition, we focused our attention on the possible detection of the retinal areas that should present the main pre-ganglionic impairment.

References: None.

Keywords: Optic Neuropathy, Diagnostic Tests

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Poster 62

Pediatric Primary Optic Nerve Sheath Meningioma

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Introduction:
Primary optic nerve sheath meningioma (PONSM) is a proliferation of meningothelial cells within the nerve sheath of the orbital or intracanalicular portion of the optic nerve. It is not common in patients younger than 20 years of age, represent less than 5% of all cases of PONSM [1].

Methods:
Two cases reports of pediatric PONSM

Results:
Case 1: A 12 year-old-boy gradually lost his right vision over 2 months. Ocular examination showed visual acuity of counting finger, limitation of ocular motility and generalized optic disc edema with optociliary shunts in his right eye. Systemic evaluation revealed multiple plexiform neurofibromas in both hands and 1 café-au-lait spot on his trunk. MRI of orbit and brain revealed right PONSM and multiple schwannomas of cranial nerves V,VI, VII,VIII, IX, and XI, and spinal nerve roots. The child was diagnosed with definite neurofibromatosis type 2. He received stereotactic radiotherapy. Case 2: A 10 year-old –boy developed gradually progressive proptosis in his left eye for 2 years. Left ocular examination showed visual acuity of 20/25, limitation of ocular motility and generalized optic disc edema with optociliary shunts. Systemic evaluation was unremarkable. MRI of orbit and brain revealed PONSM in the left eye without any abnormalities of his brain. Incisional biopsy of the tumor confirmed the diagnosis. Six months later, his left vision deteriorated to 20/200 and then stereotactic radiotherapy was performed. His vision remained stable over 6 years of follow-up.

Conclusions:
Pediatric primary optic nerve sheath meningioma seems to have aggressive clinical behavior with rapid visual decline and poor visual outcome. Stereotactic radiotherapy was shown to be effective in long-term tumor growth control and have no serious complications.

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Keywords: Optic Neuropathy, Orbit, Pediatric Neuro-Ophthalmology

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Poster 63

Syphilitic Optic Neuropathy : Reemerging Cases Over A 2-Year Period

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Introduction:
Although the ocular manifestation of syphilis can affect any structures of the eye, optic nerve involvement is not a common presentation. We report a series of 7 new cases of syphilitic optic neuropathy in a tertiary center.

Methods:
Retrospective case series

Results:
During a 2-year period (2013-2014), 11 eyes of 7 patients were diagnosed with syphilitic optic neuropathy by serologic and cerebrospinal fluid tests. All patients were male, aged between 35 and 45 years. All cases were newly diagnosed with HIV infection, the CD4 T-cell count ranged from 116 to 613 cells/microliter. Three cases (43%) presented with bilateral disc edema, 3 (43%) with unilateral disc edema, and 1 (14%) with bilateral retrobulbar optic neuropathy. Anterior chamber and vitreous reaction were found in 3 patients. Presenting visual acuity ranged from 20/20 to 20/400. Most of patients (6 eyes, 54%) had mild visual loss (≥ 20/40), 3 eyes (27%) had moderate visual loss (20/50-20/200), and 2 eyes (11%) had severe visual loss (<20/200). Blind spot enlargement was the most common type of visual field defect (7 eyes, 64%). All patients had favorable visual outcome (≥ 20/25) after treatment with intravenous penicillin G (6 patients) or ceftriaxone (1 patients).

Conclusions:
Syphilitic optic neuropathy has reemerged in our institution in the past two years. Visual loss from optic nerve involvement can be the first manifestation of syphilitic and HIV coinfection. Patients usually have optic disc edema and mild visual dysfunction. Blind spot enlargement syndrome is the common presentation. Syphilitic optic neuropathy has an excellent prognosis if the disease is diagnosed rapidly and treated properly.

References: None.

Keywords: Neuro-Ophth & Infectious Disease (Eg, AIDS, Prion), Optic Neuropathy

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Poster 64

Anterior Ischemic Optic Neuropathy as Sole Presenting Sign of Internal Carotid Artery Occlusion

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Introduction:
Anterior ischemic optic neuropathy with ophthalmic artery occlusion usually results from giant cell arteritis (GCA), but can rarely occur due to dissection or atherosclerotic occlusion of the internal carotid artery (ICA). Here we present a rare case of severe vision loss in one eye as the sole presenting symptom of ICA occlusion causing cerebral infarction.

Methods:
Case Report

Results:
A 60 year-old male presented with two days of acute, painless vision loss in the right eye, described as a “blur with kaleidoscope” effect. He denied any headache, weakness, transient vision loss, diplopia, or GCA symptoms. Exam revealed hand motion vision OD and 20/20 OS, with a 2.1 logunit RAPD and pallid optic disc edema OD. Confrontation visual field showed a denser inferior than superior global depression OD and was full OS. Sedimentation rate and c-reactive protein were normal for age. A fluorescein angiogram revealed delayed filling of the nasal and peripapillary choroid and optic disc leakage. Temporal artery biopsy was negative. The patient was lost to followup but was later found to have an inferior temporal field defect on static automated perimetry OS. Subsequent brain MRI revealed an occluded right internal carotid artery and encephalomalacia of the right temporo-parietal-occipital watershed region. CTA head and neck showed 100% occlusion of the right ICA from its origin to the cavernous sinus, with collateral reconstitution of the supraclinoid portion. The patient remained completely asymptomatic apart from vision loss and was followed on anticoagulation by the vascular surgery service.

Conclusions:
While neuroimaging is usually reserved for atypical cases, this report highlights the importance of considering intracranial vascular disease in the differential diagnosis of anterior ischemic optic neuropathy and ophthalmic artery occlusion.

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Keywords: Ophthalmic Artery Occlusion, Internal Carotid Artery, Stroke, Anterior Ischemic Optic Neuropathy, Infarct

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Poster 65

Challenges In The Management Of Apoplexy Of A Growth Hormone(GH)-Secreting Pituitary Adenoma During Pregnancy

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Introduction:
The occurrence of pituitary apoplexy during pregnancy is rare, especially with GH-secreting pituitary adenomas. The management of such a patient is challenging.

Methods:
We present a patient who had pituitary apoplexy during early pregnancy.

Results:
A 29 year old female presented with symptoms of left sided headache for 1 week. She experienced gradual visual loss in her left eye for 3 years duration. She was 8 weeks pregnant. Her visual acuity was 6/9 in her right eye, and no light perception (NPL) in her left eye with a relative afferent pupillary defect. Her left optic disc was pale. Confrontation visual field testing revealed a temporal hemifield defect of her right eye and complete loss in her left visual field. She had facial features suggestive of acromegaly and spoke in a relatively deep voice. A chiasmal lesion was suspected on account of her visual field and apoplexy considered due to the acute onset of headache.Magnetic resonance imaging (MRI) of her brain was performed and revealed a large pituitary mass, with features suggestive of hemorrhage; causing compression of the optic chiasm and optic nerves. Her serum hormonal profile showed elevated GH and insulin-like growth-factor 1 (IGF-1) levels. She underwent emergent trans-sphenoidal resection of the tumour. Improvement of visual function in both eyes was noted 2 weeks after surgery.The discussion is focused on the literature regarding the effects of MRI with and without contrast, the interpretation of the hormonal profile and the options of treating pituitary apoplexy in pregnancy.

Conclusions:
This case illustrates the challenges in the management of a rare occurrence of apoplexy of a GH-secreting pituitary adenoma during pregnancy which was managed surgically, and led to improvement of visual function. All clinicians should be mindful of the usage of MRI during pregnancy.

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Keywords: Apoplexy, Pregnancy, MRI, Pituitary

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Poster 66

The Prevalence of Mitochondrial Disease in the Adult Population – Implications for the Prevention of Maternal Transmission

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Introduction:
Establishing the prevalence of mitochondrial disease in the population is challenging due to the extensive clinical and genetic heterogeneity observed in this group of disorders. Innovative IVF techniques to prevent the maternal transmission of pathogenic mitochondrial DNA (mtDNA) mutations have been developed recently and the number of women of childbearing age who could potentially benefit from these breakthroughs in reproductive medicine need to be evaluated.

Methods:
In this national epidemiological study, we comprehensively assessed the prevalence of mitochondrial disease in the adult population secondary to pathogenic mutations involving both the nuclear and mitochondrial genomes. Patients were identified from the MRC Mitochondrial Disease Patient UK Cohort, which is a national database set up to collect extensive clinical and family history information on patients with proven mitochondrial disease throughout the United Kingdom.

Results:
The minimum prevalence figure for pathogenic mtDNA mutations was 20.4 per 100,000 compared with 2.9 per 100,000 for nuclear mutations associated with mitochondrial disease. Leber hereditary optic neuropathy secondary to the m.3460G>A, m.11778G>A and m.14484T>C mutations affected 3.7 per 100,000 of the UK population (~ 1 in 27,000). The most common pathogenic mtDNA mutation was the MELAS m.3243A>G mutation with a minimum carrier rate of 7.9 per 100,000. There are ~ 2,300 women of childbearing age in the UK harbouring pathogenic mtDNA mutations. By using the national fertility rate, this equates to ~ 150 pregnancies per year that could result in the birth of a child at high risk of developing severe mitochondrial disease.

Conclusions:
Mitochondrial disease is common affecting ~ 1 in 4,300 people in the UK. Our findings have major implications for the evaluation of interventions and for the provision of an integrated clinical service. The lack of effective treatments emphasises the importance of developing safe IVF techniques to prevent the maternal transmission of pathogenic mtDNA mutations.

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Keywords: Mitochondrial Disease, Genetic Disease, Leber Hereditary Optic Neuropathy, Epidemiology, Treatment

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Poster 67

Neuropathies In Children Involving Vision Caused By A Fall From Height

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Introduction:
Fall from heights can result in severe injuries, and account for the most common pediatric trauma cause for an emergency department visit. We report the incidence and clinical course of neuropathies in children caused by fall from heights.

Methods:
Data was obtained from the computerized medical records of all patients admitted to the emergency department of a large tertiary medical center due to fall from height between 2004-2014. Associated optic neuropathies which were assessed during the acute event and the follow-up period were analyzed, including imaging studies and associated clinical findings and outcome.

Results:
An estimated 5400 cases of pediatric falls with head trauma presented to the emergency department during the study period. Only 11 children (7 boys, 4 girls, mean age 6.4 years) were diagnosed with neuropathies causing visual disturbance and were followed. Eight were diagnosed with traumatic optic neuropathy, one of which after a 6 months delay and two with accompanying cranial nerve (CN) III injuries. Five of the patients had anisocoria or abnormal pupillary response to light upon initial presentation. The remaining two had CN VI paralysis and temporary visual loss, respectively. Visual improvement varied among all these patients.

Conclusions:
Neuropathies due to a fall from heights in children are rare. Neuropathies involving vision or ocular motility impairment are usually missed in the acute intake of emergency patients, especially in cases of monocular loss of vision. Such neuropathies might cause severe morbidity with limited improvement, and prompt interpretation with a high index of suspicion might improve the outcome. Assessment of pupillary response to light is simple and essential in these cases. Due to the potentially devastating visual outcomes of traumatic optic neuropathy, pediatric trauma centers must make an effort to rule out optic neuropathies in all patients visiting the emergency department after a fall from height.

References: None.

Keywords: Pediatric Neuro-Ophthalmology, Optic Nerve Trauma And Treatment, Orbit/Ocular Pathology, Trauma

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Poster 68

Immunosuppressive Therapy of Chinese Isolated Non-MS Idiopathic Optic Neuritis

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Introduction:
Immunosuppressive therapy is recommended for preventing the relapse of neuromyelitis optica(NMO) and NMO-spectrum diseases, but very few studies focused on isolated Non-MS idiopathic optic neuritis(Non-MS-ION).

Methods:
Non-MS-ION patients met the inclusive criteria and treated with our standard immunosuppressive therapy were retrospectively studied. Annual relapsing rate(ARR) before and after treatment were compared for all patients, recurrent Non-MS-ION and AQP4-Ab(+) subgroups. Conversion rate to NMO between patients with persistent and non-persistent were also compared.

Results:
In 165 cases with averaged age 41.2yrs, 105(63.6%) were female. NMO-like brain lesions was found on 7 cases(4.2%). AQP4-Ab was positive on 30(44.1%) of 68 cases examined. During averaged 29 months of follow-up, the differences of ARR before and after treatment were statistically significant for all 165 cases(0.46±0.84 vs 0.16±0.45, P=0.000), also in 25 cases with persistent therapy(0.72±1.00 Vs 0.13±0.29, P=0.005) and 140 cases with non-persistent therapy(0.41 ±0. 81 Vs 0.17±0.47, P=0.001). For 64 recurrent cases including 14 cases with persistent therapy and 50 cases with non-persistent therapy, the differences were also significant (1.18 ±0.99 Vs 0.22±0.53, P=0.000; 1.29± 1.02 Vs 0.19±0.33, P=0.002; 1.15±0. 99 Vs 0.23 ±0.57, P=0.000). In 30 cases of AQP4-Ab(+) subgroup, ARR was significantly decreased after treatment for the 11 patients with persistent therapy(0.67±0.8 Vs 0.08±0.21, P=0.046) but not for the 19 cases with non-persistent therapy (0.5±0.88 Vs 0.55±0.85, P=0.80). Fourteen cases(14/165, 8.5%) converted into NMO during follow-up, all of which came from the 140 cases with non-persistent therapy. In AQP4-Ab(+) Non-MS-ION subgroup, none of 11 cases with persistent therapy but 9 of 19(47.3%) patients with non-persistent therapy developed NMO and the difference was statistically significant(0% Vs 47.3%, P=0.01).

Conclusions:
Immunosuppressive therapy decreased ARR of Chinese Non-MS ION. Persistent immunosupressive therapy is needed to reduce the ARR and conversion rate to NMO for AQP4-Ab positive patients.

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Keywords: Optic Neuritis, Neuromyelitis Optica, Preventative, Immunosuppressive, Treatment

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Poster 69

How does Exogenous ROS Effect LHON Conversion?

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Introduction:
Mitochondrial DNA mutations associated with Leber's hereditary optic neuropathy (LHON) are associated with endogenous reactive oxygen species (ROS) production. Research has demonstrated that exogenous ROS generators, like smoking, are associated with an earlier age of conversion from carrier to affected state. However, the exact role of exogenous ROS in LHON is ill defined. To understand the role of exogenous ROS in LHON, we hypothesize dividing LHON into two subtypes. I: conversion is predominantly genetically determined and largely independent of exogenous ROS and II: the genetic component is necessary but insufficient for conversion and exogenous ROS exposure is required.

Methods:
To explore this theory we conducted a retrospective case-control study of 19 LHON-affected patients from a single pedigree, looking at their ages of conversion and smokers versus non-smokers. Because type II individuals require higher ROS exposure, we expect the mean of their ages of conversion to be higher and the distribution to be wider. We thus separated our study population at the 75th percentile of age of conversion and looked at the smoker to non-smoker ratio in each population using a Pearson's X^2-test.

Results:
The 75th percentile for age was 36 years and 32% patients studied were found to have an age of conversion equal to or greater than the 75th percentile. Of these patients, 83% were found to have smoked in contrast to 46% in the population with ages of conversion less than 36. Comparison of smoker to non-smoker ratio via Pearson's X^2-test revealed $X^2(1,N=19)=1.53$, $p=0.22$.

Conclusions:
While our analysis did not yield a significant result ($p>0.05$), the sample size was small and rough approximations were made to determine type I versus type II patients. However, the descriptive statistics are in line with our hypothesis suggesting there may be two different manifestations of LHON even in a single pedigree.

References: None.

Keywords: Genetic Disease, Optic Neuropathy

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Poster 70

Chronic, Painful Abducens Palsy May Require Angiography: Lesson Re-Learned From A Case Of A White-Eyed Shunt

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Introduction:
Posteriorly-draining cavernous-carotid fistulas (CCFs) ("white-eyed shunts") can present with painful cranial nerve palsies. We report a case of posteriorly-draining CCF presenting as a persistently painful, chronic left abducens palsy.

Methods:
Case Report.

Results:
A 58 year-old woman presented with left periorbital pain and diplopia, both worsened on left gaze and preceded by several months of headache. Vision, fields and pupils were normal. Her eyes were white and without proptosis. Tensions were 19/20 mmHg. She had 2-3 mm of left abduction. Cranial nerves V, VII and VIII were intact, and tear production was normal. Gonioscopy was wide open, with no blood in Schlemm's canals. No bruits were heard, and fundi were normal. Contrast-enhanced MRI of the brain and orbits were normal. On review, we suspected a slightly large left superior ophthalmic vein of questionable significance. CT angiogram revealed congestion of the vessels in the cavernous sinus on the left with early contrast opacification of the left cavernous sinus in comparison to the right, consistent with a posteriorly-draining CCF. This was confirmed by diagnostic angiogram, which showed a Barrow type D fistula with retrograde intracortical venous drainage. She was treated with endovascular coil occlusion of the fistula. At her three-month follow-up, her pain had significantly improved, with minimal improvement in her abducens palsy.

Conclusions:
Posteriorly-draining CCFs should be considered in patients presenting with chronic, painful ocular muscle palsy (Hawke et al., 1989; Acierno et al., 1995). If MRI of cavernous sinus and skull base is negative, the clinician should proceed with CT angiography or MRI angiography with contrast; if these are unrevealing, conventional catheter-based angiography should be considered.

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Keywords: Vascular Disorders, Neuroimaging, Interventional Neuroradiology

Financial Disclosures: The authors had no disclosures.

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Poster 71

Eight And A Half Syndrome-A Rare Neuro Ophthamologic Manifestation Due To Pontine Infarction

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Introduction:
Gaze hemiparesis with INO and facial nerve palsy, the aforementioned triad commonly known as the “Eight and a half syndrome” is a very rare presentation of the insults to pontine tegmentum abducent nucleus, PPRF and the ipsilateral MLF. In this case report we describe eight and a half syndrome in setting of basilar artery aneurysm.

Methods:
62 yr old gentleman with history of uncontrolled hypertension, dyslipidmia and diabetes type II presented with sudden onset of right hemiparalysis, left facial droop with decreased closure of the left palpebral fissure, scanning speech and double vision. On presentation his NIHSS was 15.He had left INO, right horizontal gaze peresis and LMN type left facial nerve palsy. Accompanying these symptoms he also had complete paralysis of the right upper and lower extremities, strength 0/5.DWI showed acute ischemic infarction of the left midbrain, pons and cerebellum in the distribution of the superior and inferior cerebellar arteries. Four vessel angiogram further revealed fusiform dilation of the basilar artery as a result of a dissecting aneurysm with no impending stenosis. Extreme tortuosity of the left cervical vertebral artery at the origin was also seen which made intervention almost impossible.The patient was discharged to sub acute rehab

Results:

Conclusions:
One and a half syndrome, first described by Fisher in 1957,is a clinical disorder characterized by conjugate horizontal palsy in one direction (the “one”)and INO in the other direction(the ”one half”).[1,2]When facial nerve is also involved the manifestation is named as “eight and a half syndrome” first described by Eggenberger in 1998[3].Here we present a rare manifestation of eight and a half syndrome secondary to basilar artery aneurysm.

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Keywords: Pprf, Ino, Eight And A Half Syndrome, Abducent Nerve, Basilar Artery

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Poster 72

Where the Lung Meets the Eye

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Introduction:
The cavernous sinus is an important neurovascular crossing point. Careful examination of patients presenting with multiple cranial neuropathies may suggest a lesion of this region but the differential is wide and often difficult to confirm.[1] Potential infectious and inflammatory etiologies as well as local malignant invasion should be addressed. However, metastases from distant sites are more rarely seen.[2]

Methods:

Results:
A 63-year-old man presented with unilateral ptosis and denied significant past medical or ocular history. A review of systems revealed headache, periorbital pain, cough, and decreased appetite. Examination showed complete left ptosis and ophthalmoplegia, symmetric 20/50 vision, diminished V_1/V_2 sensation, oral thrush, and cachexia. He was additionally febrile, hypotensive, tachycardic, confused, and ataxic. Chart review unveiled a history of uncontrolled AIDS with poor compliance. He was urgently admitted with concern for septic cavernous sinus syndrome, pan-cultured, and started on broad-spectrum antibiotics pending neuroimaging. Initial CT was negative but routine chest x-ray revealed a left hilar mass that biopsy confirmed as small cell lung cancer with post-obstructive pneumonia. MRI ultimately disclosed a lesion of the sella with extension into the left cavernous sinus consistent with metastasis for which he received palliative radiation.

Conclusions:
A cavernous sinus syndrome is suggested when two or more of cranial nerves 3, 4, 5(V_1, V_2) or 6 are impaired. The underlying etiologies are diverse and many are not only sight but life-threatening.[1,2] Imaging should be obtained rapidly and serial imaging considered when appropriate clinical suspicion exists without an initial diagnostic lesion.[3] Immunocompromised patients represent a particular diagnostic dilemma given their increased risk of opportunistic infections and potential lack of a robust inflammatory response. This case was diagnostically challenging because the patient presented alone with confusion, an undiagnosed metastatic malignancy not seen on preliminary imaging, and a distant underlying infection; appropriate clinical assessment allowed proper intervention and treatment.

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Keywords: Cavernous Sinus, Metastasis, Immunocompromise, Cranial Neuropathy

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Poster 73

Metastasis or Metamorphosis?

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Introduction:
A 36-year-old woman presented in December 2013 with double vision. Three weeks prior, she had a new headache that was relieved with an occipital nerve block. Three days before, she had acute onset of horizontal binocular diplopia that was worse with left gaze. She denied dizziness, nausea, vomiting or weight loss. Her neuro-ophthalmic exam was remarkable for a left eye abduction deficit. MRI of the brain and orbits, from an outside facility, was read as negative for an intracranial mass/lesion. In April 2014, she returned with continued diplopia and new complaints of severe headache, weight loss, night sweats, vertigo and difficulty with balance. Exam showed a left 6th nerve palsy, absent corneal reflexes, and bilateral facial paralysis. A lumbar puncture showed mild leukocytosis, elevation of protein, and normal flow cytometry and cytology. All lab tests were within normal limits. Brain MRI showed enhancement in the left cerebellopontine angle, multiple cranial nerves, skull base dura and leptomeninges. A 5-day course of IV steroids was undertaken without improvement of symptoms. Brain biopsy showed an ill-defined soft mass. Pathology showed a benign epidermoid cyst. A second tissue biopsy was done because of high suspicion for malignancy, which showed a poorly differentiated infiltrating squamous cell carcinoma. There was no evidence for a primary tumor by whole body PET.

Results:
We have two hypotheses for the origin of the SCC: metastasis from a primary tumor or malignant transformation of the epidermoid cyst. Although rare, malignant transformation of an epidermoid cyst has been reported. The close proximity of the lesions and lack of other primaries on imaging make transformation possible; however, there were no histologic sections that show direct transition of the malignancy from the epidermoid cyst.

Conclusions:
Squamous cell carcinoma of unknown origin.

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Keywords: Cranial Nerve, Neuroimaging, Neoplasm

Financial Disclosures: The authors had no disclosures.

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Poster 74

Acute Onset Internuclear Ophthlamoplegia And Migraine Headache

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Introduction:
Usually a diagnosis of exclusion in adults, ophthalmoplegic migraine is characterized by recurrent attacks of migraine headaches associated with paresis of one or more ocular cranial nerves, in the absence of any demonstrable intracranial lesion other than MRI changes within the affected nerve. Paresis of the cranial nerves third, fourth and sixth were described. Medial longitudinal fasciculus involvement and subsequent internuclear ophthalmoplegia (INO) in association with migraine headache, as well as the INO resolution with migraine abortive therapy is not reported in the literature.

Methods:
Case Report: 67 year-old right handed Caucasian female presented with acute onset horizontal binocular diplopia and blurry vision during routine household chores. Right-sided throbbing headache and mild nausea accompanied shortly. Patient reported history of HTN, HLD, ischemic heart disease and migraine headaches - one episode 40 years prior associated with limb paresis, while more recently frequent episodes associated with diplopia and/or blurry vision, relieved with rest and nonsteroidal anti-inflammatories. Examination revealed a right INO. Non-contrast head CT and CT angiogram of head and neck were unremarkable. Given prior history and clinical presentation, decision was made to treat with acute migraine therapy, consisting of intravenous hydration with normal saline and IV valproate sodium. Two hours after the therapy initiation patient reported complete resolution of the headache and nausea and significant improvement of the visual symptoms. Examination revealed improvement in the right eye adduction. 10 hours later, after repeat administration of intravenous valproate, the INO was completely resolved and patient returned to baseline functionality. Brain MRI with thin brainstem cuts was unremarkable.

Conclusions:
Attacks of migraine headaches and acute INO in a patient with history of complicated migraines could be a subtype of ophthalmoplegic migraines. Although an ischemic event should be considered in the differential, acute therapy should target the migrainous phenomenon.

References: None.

Keywords: Ocular Motility, Nystagmus, Migraine, Vascular Disorders

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Grant Support: None.

Poster 75

Traumatic Avulsion Of The Oculomotor Nerve: First Definitive Documentation On High Resolution MRI

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Introduction:
Direct traumatic oculomotor nerve injury is uncommon. In the setting of severe head trauma, third nerve root avulsion from the brainstem can result from differential mass movements and the relationship between the brainstem, supratentorial structures, and the skull bones. Autopsy studies have described traumatic avulsion of the oculomotor nerve, however detailed characterization of mechanisms of injury and precise locations of nerve damage has yet to be definitively described in vivo. We report a case where high resolution MRI imaging confirmed irreversible injury to the left third cranial nerve allowing for more informed management decisions.

Methods:
Single case report. Retrospective review of a Health Insurance Portability and Accountability Act-compliant database of a pediatric patient sustaining motor-vehicle trauma.

Results:
A 13 year-old female found unresponsive following a motor vehicle accident was noted to have a fixed and dilated pupil of 8mm on the left. On prism and alternate cover testing there was a 50-prism diopter left exotropia and a 25-prism diopter left hypotropia. She was unable to elevate, depress, or adduct her left eye. MRI of the brain demonstrated avulsion of the left oculomotor nerve from the ventral midbrain at the apparent origin of the cisternal segment.

Conclusions:
Oculomotor nerve root avulsion from the brainstem may occur in the setting of severe head trauma. High resolution MRI is the best method to detect injury to the cranial nerves. Neurosurgical techniques for possible nerve re-implantation at the brainstem have yet to be investigated, but could be a new area for clinical and surgical research guided by detailed imaging sequences.

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Keywords: Oculomotor Nerve, Pediatric, Trauma, Cranial Nerve, Neuroimaging

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Poster 76

Ocular Motor Cranial Nerve Palsies In Pituitary Apoplexy

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Introduction:
Pituitary apoplexy (PA) is caused by sudden pituitary hemorrhage/necrosis and often presents with acute neuro-ophthalmic manifestations, including ocular motor cranial nerve palsies (CNP). We describe the epidemiology and outcomes of CNP in a large single-center cohort of PA patients.

Methods:
Retrospective review of 235 patients with PA seen in our Pituitary Center [01/1995-12/2012]. Presenting neuro-ophthalmic, endocrine and radiologic data were collected; neuro-ophthalmology followup information was obtained when available.

Results:
59/235(25%) PA patients had CNP. 56/59(95%) had surgery. 27/59(50%) had neuro-ophthalmic evaluation. 26/27(96%) neuro-ophthalmic-evaluated CNP patients had headaches and 3/27(11%) altered mental status. Pre-operatively, 23/27 patients had unilateral CNP. 18/23 had single (CNVI [N=10], CNIII [N=8]), and 5/23 multiple CNPs (all involving CNIII plus CNIV [N=1], CNVI [N=1] or both [N=3]). 4/27 patients had bilateral CNPs. Median VA was 0.17 [IQR: 0-0.7; VA<20/200 in 9 eyes (6 patients)]. 24/40(62%) eyes with visual field (VF) testing had at least partial temporal hemianopia (complete in 10/40[25%]), 14 patients had chiasmopathy (including one junctional syndrome) and 3 had unilateral optic neuropathy. Post-operatively, 24/27 CNP patients had followup (median duration of followup: 7 months [IQR: 3-17]). At last post-operative followup, 7/24(29%) patients had CNP (5/7 unilateral (CNVI [N=2]; CNIII [N=1]; CNIII and CNIV [N=1]; CNIII, CNIV, and CNVI [N=1]) and 2/7 bilateral). Median VA was 0.1 [IQR:0-0.2] (VA <20/200 in 2 eyes). 15/47(32%) eyes with VF testing had at least partial temporal hemianopia (complete in 3/47(6%) eyes). 7 patients had a chiasmopathy and 2 had a unilateral optic neuropathy. CNP resolved in 3/24(12%) patients within 1 month,13/21(62%) patients within 6 months (3 lost to followup) and 17/19(89%) within one year (2 lost to followup).

Conclusions:
25% of PA patients had CNPs, associated with headaches in 96%, and visual loss in 52% of patients evaluated. 90% of patients had resolution of CNP by one year, most within 6 months.

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2. Kim SH, Lee KC, Kim SH. Cranial nerve palsies accompanying pituitary tumour J Clin Neurosci 2007;14(12):1158-1162.
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Keywords: Pituitary Apoplexy, Ocular Motility, Chiasmopathy, Tumors, Pituitary Tumors

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Grant Support: This work was supported in part by an unrestricted departmental grant (Department of ophthalmology) from Research to Prevent Blindness, Inc., New York. Dr. Hage received research grants from the Philippe Foundation (NYC, USA), the Club de Neuro-Ophtalmologie Francophone (Paris, France) and the Faculté de M&eacutedecine des Antilles et de la Guyane (bourse ann&eacutee-recherche). Dr. Bruce receives research support form the NIH/NEI (K23-EY019341)

Poster 77

Later Life Decompensation of Congenital Trochlear Palsy due to Agenesis

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Introduction:
Congenital trochlear palsy may manifest with sudden vertical diplopia due to decompensation during the later life, which may bring a diagnostic challenge. In those cases, imaging demonstration of atrophic superior oblique (SO) muscle and absent trochlear nerve may aid in determining a congenital origin.

Results:
Two patients with vertical diplopia for several years after age 50 were referred due to no improvement or sudden aggravation of the diplopia. Findings were consistent with unilateral SO palsy in both patients with a contraversive head tilt. Facial asymmetry was suggestive of a congenital cause in a patient. High resolution MRIs disclosed atrophic SO and absent trochlear nerve in the side of SO palsy in both patients.

Conclusions:
Imaging demonstration of SO atrophy and absent trochlear nerve may help diagnosing congenital trochlear palsy due to agenesis that manifests with sudden vertical diplopia during the later life due to delayed decompensation.

References: None.

Keywords: Diplopia, Trochlear Nerve, Agenesis

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Poster 78

Presentation of Primary Hodgkin's Lymphoma as Multiple Cranial Neuropathies

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Introduction:
There is a large differential diagnosis when presented with a patient multiple cranial neuropathies (MCN), including neoplastic, infectious and inflammatory causes. We report a case of probable primary Hodgkin's lymphoma (HL) presenting with multiple cranial neuropathies.

Methods:
Retrospective review of one patient with MCN found to have a mass lesion in the region of Meckel's cave on neuroimaging. History, physical examination, magnetic resonance imaging (MRI), pathology reports and treatment course were reviewed.

Results:
61 year old gentleman with history of rheumatoid arthritis on immunosuppression presented with worsening left neck pain and horizontal diplopia for four weeks. Afferent examination, including optic nerve and dilated funduscopic examination, was unremarkable. Motility examination showed 50% restriction of left abduction and decreased sensation in first and second division of the trigeminal nerve. MRI was performed and demonstrated enhancing soft tissue within the left Meckel's cave and the left foramen rotundum as well as thickening and enhancement along the falx cerebri and tentorium cerebelli. CSF analysis revealed lymphocytic pleocytosis and elevated protein with nonspecific cytology. Computed tomography of the chest, abdomen, and pelvis showed diffuse lymphadenopathy. Lymph node biopsy confirmed classic HL. Biopsy of the skull base lesion performed after intravenous steroid therapy was inconclusive for lymphoma. Patient improved with chemotherapy and his MCN improved significantly over the next three months.Neurologic symptoms from HL are a rare occurrence. A review of the literature from 1983 found that only 0.5% of patients with HL developed neurological symptoms or signs (1). Presentation of HL with multiple cranial neuropathies has not been reported, but there was a case of cavernous sinus involvement reported in a patient with known HL in 1996 (2).

Conclusions:
The diagnosis of Hodgkin's lymphoma should be considered in patients presenting with multiple cranial neuropathies as well as for lesions affecting Meckel's cave.

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Keywords: Ocular Motility, Systemic Disease

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Grant Support: None.

Poster 79

Acute Angle Closure Glaucoma In A Patient With Miller Fisher Syndrome Without Pupillary Dysfunction

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Introduction:
To report a case of an acute angle closure glaucoma (AACG) in a patient with Miller Fisher syndrome (MFS) without pupillary dysfunction.

Methods:
We present a case report of a 75-year-old male presenting with total ophthalmoplgia, complete bilateral ptosis, and gait disturbance. Two weeks prior to admission, he experienced an upper respitary infection. An initial neurologic examination demonstrated bilateral complete ptosis, total ophthalmoplegia, and severe gait ataxia. Deep tendon reflexes completely disappeared. The pupillary reaction of the right eye was nonresponsive to light and mid-dilated. Cerebrospinal fluid analysis was acellular and indicated slightly increased protein (53 mg/dl). A diagnosis of MFS was made, and intravenous immunoglobulins were administered.

Results:
One day after his admission, the patient complained of ocular pain and blurred vision in the right eye. His visual acuity was hand motion in the right eye and 6/20 in the left eye. In addition, lid swelling, conjunctival chemosis, corneal edema, and a shallow anterior chamber in the right eye were noted. A mid-dilated pupil (4.5 mm) was detected in the right eye. However, the left eye exhibited good reactivity to light. Intraocular pressure, as assessed by Goldmann applanation tonometry, was 50 mmHg, and gonioscopic findings revealed a closed angle on the right eye. After maximal tolerated medical therapy, laser peripheral iridotomy was performed. Subsequent blood tests revealed that the patient was negative for the anti-GQ1b antibody. The unilateral AACG with MFS resolved without further incident.

Conclusions:
This is the first reported case of a patient with MFS without autonomic dysfuction with AACG. We believe that pupillary dysfunction or lid ptosis due to neurological disorders may increase the possibility of AACG.

References: None.

Keywords: Miller-Fisher Syndrome, Guillain-Barré Syndrome, Acute Angle Closure Glaucoma, Pupil, Immune Mediated Neuropathy

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Poster 80

Congenital Oculomotor Nerve Paresis With Isolated Cyclic Pupillary Spasms

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Introduction:
Cyclic oculomotor nerve paresis is a rare and mostly congenital disorder. It is characterized by unilateral oculomotor nerve paresis with periodic spasms causing eyelid elevation, miosis and contraction of one or more of the extraocular muscles innervated by the oculomotor nerve. We discuss a 20-month old girl who presented initially with right partial congenital oculomotor nerve paresis. She subsequently developed permanent partial ptosis and isolated cyclic spasms of the pupil.

Methods:
A four-month old girl presented with right exotropia since birth. Over the ensuing weeks, parents noticed right pupillary size variation several times every day. They also reported right eye photophobia at 8 months of age and intermittent ptosis of the right upper eyelid at 15 months. The latter became permanent at 16 months.

Results:
At 6 months, there was right pupillary cyclical 2mm constriction for 30 seconds followed by 4mm dilatation for 30-60 seconds during which she became photophobic. The right pupil was not reactive to light or accommodation. No cycling spasms of the right extraocular muscles were seen. Right partial ptosis and a complete paresis of right eye elevation, depression and adduction were evident at 16 months. Abduction remained intact. Random brief right upper eyelid twitches were noted intermittently but there was no periodicity. The rest of her examination was unremarkable. Brain MRI was normal. The examination was unchanged on follow up. Strabismus surgery improved her exotropia but the pupillary cyclic spams persisted.

Conclusions:
Variable manifestations and progression rates of congenital cyclic oculomotor nerve paresis can be seen. Cycling, which may appear later, can be isolated or involve multiple muscles innervated by the oculomotor nerve. The mechanism is unknown but is postulated to be the result of prenatal partial damage to the oculomotor nerve with retrograde degeneration producing changes in the nucleus.

References: None.

Keywords: Ocular Motility, Pediatric Neuro-Ophthalmology, Pupils

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Grant Support: None.

Poster 81

Abducent Nerve Palsy In A Patient With Castleman Disease!

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Introduction:
Castleman disease (angiofollicular lymph node hyperplasia) is a very rare disorder characterized by non-cancerous growths that may develop in the lymph node tissue at a single site or throughout the body.

Methods:
Case report and review of literature.

Results:
We present a 44-year-old African-American female with history of Castleman's disease with large pelvic mass diagnosed in 2008 status post resection and radiation as well as type II diabetes mellitus and systemic arterial hypertension. She presented in September of 2014 with 3 weeks history of refractory headaches improving on lying down and 4 days of horizontal binocular diplopia more on left gaze following upper respiratory tract infection and persistent cough. Her visual acuity was 20/20 in both eyes with glasses. On examination, she had right longstanding blepharoptosis and left abducent nerve palsy. Her optic discs were pink, with no pallor or swelling and a cup/disc ratio of 0.1. Brain Magnetic Resonance Imaging revealed diffuse meningeal thickening. Blood patch was performed for management of suspected spontaneous intracranial hypotension with transient improvement of headaches. Myelography was performed revealing a dural defect in the region of the right C7-T1.

Conclusions:
To the best of the authors' knowledge this is the first report of cranial neuropathy in a patient with Castleman disease.

References: None.

Keywords: Castleman, Abducent, Nerve, Diplopia

Financial Disclosures: The authors had no disclosures.

Grant Support: 1. McAdams, H. Page, et al. &quotCastleman disease of the thorax: radiologic features with clinical and histopathologic correlation." Radiology 209.1 (1998): 221-228. 2. McAdams, H. Page, et al. &quotCastleman disease of the thorax: radiologic features with clinical and histopathologic correlation." Radiology 209.1 (1998): 221-228. 3. Herrada, Juan, et al. &quotThe clinical behavior of localized and multicentric Castleman disease." Annals of Internal Medicine 128.8 (1998): 657-662. 4. Meador, Toni L., and John K. McLarney. &quotCT features of Castleman disease of the abdomen and pelvis." American Journal of Roentgenology 175.1 (2000): 115-118.

Poster 82

Nivolumab Plus Ipilimumab Induced Aseptic Meningitis And Bilateral Sixth Nerve Palsy In Metastatic Melanoma Treatment.

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Introduction:
Nivolumab and Ipilimumab are recombinant human immunoglobulin monoclonal antibodies that prolong overall survival in metastatic melanoma. Reported adverse effects include orbital inflammation and hypophysitis. Aseptic meningitis is exceedingly rare with one case reported in Ipilimumab montherapy.

Methods:
Case report of a 52 year old gentleman who developed progressive bilateral sixth nerve palsy secondary to Nivolumab and Ipilimumab induced aseptic meningitis.

Results:
The patient was enrolled in a Phase 2 study of Nivolumab given sequentially with Ipulimumab in metastatic melanoma. He received his last dose of Nivolumab when he complained of intermittent horizontal diplopia. An MRI scan of the brain with gadolinium was unremarkable and he received his first dose of Ipilimumab. Three days later he presented with worsening diplopia. On examination his vision was 20/20 with -4.00 OU. He had a relatively comitant 12 diopter intermittent esotropia at distance with -1/4 bilateral abduction deficits. He was treated with a 10 base out press on prism. Two weeks later he had worsening diplopia and demonstrated a 16 diopter constant esotropia and progressive bilateral abduction deficits. Repeat MRI demonstrated diffuse leptomeningeal and cranial nerve enhancement. Lumbar puncture showed a 1 white blood cell, total protein of 80 and negative cytology. He received Solumedrol followed by oral prednisone. Follow up MRI one month later demonstrated resolution of the leptomeningeal enhancement. His ophthalmic examination showed improved abduction and an intermittent esotropia of 10 prism diopters.

Conclusions:
Progressive 6th nerve palsy can occur secondary to aseptic meningitis in patients treated with Nivolumab plus Ipilimumab. This patient is interesting in that he presented with an initial normal MRI and what appeared to be a breakdown of a strabismic myopic divergence insufficiency. Over one month, however the deviation progressed and the leptomeningeal involvement became evident.

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Keywords: Sixth Nerve Palsy, Aseptic Meningitis, Nivolumab, Ipilimumab, Melanoma

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Poster 83

Combined Third Nerve Palsy And Vertical Gaze Palsy In Midbrain Thalamic Stroke

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Introduction:
We present neuro-anatomical substrates for a rare presentation of ipsilateral third nerve palsy and vertical gaze palsy in a patient with rostral midbrain and paramedian thalamic infarct.

Methods:
Single case report and review of literature

Results:
A 56 year old male presented with a 3 day history of left hemiparesis and binocular horizontal and vertical diplopia. 3 months ago, a right posterior cerebral artery infarct had resulted in left homonymous hemianopia. At presentation he had dysarthria, left hemiparesis and appendicular ataxia. Neuro-ophthalmic examination revealed a left homonymous superior quadrantanopia (pre-existing), anisocoria (mid-dilated non-reactive right pupil, normal left pupil), right hypertropia and exotropia with limited adduction and depression and decreased bilateral vertical up-gaze saccades without ptosis. CT angiogram revealed a proximal right P1 thrombus. Non-contrast MRI head showed an acute right paramedian thalamic and right rostral midbrain infarct. 5 days later he had skew deviation and torsional nystagmus.

Conclusions:
Using high resolution MRI sequences we were able to identify the neuroanatomical substrates for this rare clinical presentation.
- Fascicular incomplete pupil involving third nerve palsy: Ksiazek et al had proposed a rostrocaudal organization of the oculomotor nerve fascicles starting with pupillary fibers followed by inferior rectus, inferior oblique, medial rectus, superior rectus, and levator palpebrae superioris. This patient's lesion most likely involved the rostral fascicles (pupillary fibers, inferior rectus, inferior oblique and medial rectus fibers) sparing the caudal fascicles.
- Bilateral vertical upgaze palsy from ipsilateral lesion of the rostral interstitial nucleus of medial longitudinal fasciculus (riMLF), interstitial nucleus of Cajal (INC) and nucleus of posterior commissure (NPC). The paramedian thalamic infarct additionally impaired up-gaze via interruption of supranuclear fibers of the medial thalamus en route to the pretectal and prerubral area.
- Skew deviation and torsional nystagmus from ipsilateral lesion of INC and/or NPC

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Keywords: Midbrain Infarct, Thalamic Infarct, Vertical Gaze Palsy, Third Nerve Palsy, Hemiparesis

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Poster 84

A Case Of Abducens Nerve Palsy Followed By Cyclic Esotropia: A Case Report And Review Of The Literature

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Introduction:
Cyclic esotropia is a rare acquired disorder in which days with esotropia and orthotropia alternate. We encountered a patient with abducens nerve palsy caused by a clival tumor who developed cyclic esotropia during follow-up without treatment.

Methods:
Case report and review of the literature

Results:
The right eye of a 6-year-old girl was found to be internally rotated by her mother in February 2009. After 17 days, the girl was referred to our ophthalmology department. On the first examination, her visual acuity was bilaterally 20/20, and cycloplegic refraction revealed no hyperopia. Both pupils measured 7.0 mm in a dark room and 3.5 mm in a bright room, and the reaction to light was rapid and complete. The right eye showed a restriction of abduction, and 25Δ esotropia was noted in the primary position. The left eye moved smoothly and fully in all directions. No abnormality was noted in the eyegrounds. Head MRI demonstrated a lobulated tumorous lesion in the retroclivus, suggesting a chordoma. On examination in the neurosurgery department, the tumor was small, and surgery was expected to be highly invasive; thus, periodic follow-up was indicated. Around August of the same year, her mother noticed alternation of days with esotropia and orthotropia. On follow-up examinations, 25-30Δ esotropia or orthotropia was noted. When there was esotropia, no oculomotor restriction was observed in either eye. A diagnosis of cyclic esotropia was made, and the patient continued to be followed up. Since no growth of the tumor or change in cyclic esotropia was observed, bilateral recession of the medial rectus muscle was performed in 2013. The ocular alignment was normalized after surgery.

Conclusions:
In our patient, cyclic esotropia occurred secondarily to abducens nerve palsy. According to our review of the literature, one case of traumatic abducens nerve palsy followed by cyclic esotropia has been reported.

References: None.

Keywords: Abducens Nerve Palsy, Cyclic Esotropia, Clival Tumor, Chiled, Surgery

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Poster 85

Functional MRI And MRI Tractography In Progressive Supranuclear Palsy-Like Syndrome

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Introduction:
Progressive supranuclear palsy (PSP)-like syndrome is a rare disorder which occurs most commonly following ascending aortic aneurysm repair, but may occur after other cardiac procedures. The syndrome, which may manifest immediately after surgery or hours or days later, usually includes supranuclear gaze palsy, dysarthria, emotional lability and gait ataxia mimicking PSP.

Methods:
Contrasted cranial and orbital fat-suppressed magnetic resonance imaging (MRI), MRI tractography and functional MRI (fMRI) were obtained on an 18-year-old woman who underwent an uneventful ascending aortic aneurysm repair and 48 hours later developed a progressive supranuclear palsy (PSP)-like syndrome manifestating with dysarthria, dysphagia (requiring a gastric tube), emotional lability and ophthalmoplegia.

Results:
Contrasted cranial and orbital fat-suppressed magnetic resonance imaging (MRI), MRI tractography and functional MRI (fMRI) were all normal.

Conclusions:
Our case attests to the occult nature of this rare and devastating syndrome and perhaps supports the contention that the dysfunction is microscopic in nature and cannot be detected even with advanced neuro-imaging.

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Keywords: Progressive Supranuclear Palsy, Aortic Aneurysm, Functional MRI, MRI Tractography, Ophthalmoplegia

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Poster 86

Abducens Palsy In A Patient With Pityriasis Rubra Pilaris

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Introduction:
Pityriasis rubra pilaris (PRP) is rare idiopathic papulosquamous dermatosis of unknown etiology. PRP has been associated with several ocular manifestations including interstitial keratitis, epithelial defects and keratinization of the conjunctiva. However, no previous studies have reported an association with cranial nerve palsy. Here we report a case of abducens palsy in a patient with PRP.

Methods:
Case report and review of literature.

Results:
A 61 year old year-old female with a history of PRP and bilateral pseudophakia presented with acute onset horizontal diplopia. She had been diagnosed with biopsy-proven diagnosis of PRP one month prior. She denied a history of recent or remote head trauma. Her medication list included a prednisone steroid taper, cyclosporine, conjugated estrogen and daily multivitamin. Her visual acuity was 20/20 bilaterally with normal pupillary function. Her examination was notable for restriction in abduction on left gaze with normal pursuit and saccadic function. Her anterior slit lamp exam and posterior fundus examination were within normal limits. Contrast enhanced MRI of the brain and orbits did not show evidence of a compressive lesion. Screening tests for hyperlipidemia and hypertension were normal. Observation and a trial of prism glasses were recommended for the patient. On repeat examination 5 months later, the patient had improvement in abduction with a smaller angle esotropia.

Conclusions:
To our knowledge, cranial neuropathy has not been reported in association with PRP. Here we present a case of abducens nerve palsy in a patient with PRP in the absence of compressive or microangiopathic causes.

References: None.

Keywords: Ocular Motility, Neuro-Ophth & Systemic Disease

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Poster 87

Characterization of Idiopathic Intracranial Hypertension (IIH) in Qatar

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Introduction:
IIH is a disease of young obese women that can lead to significant vision loss. Previous studies described the nature of IIH within the Middle East. However, no such data has been published from Qatar. Given the rising epidemic of obesity in Qatar, we hypothesize a more severe IIH presentation and worse visual outcomes.

Methods:
A retrospective chart review of IIH patients seen at the Neuro-ophthalmology clinic between January 2000 – present was done. All patients satisfied the Modified Dandy criteria.

Results:
34 patients were included; mean age of presentation was 31.6 (± 11.6) years with a 4.5:1 female/male ratio. 90.63% of patients had BMI>25. Most common presenting symptoms were headache (76.67%) and transient visual obscurations (73.33%). 93.33% had papilledema, 73.1% had visual field defects, 32.1% had reduced visual acuity, and 87.5% had thickened RNFL (average =170.4mm). On MRI, 45.5% of patients had an empty sella, and 30.3% had papilledema. Average CSF opening pressure was 36.6 cmH_2O. All patients were treated medically, no surgical interventions were performed. At an average of 6 months follow-up time: six patients were lost to follow up, 21.4% had persistent visual loss, 48% had VF defects, 77% had papilledema, and 69.2% had RNFL thickening. 42.3% of patients developed RNFL atrophy. No significant weight changes were observed.

Conclusions:
Incidence of obesity in our patients was higher than previously reported IIH studies in the gulf region [1,2,3], suggesting a more robust correlation between obesity and IIH in Qatar. Patients presented with larger VF defects, more papilledema reflected by RNFL thickening, and higher CSF opening pressure. Recovery was sub-optimal with persistent field defects in most patients and significant number of RNFL atrophy. These observations indicate a more severe course of IIH in Qatar, which necessitates introducing new therapeutic modalities and emphasizing patient education and disease prevention.

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Keywords: Idiopathic Intracranial Hypertension, Obesity, Qatar

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Poster 88

Osmometry of Cerebrospinal Fluid from Patients with Idiopathic Intracranial Hypertension (IIH)

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Introduction:
This study aims to investigate osmolality of cerebrospinal fluid (CSF) from patients with idiopathic intracranial hypertension (IIH). IIH is a disorder of increased intracranial fluid pressure (ICP) of unknown etiology. Investigating CSF osmolality could provide knowledge of underlying pathophysiological mechanisms.

Methods:
CSF samples were collected from individuals referred on suspicion of IIH from 2011-2013. Subjects included as patients fulfilled the Modified Dandy Criteria; individuals in whom IIH was refuted were included as controls. ICP was measured by lumbar puncture manometry at inclusion and in patients after three months treatment with weight loss and acetazolamide or topiramate. Osmolality was measured with a Vapor Pressure Osmometer.

Results:
We collected 90 CSF samples from 38 patients and 28 controls. We found no significant differences in osmolality between groups: Neither when newly diagnosed patients were compared with the control group ($p = 0,86$), when newly diagnosed patients were compared to the osmolality after 3 months treatment ($p = 0,97$) nor when patients with normalized pressure after 3 months had their CSF osmolality compared to their baseline values ($p = 0,79$). We found no significant differences when comparing osmolality in individuals with normal ICP from 6-25 cmH2O ($n = 47$) with: patients with moderately elevated ICP from 26-45 cmH2O ($n = 37$) ($p = 0,20$) and patients with high ICP from 46-65 cmH2O ($n = 6$) ($p = 0,88$) respectively. There was no correlation between osmolality and ICP, BMI, age and body height respectively. Mean CSF osmolality was 270 mmol/kg (± 1 SE, 95% confidence interval 267-272) for both patients and controls.

Conclusions:
CSF osmolality was normal in patients with IIH and there was no relation to treatment outcome, ICP, BMI, age and body height. Mean CSF osmolality was 270 mmol/kg for both patients and controls. Other pathophysiological mechanisms behind IIH must be searched.

References: None.

Keywords: Idiopathic Intracranial Hypertension, Pseudotumor Cerebri, High Intracranial Pressure/Headache, Cerebrospinal Fluid/CSF, Osmolality

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Poster 89

Corneal Biomechanics : A Journey Through Unchartered Territories

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Introduction:
To ascertain the relationship of corneal biomechanics with the severity of visual field loss in patients with Papilloedema due to Idiopathic Intracranial Hypertension (IIH).

Methods:
15 patients referred to the Neuro-ophthalmology department, diagnosed to have IIH were included in the study. Best corrected visual acuity, anterior segment and pupil evaluation, fundus evaluation, optic nerve photography, corneal biomechanics measured using CORVIS ST(Oculus Germany), B scan ultrasonography to detect fluid around the optic nerve and visual field analysis were performed. Corneal biomechanics were compared to the severity of visual field loss.

Results:
Patients with deformation amplitude (DA) <1.15 were considered normal, DA >1.15 subnormal and more than 1.30 is considered to have poor biomechanics. The mean DA of 8 eyes out of the total cohort was 1.10, whereas 7 eyes had a mean DA of 1.30. 6 eyes which showed progression and severe visual field defect (mean >5db) had poor biomechanics (1.30) compared to those with stable fields and non progressive IIH, suggesting that biomechanical parameters may be one of the possible factors in progression .

Conclusions:
Corneal biomechanics may be an indirect indicator of scleral biomechanics. Weaker ocular biomechanics might be associated with greater visual field loss in patients with Papilloedema due to IIH. Thus corneal biomechanics may be an indirect parameter in prognosticating IIH patients. However our cohort size is small and a study on larger cohort would be needed to bring a better insight into this domain.

References: None.

Keywords: Corneal Biomechanics, Idiopathic Intracranial Hypertension, Progression, Fluid Around Optic Nerve, CORVIS

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Poster 90

Clinical and Prognostic Significance of CSF Closing Pressure in Pediatric Pseudotumor Cerebri Syndrome

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Introduction:
The significance of CSF opening pressure (OP) in diagnostic lumbar puncture in pediatric pseudotumor cerebri syndrome (PTCS) has been well-studied.[1] Little consensus exists as to whether the closing pressure (CP) or removing large volumes of CSF has any prognostic utility.

Methods:
This is a retrospective observational series of 93 patients with definite pseudotumor cerebri syndrome (by 2013 revised criteria). Age, gender and body mass index Z-scores (BMI-Z) at diagnosis, as well as OP, CP and volume of CSF removed were abstracted. The primary outcome measure was time to resolution of papilledema by ophthalmoscopy from initial diagnosis.

Results:
No significant differences in gender, age or BMI-Z were observed between subjects with (N=35) and without (N=58) documented CP. The 35 subjects were 74% female, average 12.9yrs (4.9 SD), and had a mean BMI-Z of 1.46 (1.10 SD). Mean OP was 413 mmH_2O (98 SD). Mean CP was 173 mmH_2O (60 SD) and removed volume documented in 17 subjects ranged 7-35ml (median=16). Mean change in pressure (ΔP=OP-CP) was 240mmH_20 (median = 230). BMI-Z (r=0.38, p=0.02) and age (r=0.32, p=0.06) were both positively associated with ΔP, likely driven by higher OP related to both BMI-Z (r=0.51, p=0.002) and age (r=0.38, p=0.02). Median time to resolution of papilledema was similar (119 days vs 113 days, p=0.17) in children with ΔP below versus above the median. Median time to resolution of papilledema in children with CSF volume removed above vs. below the median was insignificantly shorter (80 vs 113 days, p=0.30).

Conclusions:
No significant effect of change in pressure or amount of CSF removed on time to resolution of papilledema in pediatric PTCS was detected.

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Keywords: Pseudotumor, Closing Pressure, Papilledema

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Poster 91

Subretinal Fluid in Idiopathic Intracranial Hypertension: Clinical Course and Outcome

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Introduction:
Decreased visual acuity at presentation in idiopathic intracranial hypertension (IIH) can be produced by several mechanisms.[1-3] When resulting from subfoveal subretinal fluid (SRF) and/or photoreceptor disruption, it is usually reversible, but visual recovery may be delayed following resorption of SRF. We examined the incidence and prognosis of SRF in IIH.

Methods:
A retrospective review of 660 patients with IIH (2009-2013) identified 10 eyes from 8 patients (1.2%) with SRF on OCT and 8 eyes from 5 patients (0.75%) with photoreceptor disruption (disruption of the IS/OS junction) without SRF on OCT, producing best-corrected visual acuity (BCVA) of 20/25 or worse on presentation. Fundus photography, spectral-domain OCT of the disc and macula, and perimetry were used to evaluate SRF, photoreceptor disruption, and visual prognosis. The volume of SRF was determined by segmentation of the macula OCT with the Iowa Reference Algorithm.

Results:
The volume of SRF correlated with BCVA at presentation (r^2 = 0.7156). On average, SRF resolved in 2.2 weeks (STD 0.4, range 2-3 weeks) after starting treatment, but there was often residual photoreceptor disruption and persistently decreased BCVA. Photoreceptor disruption subsequently resolved with complete visual recovery over an average of 1.8 weeks (STD 1.6, range 0-3 weeks) following resorption of SRF. In patients with photoreceptor disruption at presentation, visual and photoreceptor recovery occurred an average of 3.75 weeks (STD 1.9, range 1-6 weeks) after initiation of treatment. There was no significant difference in the initial BCVA of patients with SRF vs. photoreceptor disruption only (average LogMAR VA of 0.375 and 0.25 respectively, p=0.41). All recovered visual acuity to 20/20, although there was often residual photoreceptor disruption nasal to the fovea, even on extended follow-up.

Conclusions:
Vision loss from SRF is reversible in IIH, but maximum recovery after fluid resorption occurs only after subsequent photoreceptor reorganization has taken place.

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Keywords: Idiopathic Intracranial Hypertension, Subretinal Fluid, Optical Coherence Tomography, Photoreceptor Disruption

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Poster 92

Overdiagnosis Of Idiopathic Intracranial Hypertension (IIH).

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Introduction:
Primary benign headaches are common, occurring in up to 24% of young women. This, combined with the increasing prevalence of obesity and awareness of IIH, has led to an increase in costly and invasive evaluations for headache, often in the absence of documented papilledema. Our objective was to quantify overdiagnosis of IIH among patients seen on our Neuro-Ophthalmology service.

Methods:
Review of new patients seen between 11/01/2013 and 03/21/2014. Patients referred for a working diagnosis of IIH, abnormal optic nerve appearance, or suspicion of IIH were included. We applied the Diagnosis Error Evaluation and Research (DEER) taxonomy tool to classify cases according to the location and type of error in the diagnostic process.[1,2]

Results:
84/664 new patients (13%) were seen to either rule out IIH (n=43; 34 abnormal optic nerve appearance, 9 headache) or for management of IIH (n=41; 98% women, median age 31 (IQR 22–41), mean BMI 35 kg/m^2). 20/41(48.7%) patients referred for IIH did not have IIH. Final diagnoses were pseudopapilledema (9[45%]), primary headache (4[20%]), optic atrophy (3[15%]) and one each of optic disc drusen, optic neuritis, sequential NAION, dominant optic atrophy, and physiologic blind spot. 17/20 had a lumbar puncture, 2/20 had >1 lumbar puncture, 18/20 had a brain-MRI, 3/20 had an MR-venogram/CT-venogram, 1/20 had a lumbar drain, 2/20 were referred for surgery. Diagnostic errors resulted primarily from failure to appreciate or misinterpretation of a physical examination finding (13[65%]), failure to order or misinterpretation of an appropriate test (3[15%]), errors in assessment (2[10%]), and poor history (1[5%]).

Conclusions:
Diagnostic errors resulted in the incorrect diagnosis of IIH in 48.7% of patients and prompted unnecessary tests in 44%, invasive procedures in 41% and missed diagnoses in 10%. The most common error was inaccurate funduscopic examination in headache patients, reinforcing the need for rapid and easy access to neuro-ophthalmologists.[3]

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Keywords: Pseudotumor Cerebri, Idiopathic Intracranial Hypertension, Papilledema, Headache, Diagnostic Error

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Poster 93

An Update On Terson Syndrome: Prevalence And Prognosis

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Introduction:
Terson syndrome (TS), originally defined as vitreous hemorrhage (VH) in the setting of subarachnoid hemorrhage (SAH), now includes any intraocular hemorrhage (subretinal, intraretinal, subhyaloid, or vitreous) secondary to acute intracranial hemorrhage (ICH) and elevated intracranial pressure. Bedside ocular fundus imaging technology may allow for improved diagnosis of TS in patients acutely ill with ICH. We reviewed the literature for publications on the prevalence and prognostic significance of intraocular hemorrhage in patients with acute ICH.

Methods:
Medline and Embase databases (English, French, and German) were searched using the keywords “TS” and the combination of “intraocular hemorrhage” (and its subtypes, e.g., “VH,” “subhyaloid hemorrhage,” “intraretinal hemorrhage”) and “ICH” (and its subtypes, e.g., “SAH,” “intraparenchymal hemorrhage,” “hemorrhagic stroke”). We excluded studies enrolling fewer than 10 patients and cohort studies enrolling nonconsecutive ICH patients. The prevalence of TS and its subtypes was calculated, and mortality rates were compared for those with and without TS.

Results:
112 publications were included: 16 cohort studies (11 prospective/5 retrospective) and 8 case series (1 prospective/7 retrospective). 165/978 patients (16.9%) assessed prospectively had TS; 222/786 patient records (28.2%) reviewed retrospectively documented TS. The overall prevalence of TS was 21.9%. In studies reporting subtypes of intraocular hemorrhage, retinal hemorrhages were most common (63.5%), followed by subhyaloid hemorrhages (20.5%) and VH (19.6%). Mortality was higher among those with TS than those without TS (24% vs. 10%, p=0.01).

Conclusions:
TS is associated with higher mortality in patients with acute ICH. Among studies reporting subtypes of intraocular hemorrhage, VH (“classic” TS) was the least common type of intraocular hemorrhage observed, whereas retinal hemorrhages were far more common. Systematic examination of the ocular fundus for all types of intraocular hemorrhage, perhaps using new bedside fundus imaging technologies, is important for identifying ICH patients most at risk for poor outcomes and in need of ophthalmic follow-up.

References: None.

Keywords: High Intracranial Pressure, Subarachnoid Hemorrhage, Retina, Fundus Imaging

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Poster 94

Aberrant Presentation of Pseudotumor Cerebri

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Introduction:
The purpose of this abstract is to illustrate a case of Pseudotumor Cerebri that presented with a third nerve palsy instead of the typical sixth nerve palsy. A 24-year-old white woman presented with a two day history of headache and blurred vision. Bilateral papilledema and a complete third nerve palsy were noted during her hospital admission.

Methods:
Neuro-Ophthalmic evaluation, Lumbar Puncture, Computerized Tomography (CT) of the brain with and without contrast, CT Angiography, and Magnetic Resonance Venography were also performed while she was admitted at a local hospital. She was examined by Ocular Coherence Tomography (OCT) and Funduscopic exams on follow up visits. Orthoptic examination was done regularly.

Results:
Neuro-ophthalmic evaluation showed bilateral papilledema and complete third nerve palsy on the right side. Non-traumatic Lumbar Puncture showed an elevated opening pressure at 33cm H2O, but normal cytology, culture, protein, and glucose. The CT with and without contrast, CTA, and MRV showed normal cerebral and vascular anatomy. OCT showed NFL thickness of 339 microns OD and 264 microns OS. Funduscopic exam yielded optic disc edema bilaterally. Orthoptic evaluation showed a right complete third nerve palsy. Her symptoms and findings resolved when the patient was treated with Prednisone 10mg QD and Acetazolamide 1000mg QD over the course of 10 weeks.

Conclusions:
In light of the series of negative imaging, findings on Lumbar Puncture, clinical presentation, and the patients' response to the standard of care in the treatment of Pseudotumor Cerebri, it can be concluded that her third cranial nerve palsy was directly associated with this condition. This is an isolated and unreported presentation of an otherwise common disease. To conclude, any patient with sudden onset third nerve palsy should be secondarily worked up for Pseudotumor Cerebri if vascular and cerebral causes have been appropriately ruled out.

References: None.

Keywords: Pseudotumor Cerebri, Ocular Motility, High Intracranial Pressure/ Headache

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 95

Jugular Vein Thrombosis as a cause of Intracranial Hypertension

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Introduction:
Cerebral venous sinus thrombosis is one of the well-known causes of increased intracranial pressure (ICP)[1]. Jugular vein thrombosis as a sole cause of increased ICP was rarely described before [2,3].

Methods:
Retrospective case series

Results:
Two patients with increased ICP secondary to jugular vein thrombosis are presented. Case 1: a 38-y-old healthy cardiologist who presented with complaints of localized pain at the right mastoid process and along the sternocleidomastoid muscle. A week later he noticed a blurred vision in the lateral field of his left eye. Ocular examination was unremarkable except bilateral papilledema. Brain CT and MRI were normal. LP showed an opening pressure of 430 mm H_2O and normal content. Thrombosis of the right jugular vein was demonstrated with Doppler of the cervical veins, and confirmed by CTV of the brain and neck. Case 2: 37 y-old female presented to the emergency room with complains on headache, vomiting and chest pain. MRI/MRV of the brain was normal. Chest CT/CTA revealed massive left pulmonary emboli. She presented to the ophthalmology clinic two months later with diplopia consistent with divergence insufficiency and right jugular vein thrombosis was demonstrated by Doppler. LP was not done because of anticoagulation until 6 months later, when she developed papilledema. Opening pressure was 380 mm H_2O.

Conclusions:
Unilateral jugular vein thrombosis may cause increased ICP and should be considered in the differential diagnosis of patients with increased ICP-related signs and symptoms.

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Keywords: Jugular Vein, Thrombosis, Intracranial Hypertension, Papilledema

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 96

Autism Spectrum Disorder in Pediatric Pseudotumor Cerebri Syndrome

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Introduction:
Having recently cared for pediatric patients with suspected pseudotumor cerebri syndrome (PTCS) and concurrent autism spectrum disorder (ASD), we examined our cohort for additional evidence of this association.

Methods:
Design was a retrospective observational case series. Possible PTCS subjects ages 2-18 years were identified by ICD-9 search and review of a pediatric neuro-ophthalmologist's database (July 1993-April 2013). Recently revised diagnostic criteria[1] assigned "definite" (n=78) and "probable" (n=10) cases. "Suspected" cases met all criteria but were missing either LP (n=47), MRI/MRV (n=36), or documented papilledema (n=15). Remaining cases were considered "not PTCS" and were excluded. ASD diagnoses within this PTCS cohort were identified by ICD-9 search and database review. Patient-specific factors extracted from the medical record included demographics, anthropometrics, and where relevant, ASD diagnostic criteria and common co-morbidities.

Results:
In this cohort (n=186), 3 subjects had concurrent ASD per sub-specialist assessment. All 3 were non-obese males; 2 had suspected PTCS missing only an MRI/MRV, and 1 had definite PTCS. The most common ASD co-morbidities included intellectual disability (3/3), language delay (3/3), sleep difficulty (3/3), aggression (3/3), self-injury (2/3), motor abnormality (2/3), and ADHD (2/3). The rate of ASD among all subjects with definite, probable, or suspected PTCS was 1.6% (3/186). The rate of ASD among non-obese males was between 6.8% (3/44, conservatively assuming all boys missing anthropometric measurements were non-obese), and 9.1% (3/33, assuming all boys missing anthropometric measurements were obese). These rates seem higher than would be expected from ASD population estimates (0.62-2%).[2] Since April 2013, two subsequent PTCS cases in boys with ASD have been identified: one obese with probable PTCS, and one non-obese with definite PTCS.

Conclusions:
This experience suggests a possible association between ASD and pediatric PTCS among non-obese boys. Further studies with larger sample sizes are needed to confirm these findings and to elucidate potential underlying mechanism(s).

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2. Meng-Chuan, Lombardo, Baron-Cohen, Autism, Lancet, 383, 896-910, 2014.

Keywords: Pseudotumor Cerebri, Pediatric Neuro-Ophthalmology

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Poster 97

Lumbar Drain in Fulminant Intracranial Hypertension

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Introduction:
Fulminant intracranial hypertension (FIH) is a subtype of intracranial hypertension characterized by rapid severe progressive vision loss. The current practice recommends ventricular peritoneal shunt (VPS), lumbar peritoneal shunt (LPS), or optic nerve sheath (ONSF) be performed immediately to halt or reverse vision loss [1]. These interventions carry significant risk of morbidity with up to 75% of shunts failing at 2 years [2]. Here we describe the successful management of 2 teenagers with FIH with a temporary lumbar drain.

Methods:
A chart review of the clinical course of 2 female teenagers with FIH treated immediately with lumbar drain followed by medical therapy.

Results:
Two obese pubertal girls with acute severe bilateral visual loss (case 1: light perception OD and 20/800 OS; case 2: 20/400 OD and counting fingers OS) of less than 2 weeks duration had bilateral papilledema (grade 5) and an abducens palsy. Both patients had normal neuroimaging, intracranial pressure >35 cm H_2O, and initially treated with acetazolamide (1500 mg daily or less than 12 mg/Kg). Each received 1g/day of intravenous methylprednisolone, 2g/day acetazolamide and placement of a lumbar drain (11 days for case 1 and 3 days for case 2). They responded with marked decrease in the papilledema, resolved abducens palsy and improvement in vision (Case 1 at 18 months visual acuity of 20/200 OD and 20/50 OS; case 2 at 3 months visual acuity of 20/70 OD and 20/60 OS).

Conclusions:
A temporary lumbar drain may be considered in cases of FIH and can circumvent the need for a cerebrospinal fluid diversion procedure or optic nerve sheath fenestration.

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Keywords: Fulminant Intracranial Hypertension, Lumbar Drain, Papilledema, Pediatric Patient, Severe Vision Loss

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Poster 98

Papilledema With Unilateral Occlusion Of Internal Jugular Vein

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Introduction:
To report and review a case of papilledema and increased intracranial pressure in setting of unilateral complete occlusion of internal jugular vein

Methods:
This is a descriptive case report based on clinical records, patient observation and analysis of diagnostic studies.

Results:
A 45-year-old man, who had history of squamous cell laryngeal carcinoma, was found to have papilledema on his ophthalmic evaluation 6 months after the completion of chemotherapy and radiation. MRI brain and MRV brain were unremarkable and lumbar puncture showed opening pressure was 35cmH2O at lateral decubitus position. The patient started Diamox but could not tolerate and had to stop. CTA neck was done for the evaluation of tightening and feeling hard in the right side of neck and it showed complete occlusion of the right jugular vein and patent left jugular vein. The patient started Topamax and it was titrated up to 100mg twice a day. Without improvement of headache and blurry vision with the medical treatment, ventriculoperitoneal shunt placement was performed. After the shunt placement, the patient noticed his blurry vision and also headache had improved.

Conclusions:
This is a case of papilledema and increased intracranial pressure in setting of complete occlusion of unilateral jugular vein. Bilateral occlusion or stenosis of jugular veins have been known to cause the increased intracranial pressure. It is uncommon but complete occlusion of unilateral jugular vein also could be related to increased intracranial pressure. MRV or CTV of neck may be considered as a work-up for the medically refractory idiopathic intracranial hypertension.

References: None.

Keywords: High Intracranial Pressure/Headache, Neuroimaging

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Poster 99

Papilledema Secondary to Internal Jugular Vein Thrombosis in a Dialysis Patient

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Introduction:
We report a case of papilledema due to unilateral jugular venous thrombosis resulting from temporary hemodialysis using a jugular venous approach.

Methods:
A 64-year old thin woman presented for neuro-ophthalmology consultation complaining of intermittent graying of vision lasting seconds at a time, which was not exacerbated by positional changes. The patient denied headache, diplopia, vision loss, or pulsatile tinnitus.

Results:
Bilateral disc edema was found on physical examination. Humphrey visual field demonstrated mild central depression in the right eye, while the left eye showed moderate enlargement of the physiologic blind spot, an inferonasal step, and a superior arcuate scotoma. Brain MRI was unremarkable, while the brain MRV demonstrated a congenitally hypoplastic left vertebral artery. A venous Doppler of the neck was ordered given her history of hemodialysis via the right internal jugular vein (IJV) demonstrating absence of Doppler flow consistent with thrombosis. Subsequently, a lumbar puncture performed in the lateral decubitus position revealed opening pressure of 40 cm H2O and normal CSF constituents.

Conclusions:
In this case, the thrombosed jugular vein would have gone undetected based upon the findings on initial imaging. A thorough history and high level of clinical suspicion led to further testing which elucidated the etiology of the patient's bilateral disc edema. The elevated ICP appeared to be a consequence of right IJV thrombosis superimposed upon a congenitally atretic left vertebral artery resulting in cerebral venous hypertension. At presentation, there was already evidence for visual loss secondary to papilledema. It is important for physicians to be aware of possible consequences of IJV access thereby enabling rapid evaluation to prevent progressive visual loss in this unusual clinical scenario. This case brings into question whether thrombosis of the IJV found incidentally in dialysis patients should prompt fundus examination looking for evidence of papilledema.

References: None.

Keywords: Papilledema, Venous Thrombosis, Hemodialysis, Cerebral Venous Hypertension

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Grant Support: None.

Poster 100

Ultramicroscopic study of the Optic Nerve Sheath in Patients with Severe Vision Loss from Idiopathic Intracranial Hypertension- Methodology

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Introduction:
Very little is known about the anatomy and pathology of the optic nerve sheath (ONS) in normal and diseased states. The objective of our study is to explore microscopic changes in the ONS in patients with severe and/or progressive vision loss from IIH.

Methods:
ONS specimens were obtained from patients with IIH after ONS fenestration (cases) and painful blind eye after enucleation (controls). Both procedures were performed by a single surgeon. A 2 x 1 mm ONS window was obtained, divided into 2 parts, fixed and stained per following protocol.Light Microscopy (LM): All specimens were formalin fixed, stained using Hematoxylin-Eosin and examined at 10x and 40x magnification.Transmission electron microscopy (TEM): All specimens were immediately fixed (in Operating room) using 4% paraformaldehyde and 3.5% glutaraldehyde on ice; washed in Cacodylate buffer; postfixed using Osmium tetroxide/buffer mixture; dehydrated through graded concentrations of ethanol washes; and resin embedded. Ultrathin sections were obtained, stained and examined in Philips Tecnai Biotwin 12 TEM at 2900X magnification.Polarization microscopy (PM): All specimens were stained using Picrosirius red and examined under polarization microscope using previously published methods. (Junqueira et al., 1979) Masked experts in LM, TEM and PM performed evaluations for specimen quality (desiccation, trauma and staining) and tissue anatomy (cellularity and collagen arrangement).

Results:
Of 13 subjects and 16 eyes enrolled, 7 specimens (6 cases and 1 control) met inclusion and quality control criteria for analysis. Tissue was not obtained in 4 eyes at surgery. 2 specimens were excluded due to alternative diagnosis (meningioma, panophthalmitis). 3 specimens were excluded due to tissue desiccation resulting from increased time interval from resection to tissue fixation.

Conclusions:
Adequate quantity and quality ONS specimens were obtained in patients undergoing ONS fenestration and enucleation. Since ONS is susceptible to desiccation, tissue should be fixed immediately in the operating room.

References:
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Keywords: Optic Nerve Sheath, Pseudotumor Cerebri, High Intracranial Pressure/Headache, Orbit/Ocular Pathology

Financial Disclosures: The authors had no disclosures.

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Poster 101

Ultramicroscopic study of the Optic Nerve Sheath in Patients with Severe Vision Loss from Idiopathic Intracranial Hypertension- Results

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Introduction:
The objective of our study is to describe microscopic changes in the optic nerve sheath (ONS) of patients with severe and/or progressive vision loss from IIH.

Methods:
ONS specimens were obtained at ONS fenestration in IIH (cases) and enucleation for painful blind eye (controls). Both procedures were performed by a single surgeon. After fixation and staining, specimens were examined by masked experts using light (LM), transmission electron (TEM) and polarization (PM) microscopy for specimen quality and tissue anatomy (cellularity and collagen structure). (Details in accompanying abstract).

Results:
Of 12 specimens, 7 (6 cases, 1 control) met diagnostic and quality criteria. For cases: Mean age was 31.25y; mean disease duration 57 days; Mean CSF OP 40.25cm water. Papilledema grade s were II (3 eyes); III (1 eye); IV (2 eyes). 5/6 patients showed severe visual field loss (MD> 15 dB); 3/6 had acuity worse than 20/40 and 2/6 had RAPD. All had normal CSF contents. Control ONS was obtained from an enucleated eye of a 18y with childhood ocular trauma.Collagen abnormalities on TEM: irregular arrangement (all cases), collagen disruption and increased extracellular fluid (5/6 cases) while control ONS showed regular, compact, normal collagen. PM showed marked decrease in green yellow birefringence (<20% in all cases with <5% in 4 cases) compared to control ONS (75% birefringence) which confirmed abnormal collagen content and arrangement in cases. All 6 cases showed increased cellularity on LM and/or TEM with active fibroblasts (3/6 cases) and chronic inflammatory cells (lymphocytes) in all 6 cases.

Conclusions:
Disruption and disorganization of dural collagen in the ONS from IIH points to significant shear forces on distal ONS from raised ICP while increased cellularity indicates tissue repair. These mechanical and inflammatory components could contribute to visual loss in IIH. Early aggressive medical and/or surgical treatment may be beneficial in IIH.

References: None.

Keywords: Optic Nerve Sheath, Pseudotumor Cerebri, High Intracranial Pressure/Headache, Orbit/Ocular Pathology, Dura

Financial Disclosures: The authors had no disclosures.

Grant Support: Research to prevent blindness

Poster 102

Exploratory Study of the Relationship between the Levonorgestrel-Releasing Intrauterine System and Idiopathic Intracranial Hypertension

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Introduction:
Unconfirmed reports have linked the levonorgestrel-releasing intrauterine system (LNG-IUS aka Mirena), a long-acting contraceptive, to idiopathic intracranial hypertension (IIH). In this pilot study, we assessed signs and symptoms of IIH among a cohort of patients using LNG-IUS.

Methods:
A series of 473 IIH patients seen between 2008 and 2013 was screened for female gender, age ≥ 18, and absence of causative etiologies. Of 176 eligible participants, 59 completed birth control histories by telephone.

Results:
Eight of these 59 patients (14%) were using an LNG-IUS within 3 months of onset of IIH symptoms. Nine patients (15%) were on another contraceptive, and 42 (71%) were not using any contraceptives. All LNG-IUS users developed symptoms while the device was *in situ*. There were no significant differences between LNG-IUS users and non-users in terms of age (30±6 vs 32±9, p=0.62), body mass index (35±9 vs 35±7, p=0.92), history of recent weight gain (50% vs 25%, p=0.16) or presenting symptoms. Signs were also similar between the two groups: opening pressure (357±101 vs 404±13, p=0.25), Frisén papilledema grade (stage 2 most frequent, worse and fellow eye, p=0.09), perimetric mean deviation (-5.6±5.5 vs -6.2±7.5 worse eye, p=0.83; -2.9±3.1 vs -4.1±5.4 fellow eye, p=0.54; -2.7±2.7 vs -1.8±3.0 difference between eyes, p=0.38), and LogMAR best corrected visual acuity (0.06±0.11 vs 0.09±0.30 worse eye, p=0.81; -0.01±0.10 vs 0.05±0.29 fellow eye, p=0.56; 0.08±0.09 vs 0.04±0.11 difference between eyes, p=0.42).

Conclusions:
Our preliminary findings suggest that IIH patients using an LNG-IUS have clinical features comparable to those not using an LNG-IUS. We are currently investigating the incidence of IIH among users of LNG-IUS and will present these data at the Annual Meeting. Although a causative role for LNG-IUS has not been established, until further data are collected, we recommend augmenting the routine evaluation for IIH with a birth control history.

References: None.

Keywords: Pseudotumor Cerebri, High Intracranial Pressure/Headache, Levonogestrel, Contraception, IUD

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Poster 103

Coning Following Lumbar Puncture In A Patient With Idiopathic Intracranial Hypertension

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Introduction:
Lumbar puncture is performed frequently in patients with idiopathic intracranial hypertension. Cerebellar tonsillar descent is not uncommon, but frank herniation (coning) is extremely rare.[1] We are aware of only one previous case reported in the literature.[2] We describe a case in which the patient coned following a lumbar puncture, necessitating acute neurosurgical intervention.

Methods:
Case Report

Results:
A 30 year old obese Caucasian woman with well-controlled idiopathic intracranial hypertension (IIH) presented to the emergency department with a week's history of severe bifrontal headache, associated with nausea, photophobia and neck pain. Neurologic examination was unremarkable apart from bilateral papilloedema. She had had three therapeutic lumbar punctures (LP) previously, all of which showed high opening pressures and non-inflammatory CSF. Her brain MRI at initial diagnosis was in keeping with IIH. She had also had a CT venogram which showed hypoplasia of the entire left venous system and was waiting for insertion of a venous stent at another hospital. A therapeutic lumbar puncture was performed under fluoroscopic guidance. Her CSF opening pressure was 47 cmH_2O and 20ml of CSF was removed. 12 hours later, she developed severe (grade 10/10) global headache with excruciating neck pain. She was unable to lie flat and held her neck in extreme extension. This was followed 12 hours later by hypotension, reduced level of consciousness, and anisocoria. A CT brain showed tonsillar herniation. She was treated by external ventricular drain and then bifrontal craniectomy.

Conclusions:
This patient also had renal tubular acidosis and she was quite acidotic at the time of presentation. It is speculated that this may have been related to the pathophysiology of the coning, explaining why she suffered this unusual complication of lumbar puncture.

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Keywords: Idiopathic Intracranial Hypertension, Cerebellar Tonsillar Herniation, Coning, Renal Tubular Acidosis

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Poster 104

Long term follow-up of PTC: pre-pubertal children Vs adolescents and adults

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Introduction:
Pseudotumor-cerebri syndrome (PTCS) can produce a prolonged or recurrent course. Data in the literature regarding the long term results of the disease is limited. The aim of this study was to evaluate the long term results of the disease course, recurrence rates, and final visual outcome of PTCS in pre pubertal children and adolescents and adults strictly diagnosed for PTCS

Methods:
A retrospective observational study.
Included were patients with at least 5 years of follow-up. Excluded were patients with any systemic disease that can cause elevated intracranial pressure.Patients were divided into pre-pubertal children (group A) and all the others (group B).
Main outcome measures were final visual outcome and recurrences

Results:
included were 61 patients (46 females, 15 males). 16 were pre-pubertal children (9 girls 7 boys). Mean age at diagnosis was 9.9 years (5-13) for group A and 28 for group B. Mean follow-up time was 8.9 years for both groups ((A: 5-11; B: 5-32)Mean duration of treatment was 2.5 years for both groups. Overall 40% had recurrent event; 9/16 (56 %) in group A and 14/45 (31 %) in group B, Recurrent attack occurred within 0,8 years from treatment cessation in group A and 2.8 years in group B.9 patients needed surgical intervention (2 group A, 7 group B), mean in 3 years (3 months - 7 years) after initial diagnosis.
Optic neuropathy in at least one eye was seen in 28/61 (60%) [10/16 (62%) group A, 18/45 (40%) group B]

Conclusions:
in spite of the limitation of a small retrospective cohort, we confirmed recurrence of PTC events to occurs years after remission, thus, revealing the importance of longer follow up. Prepubrertal children tend to experience recurrences earlier than adults; but develop optic neuropathy similar to adolescents and adults

References: None.

Keywords: PTC, Long Term, Prepuberty, Children, Outcome

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Poster 105

Hemodialysis Graft-Induced Intracranial Hypertension

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Introduction:
Intracranial hypertension (IH) is rarely associated with peripheral hemodialysis shunts, presumably in association with central venous stenosis.[1,2] Hemodialysis Reliable Outflow (HeRO™) grafts are designed to bypass pre-existing central venous stenosis by connecting the brachial artery with the venous circulation through the ipsilateral internal jugular (IJ) vein.[3] We report a case of IH immediately after placement of a HeRO graft and discuss possible pathophysiology.

Methods:
Case report with review of the English literature.

Results:
A 60-year-old woman with a nonfunctioning right arm hemodialysis arteriovenous (AV) shunt developed blurred vision and optic disc edema three days following placement of a left-sided HeRO graft. Brain MRI/MRV showed signs of IH and lumbar puncture CSF opening pressure was 38 cm H_20. There was 60-70% focal stenosis of a right subclavian vein stent overlying the ostium of the right internal jugular vein and a HeRO graft entering the left IJ vein, resulting in superior vena cava syndrome with IH and papilledema. A ventriculoperitoneal shunt was placed, followed by papilledema resolution and vision improvement. At least 12 cases of presumed IH from central venous stenosis and hemodialysis AV shunts have been published: none involving a HeRO graft. All cases involved brachiocephalic vein stenosis/occlusion (10/12) or IJ vein occlusion (2/12). All were treated with venoplasty +/- AV shunt ligation, and 1/12 was additionally treated with a lumboperitoneal shunt.

Conclusions:
Despite increasing venous flow in patients with central venous stenosis, IH has not been reported in association with HeRO grafts, suggesting the contribution of additional factors to the pathogenesis of hemodialysis graft-induced IH. Although usually treated by graft ligation or venoplasty +/- stent, CSF shunting without graft ligation is also a treatment option in patients with isolated IH whose venous anatomy is seriously compromised. Imaging of chest/neck veins in hemodialysis patients with unexplained IH should be considered in cases with previous AV shunts.

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Keywords: High Intracranial Pressure, Pseudotumor Cerebri, Vascular Disorders, Neuroimaging

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Poster 106

Incidence of Idiopathic Intracranial Hypertension (IIH) Among Users of Tetracycline Antibiotics

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Introduction:
Previous studies have shown an association between the use of tetracycline antibiotics and the development of IIH. We sought to calculate the incidence of tetracycline-associated IIH in the University of Utah patient population.

Methods:
Using the newly completed REDCap IIH database at the University of Utah Moran Eye Center we identified 45 patients diagnosed with IIH secondary to tetracycline use during the period 2007-2013. Utilizing the FURTHeR database, we then queried the University of Utah Enterprise Data Warehouse (a database of all individuals seen at University of Utah hospitals and clinics) for both men and women between the ages of 12 and 50 who were ever prescribed a tetracycline antibiotic (doxycycline, minocycline, tetracycline, tigecycline, demeclocycline) over the same time period.

Results:
We found that 960 patients between the ages of 12 and 50 were prescribed a tetracycline antibiotic from 2007-2013 out of a total of 876,358 patients in the database with the same age and year restrictions. Dividing our 45 patients with IIH secondary to tetracycline use by the population at risk (960) and seven patient-years of patient-study and multiplying our result by 100,000 years, we calculated the incidence of tetracycline associated IIH to be 670 per 100,000 patient-years of study.

Conclusions:
This investigation provides the first calculation of the incidence of IIH among patients taking this class of antibiotics. The incidence of IIH among users of tetracycline antibiotics is greater than the incidence of IIH in the general population. Although these data do not provide a causal link between IIH and antibiotics, this observation further substantiates the hypothesis that tetracycline antibiotics may cause IIH in susceptible individuals.

References: None.

Keywords: Idiopathic Intracranial Hypertension, Pseudotumor Cerebri, Tetracycline, Antibiotics, Incidence

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Poster 107

CSF Characteristics in Patients with High Frisén Papilledema Grades from the IIHTT

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Introduction:
Papilledema is optic disc edema due to increased intracranial pressure. The severity of papilledema grade may be related to the density of trabeculations in the subarachnoid space, magnitude of CSF pressure, or another mechanism. We investigated the relationship of CSF pressure to high Frisén papilledema grades (4 and 5), and the response to randomized treatment with acetazolamide plus diet versus placebo plus diet in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).

Methods:
Papilledema was present and graded in all IIHTT subjects, each of whom had mild to moderate visual field loss. In the IIHTT, 165 patients met inclusion criteria with lumbar puncture (LP) CSFp > 250 mm H_2O, or > 200 mm H_2O with other compelling IIH clinical/imaging criteria. All participants were asked to repeat the LP 6 months later. We correlated CSF pressure (CSFp) with Frisén grade and treatment category.

Results:
Fifty patients had high Frisén grade (HFG). Of these, 21 had CSFp <350 and 29 had CSFp > 350. HFG was found in 22% of patients having CSFp <350, and 39% of patients having CSFp >350 (p = 0.0262). 6 months LP was performed in 13/29 patients having both CSFp > 350 and HFG. In this group, eleven patients were on acetazolamide. All of these improved: Seven by Frisén grade of 0-1, one by 2, and three by 3. Mean CSFp decreased from 446.5 to 233.5. In contrast, the two patients in this category on diet alone sustained persistently high CSFp and unchanged HFG. The one patient who required optic nerve sheath fenestration was on diet alone.

Conclusions:
Higher CSFp was associated with significantly higher (worse) Frisén grade. Treatment with acetazolamide improved patients with HFG.

References: None.

Keywords: High Intracranial Pressure/Headache, Pseudotumor Cerebri

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 108

Visual Outcomes After Treatment of Venous Sinus Stenosis with Dural Venous Sinus Stenting

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Introduction:
Dural venous sinus stenting (DVSS) has been utilized for years to treat Idiopathic Intracranial Hypertension (IIH), but the literature is scant illustrating its utility in venous sinus stenosis. In most clinical studies that involve this technique, there is an overwhelming group of patients with IIH with few that have known venous sinus abnormalities causing visual symptoms at the time of diagnosis. Although DVSS has been found to be safe and effective at lowering intracranial pressure, this study reviews the effect on the visual system after DVSS with or without addition of acetazolamide.

Methods:
Two patients, ages 19 and 35,with an initial diagnosis of venous sinus stenosis will be reviewed. Visual acuity, color vision, visual fields, alignment, and optic nerve abnormalities were noted preoperatively, immediately postoperatively and during extended follow-up.

Results:
Initial visual acuity ranged from 20/20 to LP and MD were (x) on visual field testing prior to surgery. At long-term follow-up, average visual acuities ranged from 20/20 to 20/50 and one patient improved by visual field testing. Optic nerve edema recorded pre- and post- operatively were found to have improved immediately after DVSS. One patient needed angioplasty for the thrombosis before DVSS, as well as evaluation for coagulopathy; this second patient required additional treatment with acetazolamide to improve visual acuity and reduce optic disc edema noted on examination and on subsequent optical coherence tomography.

Conclusions:
There are few studies evaluating the use of dural venous sinus stenting to treat venous sinus stenosis. While medical management and close targeted monitoring remain a cornerstone of management, this technique may become another surgical option to treat venous sinus stenosis. Additional medical and hematologic management may be required to prevent additional vision threatening disease.

References: None.

Keywords: Venous Sinus Thrombosis, Dural Venous Sinus Stenting

Financial Disclosures: The authors had no disclosures.

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Poster 109

Relationship between High Opening Pressure on Lumbar Puncture and Failure of Optic Nerve Sheath Decompression to Prevent Progressive Visual Loss in Patients with Idiopathic Intracranial Hypertension.

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Introduction:
To our knowledge, there have been no prior published studies that address the relationship between high opening pressures and progression of visual loss despite optic nerve sheath decompression (ONSD) in patients with idiopathic intracranial hypertension (IIH). Past experience suggests that very high opening pressures (50cm water) place patients at higher risk for ONSD failure. If this hypothesis is confirmed, this knowledge will aid in decision making regarding when it is appropriate to proceed with an ONSD versus a lumbo-peritoneal (LP) or ventriculo-peritoneal (VP) shunt as the initial procedure in patients with IIH who have opening pressures of 50 or greater.

Methods:
Retropsective chart review of patients with IIH who underwent ONSD between January, 1992 and January, 2014. The primary question will compare the failure of ONSD to prevent progressive visual loss in patients with opening pressures less than 50, to those with opening pressures of 50 or greater. Also, if the data allow, we will construct a graph based on categories of opening pressure (e.g. 35-40, 41-45, 46-50, etc.) and their relationship to the failure rate. The definition of failure of the ONSD to protect vision will be the progression of visual loss or persistence of papilledema, leading to a VP or LP shunt within 3 months of the ONSD.Inclusion criteria will be diagnosis of idiopathic intracranial hypertension, recorded opening pressure on lumbar puncture, and papilledema on fundus examination. Exclusion criteria will be a diagnosis other than IIH, prior VP or LP shunt procedure, lack of a recorded opening pressure on lumbar puncture, or subsequent VP or LP shunt to treat uncontrolled headache rather than vision loss.

Results:
Pending.

Conclusions:
Pending.

References: None.

Keywords: Pseudotumor Cerebri, Optic Neuropathy, High Intracranial Pressure/Headache

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Poster 110

Venous Sinus Stenting For Treatment Of Increased Intracranial Pressure Secondary To Venous Sinus Stenosis

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Introduction:
Medical treatment, CSF shunting and optic nerve sheath fenestration are the standard treatments for increased Intracranial Pressure (ICP). Venous sinus obstruction is a well-known cause of secondary elevation of ICP. Venous sinus stenting provides a novel, alternative surgical treatment in cases of venous sinus stenosis.

Methods:
Twelve consecutive patients with papilledema, increased ICP and MRV signs of dural sinus narrowing underwent direct retrograde cerebral venography and manometry. All patients demonstrated radiological signs of obstruction of the venous lateral sinuses. The CSF opning pressure was measured via lumbar puncture in all patients prior to venography. Funduscopic examination demonstrated papilledema for all patients. Venous stening was offered to all patients.

Results:
Six patients opted to undergo venous stenting (Group-A) and 6 were managed conservatively with acetazolamide and monitoring (Group-B). Pressure gradients were measured across the venous stenosis, and was 20 mm Hg in Group-A and 13 mm HG in Group-B (p=0.11). The CSF pressure on lumbar puncture ranged from 26.5 to 55 CmH_2O (mean 40.6 +/- 11.2 CmH2O) with bland composition. Mean ICP for Group-A was 48.4mmHg, while it was 35.3mmHg in Group-B. Average binocular retinal nerve fiber layer thickness (RNFL) at presentation was 310 microns in Group-A and 210 in Group-B (p=0.002). However, binocular RNFL at 3 months was 80.6 microns in Group-A and 124.5 in Group-B (p=0.08). Average acetazolamide dosage at 2-4 weeks was1200mg/day in Group-A and 1083mg/day in Group-B (p=0.9). However, at 6 months, the mean acetazolamide dosage was 900mg/day in Group-A and 1666mg/day in Group-B (p=0.19). Papilledema resolved in all patients at 3-6 months.

Conclusions:
Patients with increased ICP and evidence of drual sinus narrowing on MRV should be evaluated with direct cerebral venography and manometry. In patients with venous sinuses stenosis endovascular stenting seems to be a successful treatment with a trend towards quicker resolution of papilledema and less need for acetazolamid at 2-4 weeks when compared to conservative treatment.

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Keywords: Intracranial Pressure, Dural Sinus, Stenting, Papilledema

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 111

Pediatric Primary Pseudotumor Cerebri Syndrome (PTCS): A Detailed, Retrospective, Multicenter Analysis Of Anthropometrics

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Introduction:
Obesity, gender, and pubertal status influence the risk for pediatric PTCS. Preliminary studies have identified three subtypes of pediatric PTCS, based on anthropometrics. In an international, collaborative effort, this study was designed to refine this observation further.

Methods:
This multi-site study included 5 tertiary pediatric centers. Cases of PTCS were identified retrospectively, based on ICD9 code 348.2 and/or pediatric neuro-ophthalmologist database. Diagnosis of definite and probable PTCS was defined by applying updated PTCS diagnostic criteria (2013). Anthropometric data were abstracted and standardized growth charts determined age-/sex-specific height, weight, and BMI Z-scores. Where available, Tanner staging documented development of secondary sexual characteristics.

Results:
162 definite (n=155) or probable (n=7) cases of primary PTCS were identified (64% female, mean age 11.9±4.4yrs). There was a positive association between BMI Z-score and age ($r=0.48$, $p<0.001$; $n=162$), that, using linear regression analysis, crossed the 'overweight threshold' (BMI Z-score≥1.04) at 9.4yrs and 'obese threshold' (BMI Z-score≥1.64) at 14yrs. In children younger than 9.4yrs, no significant association was observed between height Z-score and age ($r=0.18$, $p=0.21$, $n=48$). There was a negative relationship between height Z-score and age in children ≥9.4yrs ($r=-0.31$, $p=0.0008$, $n=113$), crossing the x-intercept at 15.6yrs. Data on Tanner staging or menarchal status was available in 38 cases. Before 9.4yrs, 4/5 girls were pre-pubertal. After 14yrs, 17/17 girls were post-menarchal. Limited data were available for intermediate ages and boys.

Conclusions:
Before age 9.4 years, pre-pubertal children with PTCS tend to be normal weight. After age 9.4 years, early adolescents with PTCS are typically overweight, and taller for age and sex than peers, suggesting linear growth acceleration. Older, obese, late- or post-pubertal adolescents with PTCS are normal height. Defining key pubertal events that influence the development of pediatric PTCS may guide an understanding of endocrine 'triggers' and, in turn, the pathogenesis of this complex condition.

References: None.

Keywords: Pediatric Pseudotumor Cerebri Syndrome, Anthropometrics, Obesity, Pubertal status

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Poster 112

Endovascular Venous Stenting In Treatment Of Primary Idiopathic Intracranial Hypertension

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Introduction:
Idiopathic Intracranial Hypertension (IIH) is a syndrome of elevated intracranial pressure that can be primary or secondary. In its primary form, it is usually a diagnosis of exclusion. Current treatment options both medical and surgical have varying success rates. We wish to present a small series of patients wherein a select group of patients presenting with primary IIH were treated with endovascular venous stenting.

Methods:
Patients with clinical features of headaches and visual blurring and/or acuity loss underwent detailed ophthalmological evaluation between Jan 2013 and Aug 2014. Those with local causes were excluded and the rest underwent contrast MRI and MR venograms. Those without secondary cause of raised ICP were evaluated for established imaging markers of primary IIH. These patients were managed medically with Acetazolamide and targeted weight loss. Patients not responding to medical therapy underwent cerebral angiography & direct retrograde cerebral venous pressure manometry (DRCVM). Patients with pressure gradients greater than 8 mm Hg underwent venous stenting. Detailed clinical and ophthalmological evaluation was performed 1,3 and 6 months post procedure.

Results:
2121 patients were evaluated prospectively for headaches and visual symptoms. 74 patients had no local cause and underwent contrast enhanced MRI and MRV. 61 patients had secondary causes of raised ICP. 13 patients were medically treated. 3 of these patients showed good clinical response. 2 patients refused endovascular treatment. 8 patients underwent angiography, DRCVM and venous stenting. In the endovascular group there was 100% technical success. 7 of the 8 patients (87.5%) were stented unilaterally and 1 patient (12.5%) bilaterally. Follow up showed resolution of headaches in 7 out of 8 patients (87.5%). Papilloedema resolved in all 8 patients. Visual acuity improvement was in 6 out of 8 (75%) patients.

Conclusions:
Endovenous stenting is a safe, easy and effective method of treating patients with primary IIH.

References: None.

Keywords: Pseudotumor Cerebri, Interventional Neuroradiology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 113

Idiopathic Intracranial Hypertension Mimicking Foster kennedy Syndrome

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Introduction:
To report a case of pseudo- Foster kennedy Syndrome due to idiopathic intracranial hypertension (IIH).

Methods:
A case report.

Results:
A 56-year-old man complained of transiently blurred vision in the right eye for 1 month. The patient denied diplopia, headache, or vomitting. His past medical history was unremarkable, neither previous trauma, nor any medication including vitamin A was recorded. Ophthalmic examination revealed a best corrected visual acuity of 20/20 and 20/400 in the right and left eye, respectively. His anterior segment was normal except a relative afferent pupillary defect in the left eye, fundus examination revealed grade II optic disc edema in the right eye and a pale disc in the left eye, the macula and peripheral retina was normal in both eyes. The intraocular pressures was normal in both eyes. Visual field test revealed normal in the right eye and diffuse depression in the left eye. Fundus fluorescein angiography showed late hyper fluorescence of optic disc in the right eye and hypofluorescence of optic disc in the left eye. Cranial MRI and MR venogram was both normal. A lumbar puncture revealed cerebrospinal fluid (CSF) pressure of 40 cm water. CSF analysis including cell counts, protein, and glucose were both within normal limits.

Conclusions:
pseudo- Foster kennedy Syndrome is a rare appearance of IIH.

References: None.

Keywords: Idiopathic Intracranial Hypertension, Pseudo- Foster Kennedy Syndrome, MRI, Cerebrospinal Fluid, Visual Field

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 114

Going For The Jugular! Paragangliomas, Papilledema, and Vision Loss

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Introduction:
Paragangliomas are relatively benign neuroendocrine tumors that often arise from the jugular bulb. They are known to present as masses in the neck or with hearing loss, pulsatile tinnitus, and manifestations of lower cranial nerve palsies. Much less recognized is their tendency to cause increased intracranial pressure and papilledema by obstructing jugular venous outflow. Only 7 such cases have been reported, and with minimal ophthalmic documentation.

Methods:
We describe 3 cases examined at a single academic medical center.

Results:
Case 1 had papilledema detected on routine optometric examination in a visually asymptomatic patient who had mild visual field loss. Imaging of the brain was normal, but an astute radiologist detected a left neck mass. No intervention took place and findings remained unchanged after 6 months. Case 2 presented with transient obscurations of vision (TOVs) and had papilledema that led to a head CT that disclosed bilateral neck masses. She received external beam radiation therapy that slightly reduced the size of the masses, but she developed optic disc pallor and persistent visual field loss. Case 3 with bilateral paragangliomas developed TOVs after surgical extirpation of a right neck paraganglioma and obliteration of the right jugular vein. Acetazolamide treatment stemmed the TOVs but mild optic neuropathy persisted.

Conclusions:
These 3 cases provide more ample evidence that jugular paragangliomas may be an overlooked cause of the pseudotumor cerebri syndrome, and that papilledema may not be recognized when a jugular paraganglioma is diagnosed or after it has been treated. Such lapses have led to disabling vision loss from damage to the optic nerves in longstanding papilledema.

References: None.

Keywords: Paraganglioma, Papilledema, Jugular

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Poster 115

Visual Outcomes Following Optic Nerve Sheath Fenestration

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Introduction:
Idiopathic intracranial hypertension (or pseudotumor cerebri) is a condition of increased intracranial pressure in the absence of vascular lesion or intracranial mass[1]. Symptoms of IIH include headache, pulsatile tinnitus, transient visual obscurations, and diplopia. Untreated IIH can present with the long-term sequela of visual loss[2]. In approximately 10% of patients with untreated IIH, visual loss will progress to the point of meeting the legal criteria for blindness[3]. The objective of this study was to determine the safety of optic nerve sheath fenestration (ONSF) for the treatment of patients with intracranial hypertension in the immediate 6 month post-operative period and its efficacy in reducing optic disk edema.

Methods:
Design: Retrospective, non-comparative interventional case seriesParticipants: Two hundred and seven eyes in one hundred and four patients undergoing ONSF between the years 2005 and 2014Outcome Measures: Papilledema grade based on modified Frisen scale and mean deviation of Humphrey visual field

Results:
207 eyes of 104 patients (101 IIH, 2 IH due to dural sinus thrombosis) were included in the study. The patients were 96.1% female (N = 100) and 3.9% male (N = 4). The average patient age was 28.8 years (SD +/- 9.5 years) and had a mean opening pressure of 39.85 cmH20 (SD +/- 8.4 cmH20). Mean follow-up period was 6.0 months (SD +/- 5.9 months). Papilledema resolved in 76.1% of eyes at 1 week (N = 102), 75% of eyes at 1 month (N = 90), and 71% of eyes at 6 months (N = 94). Visual field comparison had a mean of the paired differences at 1 week, 1 month, and 6 months of 1.59dB ($p < 0.01$), 2.53dB ($p < 0.01$), and 1.30dB ($p = 0.016$), respectively.

Conclusions:
ONSF is effective in reducing optic disk edema and does not cause vision loss in the 6-month post-operative period regardless of severity of IIH (as judged by elevation of opening pressure measured at pre-operative assessment).

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Keywords: Pseudotumor Cerebri, Visual Fields

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Poster 116

New Side Effect of Acetazolamide: Palinopsia

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Introduction:
Palinopsia is a rare phenomenon in which viewed images persist after the original visual stimulus is removed, and can last from minutes to months [1]. The pathophysiology behind palinopsia is still unclear but hypothesizes include an exaggeration of normal after imaging, seizure disorders, psychogenicity, or drug induction [2.]. Drugs that have serotonin receptor activity such as LSD, trazodone, nefazodone, and topiramate are known to produce palinopsia[3].

Methods:
Single case and literature review: a 30 year old woman, college professor, developed symptoms typical of idiopathic intracranial hypertension. Risk factors included only obesity. There was no history of psychiatric illness. Visual exam demonstrated papilledema with normal acuity, color vision, visual fields, and motility. Treatment was begun with acetazolamide with titration to 2000 mg daily. At high dose patient noticed ghost images trailing behind her moving hand. In addition, she began to see an image first viewed on Facebook of a lotus pod flower. The image appeared on walls, faces, and behind closed eyelids for the next month. The patient understood the images were not real but they invoked anxiety and insomnia. Acetazolamide was discontinued with almost immediate resolution. The patient refused a rechallenge.

Results:
The mechanisms of action of topiramate are unclear but include direct or indirect action on serotonin receptors, and as a weak inhibitor of type II and type IV carbonic anhydrase [4]. The present case suggests that perhaps carbonic anhydrase inhibition its mechanism of action.

Conclusions:
Acetazolamide should be added to the list of drugs producing palinopsia.

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Keywords: Palinopsia, Idiopathic Intracranial Hypertension, Acetazolamide, Topiramate

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Poster 117

Endovascular Intervention In A Chronic Case Of Idiopathic Intracranial Hypertension (IIH)

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Introduction:
Idiopathic intracranial hypertension (IIH) is characterized by increased intracranial pressure (ICP) in the absence of any known causative factor. Severe headache and visual field disturbance are usually the primary symptoms. If high ICP is left untreated, there is a high risk of continued visual deterioration with risk of blindness. IIH is primarily managed medically. Surgery (CSF diversion procedures with lumboperitoneal shunting or ventriculoperitoneal shunting and optic nerve fenestration) is reserved for patients who have failed medical therapy (20%). Endovascular stenting of the dural venous sinus stenosis in cases of documented venous pressure gradient has shown significant promise in a select subgroup of patients, both in terms of visual and headache outcomes.

Methods:
Correlation of clinical presentation, imaging with procedural technique and preliminary response by means of a case report.

Results:
A 34-year old female presented with severe headache and worsening vision. On exam, she was found to have bilateral papilledema. MRI brain evidenced empty sella. MR venography showed focal area of stenosis in the left dominant transverse-sigmoid (TS) sinus. Lumbar puncture (LP) was performed, showed elevated opening pressure (OP) of 47 mm Hg. Cerebral angiography with venous sinus manometry showed a pressure gradient of greater than 20 mm Hg across the left TS sinus. Stenting of the left TS sinus was performed with pressure normalization across the stented segment. She went home on aspirin and clopidogrel. She later reported significant improvement in both vision and headaches. Post-stenting LP showed an OP of 18 mm Hg. Follow-up cerebral angiogram in 3 months showed patent left TS sinus stent. Clopidogrel was subsequently discontinued.

Conclusions:
Medical management is usually the first line treatment of IIH. Surgery has shown benefit in the resistant cases of IIH with no randomized controlled trial for comparison. Stenting of dural venous sinuses is the newer and safe alternative for the refractory cases of IIH, although limited clinical data is available about the long term procedural benefit.

References: None.

Keywords: Idiopathic Intracranial Hypertension (IIH), Papilledema, ICP, Angiogram, Stent

Financial Disclosures: The authors had no disclosures.

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Poster 118

Optical Aberrations- A Trigger Factor For Migraine?

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Introduction:
Migraine is a neurovascular disorder encompassing a wide clinical spectrum of signs and symptoms. The objective of this study was to evaluate whether aberrations of the eye can be trigger factors for migraine.

Methods:
This was an observational, cross-sectional study. 30 patients in the age group of 18-35 years with migraine and a spherical equivalent ≤ -0.75 were included. The control group consisted of subjects with the same inclusion criteria as the patient group but without a history of headache. All subjects underwent Schirmer's test to exclude dry eyes. A masked investigator measured the aberrations of the eye on the Optical Path Difference III (OPD-III Nidek, Japan). Only mesopic wavefront sizes were considered for the study.

Results:
The mean age group of patients with migraine was 26.21 ± 6.23, and that of the controls was 27.31± 6.19. The root mean square (RMS) of total aberrations in the right eye of patients with migraine was 1.63 $\pm$ 0.86 and left eye was 1.54 ± 0.88. The RMS of total aberrations in the right eye of the control group was 0.93 ±0.33 and the same in the left eye was 0.93 ± 0.42. 63% of patients with a history of 'light' as a trigger factor for migraine had a statistically significant ($p<0.001$) increase in total, higher order aberrations and coma RMS values.

Conclusions:
Ocular aberrations may be a trigger factor for migraine. Wavefront analyzers have enabled visual scientists and clinicians to broaden the perspective on the refractive phenomenon in the eye and their influence in health and disease.Studying ocular aberrations during the acute ictal phase and comparing them to normal would give us a better insight and allow a multidisciplinary approach to patients suffering from headache.

References: None.

Keywords: Migraine And Trigger Factors, Ocular Aberrations, Wavefront Analyzer, OPD III, Non-Organic Visual Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Poster 119

An Interesting Field of Study

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Introduction:
Patients with vague visual complaints may have unrealized visual field defects. Detecting defects with confrontational fields is an important diagnostic skill. Homonymous defects are particularly important as they are associated with stroke, tumor, or trauma in approximately 90% of cases. However, other rare causes of homonymous defects must be considered.

Methods:
The following 4 unusual cases presented in the last 6 months.

Results:
In January, 2014 a 70 year-old man presented with visual distortion. Exam showed a left homonymous hemianopsia, right gaze deviations, and dysmetria. Continuous electroencephalogram (EEG) monitoring demonstrated status epilepticus and MRI showed a 1 centimeter hemosiderin lined lesion in the right occipital lobe suggestive of cavernoma. The hemianopsia resolved with anti-epileptic medication and the cavernoma is being observed. In March, 2014 a 47 year-old man presented with complaints of swirling colors and shadows in his left eye. Exam revealed a left homonymous hemianopsia and episodes of right gaze deviation. Two bilateral occipital seizures occurred during continuous EEG and MRI showed restricted diffusion of the right occipital lobe. The hemianopsia resolved with anti-epileptic medication and the MRI findings were presumed secondary to seizure. In April, 2014 a 41 year-old woman presented with complaints of dizziness and right sided blurriness. She had a right homonymous hemianopsia and MRI revealed enhancement posterior to the left lateral geniculate consistent with a multiple sclerotic plaque. The deficits resolved with intravenous solumedrol. In May, 2014 a 28 year-old woman presented with headache and shadows in her right periphery. Exam showed a right superior homonymous quadrantanopsia and MRI demonstrated enhancement of the left occipital lobe. The MRI findings were consistent with reversible vasoconstriction syndrome related to recent excessive energy drink consumption. The symptoms resolved after stopping the drinks.

Conclusions:
Vague complaints can be misleading. However, a careful history and exam can alert clinicians to rare diagnoses.

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Keywords: Visual Fields, Neuroimaging, Diagnostic Tests (ERG, VER, OCT, HRT, Mferg, Etc)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 120

Visual Field Assessment In The "Split-Brain" Patient: Effect Of The Method/Laterality Of Obtaining Patient Responses On Apparent Visual Field Defect Size

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Introduction:
Corpus callosotomy is an important tool in the management of certain refractory epilepsies, but may cause an interhemispheric disconnection syndrome.

Methods:
A 23 year old right-handed man underwent complete corpus callosotomy for intractable epilepsy. Post-operatively, he had features of the callosal disconnection ("split-brain") syndrome, including anomia for objects presented in the left visual field or left hand, left-sided ideomotor apraxia, and "alien limb phenomenon" in the left hand. When asked to respond verbally to confrontation finger counting, he appeared to have a dense left homonymous hemianopia. An MRI showed post-surgical changes in the corpus callosum, but no lesions within either hemisphere. Visual fields were carefully mapped via several different methods: confrontation finger counting with verbal responses and with saccades, and Goldmann perimetry using the right hand to press the buzzer, using the left hand to press the buzzer, and with saccades to the stimulus light.

Results:
Some degree of left homonymous hemianopia was found with all methods, but there was a strong dissociation between the size of the visual field defect and the method by which the patient was asked to respond to left visual field stimuli. He appeared to have a complete left homonymous hemianopia when asked to respond verbally or by pressing the buzzer with his right hand, but had only a partial left inferior homonymous quadrantanopia when allowed to respond with saccades or by pressing the buzzer with his left hand. Of all protocols, saccadic responses produced the smallest visual field defect. Interestingly, the right homonymous hemifield was much less dependent on the method of response.

Conclusions:
The extent of a split-brain patient's visual field defect depends on the method of assessment. By varying the protocol for visual field testing in such a patient, one can expose the intra- and inter-hemispheric connections underlying the normally unified visual experience.

References: None.

Keywords: Visual Fields, Higher Visual Functions, Perimetry, Diagnostic Tests

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 121

Binasal Hemianopsia

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Introduction:
To report and review a case of binasal heteronymous hemianopic visual field defect and its clinical course and review historical cases of binasal hemianopsia.

Methods:
This is a descriptive case report based on clinical records, patient observation and analysis of diagnostic studies.

Results:
A 25-year-old woman presented with 4-week history of new onset of headache and visual disturbance. The headache is described as sharp, 10/10, frontal, constant and the visual disturbance is described as difficulty reading, photophobia with no eye pain and no eye movement pain. Her optometrist found that she had binasal visual field defect and referred her for Neuro-Ophthalmic evaluation. On examination, the patient had dense binasal heteronymous hemifield defect without macular sparing on confrontation and also Humphrey automated perimetry. The patient endorsed more increased photosensitivity consistently when the temporal hemianopic retinas were stimulated by slit beam of light. The rest of Neuro-Ophthalmic examination was unremarkable. MRI brain with and without contrast and MRA head were performed and they were unremarkable. Detailed and repeated ophthalmic examination showed no change and further studies including OCT, ERG and VEP were performed and they were unremarkable as well. For her symptomatic management, a week course of oral corticosteroid was initiated. After completion, repeat visual field test showed near complete resolution of the right nasal hemifield defect and mild improvement of the left nasal hemifield defect. The patient started topiramate for headache prevention and her visual field defect continued to improve along with improvement of her headache. .

Conclusions:
This is a case of complete binasal heteronymous hemianopsia in setting of new onset migraine. The binasal hemianopsia is uncommon but can occur due to more commonly ocular factors and also intracranial pathologies. The increased photosensitivity of the hemianopic retina could be useful clinical information to judge organic vs nonorganic hemianopsia.

References: None.

Keywords: Visual Fields Defect, Perimetry, Non-Organic Visual Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 122

Voice Processing In Developmental Prosopagnosia

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Introduction:
Prosopagnosia is a selective impairment of face recognition, but voice recognition, another function involving the anterior temporal lobe, has rarely been evaluated to confirm that it is modality-specific. Our previous work has shown that acquired prosopagnosic patients with right anterior temporal lesions have intact voice recognition, while bilateral anterior temporal lesions can impair both face and voice recognition. The anatomic basis of the developmental form of prosopagnosia remains uncertain, and the status of voice recognition is also not known.

Methods:
We studied 73 control subjects and 10 subjects with developmental prosopagnosia, whose diagnosis was confirmed on tests of famous face familiarity and short-term familiarization, the Warrington Recognition Memory Test and the Cambridge Face Memory Test. We developed two novel tests: a match-to-sample test of voice discrimination and a test of short-term familiarity for voice recognition, and administered a questionnaire about face and voice identification in daily life.

Results:
Nine subjects had intact voice discrimination and voice recognition, with scores superior to those for face recognition. One subject was impaired on voice discrimination and borderline for voice recognition, with equivalent degrees of impairment for both face and voice recognition. The questionnaire results show that the prosopagnosic subject that showed mild impairment in voice processing was unaware he had any voice processing impairments.

Conclusions:
Most subjects with developmental prosopagnosia have a modality-specific disorder of face recognition. However, there may be heterogeneity—in some subjects, prosopagnosia may be one component of a multi-modal impairment of person recognition. Tests of voice recognition may help increase the accuracy and specificity of the process of diagnosing prosopagnosia.

References: None.

Keywords: Developmental, Prosopagnosia, Recognition, Voice, Face

Financial Disclosures: The authors had no disclosures.

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Poster 123

Building a Repository For Posterior Cortical Atrophy

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Introduction:
Posterior cortical atrophy (PCA) is a rare progressive neurodegenerative disease with prominent cortical visual dysfunction, also known as the visual variant of Alzheimer's disease. Since initial description by Benson in 1988, PCA has been described in small case series and case reports, but only over the last decade has attention been increased. Clinical presentation is heralded by subjective vision loss, yet a normal ophthalmic examination, although there is not yet definitive diagnostic criteria.

Methods:
First we conducted a literature review to better understand the signs and symptoms that have been reported. Then, we established a repository to collect patient data with the goal of better understanding the most common signs and symptoms. We hope this will aid in creating diagnostic criteria for the disease.

Results:
Literature review demonstrates that PCA has both a large economic burden on a population scale and a significant emotional burden on a personal/family scale. Common signs and symptoms, as well as radiologic and lab abnormalities were investigated and used as the basis for the questions in the repository. The process for and hurdles encountered in developing a repository are discussed.

Conclusions:
Earlier diagnosis is key to developing new treatments, hopefully aimed at impacting PCA in a disease modifying state. The only way to ensure earlier diagnosis is by developing more concrete diagnostic criteria and increasing awareness. We developed the only PCA repository to our knowledge and hope this will lead to firm diagnostic criteria in the future.

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Keywords: Posterior Cortical Atrophy, Atypical Alzheimer's Disease, Higher Visual Functions, Repository, Higher Visual Cortical Functions

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Grant Support: None.

Poster 124

Subretinal Choroidal Neovascularization Associated with Unilateral Papilledema and IIH: Case Report

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Introduction:
Choroidal Neovascularization (CNV) secondary to Idiopathic Intracranial Hypertension (IIH) is rare. CNV produces visual obscurations, decreased visual acuity(VA), and permanent retinal damage if the CNV moves toward and into the fovea. The biomechanics of the inception of CNV with IIH are not fully understood, hypothetically pressure exerted by a swollen optic disk may create a discontinuity in the Bruch's Membrane resulting in growth of vessels under the RPE and sensory retina. Hypoxia due to axonal swelling may create necessary conditions for angiogenesis and vasculogenesis via expression of VEGF, HSCs, and other angiogenic cytokines in subretinal space. CNV associated with IIH may successfully regress following intervention, but there is no consensus on a treatment choice.

Methods:
A 51 year old obese woman with history of untreated IIH and weight gain complained of worsening vision in right eye over two months. Visual exam showed VA 20/200 OD with Afferent Pupillary Defect, and 20/20 OS. Fundoscopic exam showed diffuse disk swelling right eye only. Visual fields were normal OS and showed enlarged blind spot OD with arcuate defects and cecocentral depression. Lumbar puncture opening pressure of 300cm with acellular fluid, normal chemistry, and negative cytology. Subsequently, Orbital CT is normal and OCT revealed RNFL thickness at 173µ OD with substantial subretinal fluid consistend with CNV and 93µ OS. In addition there was a subretinal CNV with hemorrhaging.

Results:
The immediate cause of rapid visual failure was uncertain until OCT identified the CNV. Once, identified therapy was initiated with Bevacizumab with resultant resorption of subretinal fluid, persistence of CNV, and without change in VA.

Conclusions:
Optical Coherence Tomography can be useful in the identification of Choroidal Neovascular Membrane, a condition that should beconsidered in patients with IIH with rapid visual decline. Failure to respond to Bevacizumab may be due to the presence of hemorrhaging, a finding that has been reported previously in other therapeutic attempts.

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Keywords: Idiopathic Intercranial Hypertension, Choroidal Neovascular Membrane, OCT Scans, Papilledema

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Poster 125

The Initiation Of Smooth Pursuit Eye Movements In Anisometropic Amblyopia

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Introduction:
Amblyopia is a spatiotemporal visual impairment caused by abnormal visual experience early in development. Recent studies have shown that amblyopia impacts visuomotor behaviors in addition to impairing sensory functions. Here we investigate the effects of anisometropic amblyopia on smooth pursuit eye movements responsible for accurately maintaining moving objects on the fovea. We hypothesize that given the visual processing delays in amblyopia there will be a significant delay in the initiation of pursuit in patients during amblyopic eye viewing.

Methods:
Fourteen visually normal controls and 9 people with anisometropic amblyopia participated. The participants were presented with a red laser moving at ±15°/s horizontally for approximately one second for 40 trials. The experiment was repeated for each participant under three viewing conditions in the following order: amblyopic/nondominant eye, binocular, and fellow/dominant eye viewing. Outcome measures were pursuit initiation latency, open-loop gain (eye/target velocity ratio 100 ms post-onset), and steady state gain (eye/target velocity ratio throughout movement).

Results:
When viewing monocularly with the amblyopic eye, patients took longer to initiate pursuit movements (203±20 ms) compared to controls viewing with their nondominant eye (183±17 ms, p=0.004). However, the latency of pursuits in patients during binocular (168±17 ms) and monocular fellow eye (176±22 ms) viewings was comparable to controls (binocular: 172±19 ms and dominant eye: 169±15 ms respectively). Mean open-loop gains and steady state gains did not differ significantly between the two groups.

Conclusions:
This study provides novel evidence of delayed initiation of smooth pursuit eye movements in people with anisometropic amblyopia with the amblyopic eye viewing. A similar observation was documented previously for saccadic eye movements in anisometropic amblyopia, and we suggest that it might be due to a delay in visual processing of target motion in amblyopia. Once initiated, however, smooth pursuit movement accuracy in amblyopic participants is equivalent to that seen in visually normal observers.

References: None.

Keywords: Ocular Motility, Smooth Pursuit Eye Movement, Amblyopia, Visual Processing

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 126

The Pulfrich Phenomenon: An Objective Signature-Biomarker of MS Pathophysiology

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Introduction:
The Pulfrich Phenomenon (PF) is the illusory perception that an object moving linearly along a 2-D plane, appears to instead move in an elliptical 3-D trajectory. The PF is thought to reflect inter-eye differences within the visual processing network. We have developed an innovative method by which we can ascertain both the presence and magnitude of the PF.

Methods:
MS patients with a history of acute optic neuritis (AON) and a control group were asked to indicate whether movement of a pendulum bob followed a 2D linear versus a 3D elliptical object-motion trajectory. In the case of the latter, participants were asked to ascertain the magnitude and direction of the 3D motion, by virtue of the bob's approximation with respect to one of five colored wires oriented horizontally in close proximity to the bob. Subjects were asked to make the same approximations following monocular application of graduated neutral density filtering (G-NDF).

Results:
Monocular application of G-NDF to controls resulted in the stereotypic illusion of PF, the magnitude of which intensified and corresponded to increasing levels of filter tinting. Alternately, the application of the G-NDF to AON eyes produced a PF of greater prominence whereas filtering the less affected eyes resulted in attenuation of the PF through consequent neutralization of the interocular brightness disparity brought on by disease.

Conclusions:
We have designed a novel, objective method by which to characterize the presence and magnitude of PF in normal subjects (via G-NDF), and MS patients with AON history. Application of G-NDF to the less affected eye in MS patients experiencing PF can be employed to identify the magnitude of filtering necessary to abolish the effect. Furthermore, PF can be employed as a pathophysiologic signature-biomarker for the investigation of changes in visual system architecture and corresponding functional consequences.

References: None.

Keywords: Pulfrich, Psychophysics, Multiple Sclerosis, Acute Optic Neuritis

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Grant Support: None.

Poster 127

Distractibility In Multiple Sclerosis: A Potential Cause Of Morbidity

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Introduction:
Objective: To undertake a pilot study to elucidate objective and reproducible ocular motor abnormalities reflecting cognitive dysfunction in multiple sclerosis (MS). MS patients near universally suffer fatigue and impaired concentration, often prior to clinically evident "eloquent" lesions. Pathology in MS is diffuse, affecting widespread interconnecting networks subserving cognition. Dysfunction in these networks represents the commonest manifestations of MS impacting gainful employment, provoking demoralization, and compromising quality of life. An ominous consequence of cognitive impairment involves the predilection for dysphoria, reduced socialization and abulia, compromising adherence to treatment and healthy living.

Methods:
Methods: We employed paradigms of cognitive network-mediated activation, inhibition and executive function in the integrated ocular motor system. Patients were instructed to perform saccadic eye movements toward or away from a visual stimulus. We also investigated the capacity of subjects to persist with a task and suppress distraction, the paradigms being: 1. Appearance of a differentially colored cross, directing the subject to make a prosaccade to a visible target or an antisaccade away from the target. 2. Subjects were instructed to pursue a target and not look at distractor targets occurring unpredictably.Error rate represented the primary outcome. Further, we assessed eye movement onset latency as a measure of central nervous system (CNS) information processing speed.

Results:
Results: Saccadic latency was significantly prolonged in MS patients compared control subjects. MS patients exhibited a significantly higher error rate suggestive of compromise in ‘top-down’ inhibitory mechanisms (emanating from the dorsolateral prefrontal cortex and other cognitively eloquent regions). Patients showed greater susceptibility to distraction in smooth pursuit paradigms.Characterising and quantifying these deficits may permit the development of focused rehabilitation and allow evaluation of response to new neurotherapeutic agents.

Conclusions:
Conclusions: Results in this pilot study corroborate the hypothesis that MS patients exhibit slowed information processing speed and have difficulty suppressing distraction. Our patients demonstrated significant prolongation of onset latency for saccadic eye movements.

References: None.

Keywords: Demyelinating Disease, Higher Visual Cortical Functions, Diagnostic Tests

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 128

Disconjugacy Of Eye Alignment Is Greater With Near Fixation During Binocular Viewing In Amblyopia

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Introduction:
To determine whether ocular disconjugacy in amblyopic subjects is dependent on viewing condition.

Methods:
Binocular eye movements were recorded at 500 Hz using the EyeLink 1000 eye tracker (SR Research Ltd., Ontario, Canada). Twenty subjects (nine normal and eleven amblyopic; age: 8-45 years) were asked to fixate on a blue cross subtending 0.5° at a near distance of 57 cm or at a far distance of 4 m for 20-second epochs of binocular or monocular viewing. Disconjugacy of eye alignment was estimated by the area of the 68% bivariate contour ellipse (BCEA) for the difference between right and left eye positions, by the percentage of fixation time within a 0.1°x 0.1° range, and microsaccade characteristics. Mean ± standard error of the mean were shown, log(BCEA) was used to normalize the distribution, and significance testing was performed with the Student's t-test.

Results:
Normal subjects during binocular viewing showed a 68% BCEA of 0.75 deg^2 ± 0.09 deg^2 with near fixation and 0.81 deg^2 ± 0.14 deg^2 with far fixation (P=0.69) while subjects with amblyopia during binocular viewing showed a 68% BCEA of 5.60 deg^2 ± 0.78 deg^2 with near fixation and 3.08 deg^2 ± 0.31 deg^2 with far fixation (P=0.01). Mean percentage of conjugate fixation time for normal subjects was 99.5% ± 0.3% for near fixation and 99.6% ± 0.1 for far fixation (P=0.66), and for amblyopic subjects was 98.4% ± 0.2% for near fixation and 99.2% ± 0.1% for far fixation (P=0.02). Disconjugacy was associated with more rapid slow drift, more microsaccades, and more square wave jerks. Monocular viewing trials showed more disconjugacy than binocular trials for normal subjects but not for amblyopic subjects.

Conclusions:
Disconjugacy increases with near fixation for amblyopic subjects during binocular viewing due to increased slow drift and microsaccades. Further research is required to determine which metrics have greater diagnostic utility in amblyopia.

References: None.

Keywords: Higher Visual Functions, Nystagmus, Ocular Motility, Pediatric Neuro-Ophthalmology, Higher Visual Cortical Functions

Financial Disclosures: RG, KI, BG, DLG, and HSY have a pending patent application for the above technology with The Johns Hopkins University

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Poster 129

An Adjustable Magnetic Prism Carrier for Strabismus Evaluation

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Introduction:
The analysis and quantitation of strabismus can be challenging to examiner and patient, especially when the deviation is large or complex. This can be due to the difficulty of holding multiple prisms in proper alignment and also the difficulty of conducting trials of prisms during real life use for prolonged periods. Most trial frame sets have limits on prism size. We have designed a continuously adjustable, head mounted magnetic prism carrier (MPC) which allows for placement of any strength prism in proper alignment to facilitate strabismus evaluation.

Methods:
We analyzed the ideal goals of a prism carrier device and based on those designed a simple carrier mechanism available in 2 forms. The features sought included the ability to: easily and incrementally adjust the location of the prisms in 3 dimensional space, allow the use of multiple or thick prisms with extreme stability, manipulate the prisms independent of wearing glasses or trial frames, hold the prisms held in place without the participation of the examiner to allow patients to perform trial wearings prior to prescribing, achieve all these goals in children as well as adults. Devices were used on an unselected series of child and adult patients. Patients underwent strabismus analysis in primary gaze with handheld prisms and the MPC. Examiners were queried as to the comparative ease of use. Patients were queried as to comfort of the exam.

Results:
The devices were used successfully in all patients and tolerated well without inducing discomfort or fear, when used with children. Examiners reported the MPC was equal or easier to use in all cases. Prism exchange was easier with the MPC for moderate to larger deviations.

Conclusions:
The continuously adjustable magnetic prism carrier, is a simple useful instrument which can facilitate an often challenging diagnostic process with limited cost, shorter exam time and equal accuracy.

References: None.

Keywords: Adult Strabismus, Diagnostic Tests, Ocular Motility

Financial Disclosures: David Bardenstein MD InventorDevice Licensed through University Hospitals of Cleveland to Gulden Ophthalmic

Grant Support: Rainbow Pediatric Innovation Fund Jeanne P Schroeder Fund

Poster 130

Patient Satisfaction With Prismatic Correction Of Diplopia

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Introduction:
We retrospectively evaluated the percentage of patients with an ocular motility disorder that opted for strabismus surgery versus prismatic correction.

Methods:
All new patients billed between March and June 2013 with a 378.xx ICD9 code were selected for chart review. We assessed whether the diplopia was managed with observation, occlusion, prism glasses, or strabismus surgery. Patients diagnosed with ocular myasthenia gravis were excluded, while diplopic events from a cranial nerve palsy were analyzed separately. Other factors taken into consideration were patient satisfaction with prism glasses, previous strabismus surgery, if surgery was discussed as an option, and if pathology was evident on radiologic studies.

Results:
122 patients with a total of 140 independent diplopic events were reviewed in regards to management. Of these diplopic events, 34% resulted from a cranial nerve palsy. In the remaining diplopic events, surgery was discussed with 20 % of patients of which 39% selected surgical management. Prism glasses were prescribed to 58% of patients, of which 82% admitted to improvement. In the patients diagnosed with a cranial nerve palsy as the cause of their diplopia, prism glasses were prescribed to 38%, while only 20% selected surgical management

Conclusions:
A large volume of patients present to neuro-ophthalmology practices with ocular motility disorders. In this setting it is important that the neuro-ophthalmologist and strabismologist work together to manage the diplopia. Strabismus surgery was discussed as an option with the patient when deemed appropriate. Diplopic events resulting from a cranial nerve palsy spontaneously resolved in 62% of cases, and therefore did not require management with either prism glasses, surgery, or occlusion. Other factors such as positive imaging studies and failure to follow-up may explain the trend towards non-surgical management. Therefore, it can be concluded that the majority of patients presenting with diplopia were satisfied with conservative non-surgical management.

References: None.

Keywords: Adult Strabismus, Diplopia, Ocular Motility, Cranial Nerve Palsy, Strabismus Surgery

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 131

Duane Retraction Syndrome in Duchenne Muscular Dystrophy

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Introduction:
Patients with Duchenne muscular dystrophy (DMD) almost always have clinically normal eye movements, although two DMD patients have been described previously with Duane retraction syndrome (DRS), the most common congenital cranial dysinnervation disorder (CCDD). We describe the clinical features of a boy with Duchenne muscular dystrophy, bilateral Duane retraction syndrome, and other neurologic problems.

Methods:
This child was followed for more than a decade by Pediatric Neurology and Neuro-ophthalmology. His chart was reviewed, including the results of a muscle biopsy. Multiplex ligation-dependent probe amplification (MLPA) was used to interrogate the 79 exons of the *dystrophin* gene.

Results:
The clinical diagnosis of Duchenne muscular dystrophy was based on the proband's clinical course of progressive proximal weakness, very elevated creatine kinase levels, and a muscle biopsy showing significant dystrophic changes including contracted, degenerative, and regenerative fibers. He had bilateral DRS with otherwise normal ocular motility. He also had developmental delay, mild mental retardation, and seizures. MLPA documented duplication of exons 3 and 4 of the *dystrophin* gene.

Conclusions:
This boy had syndromic DRS in which bilateral type 3 DRS occurred in association with genetically and clinically proven DMD, developmental delay, mental retardation, and seizures. He is the third patient to be reported with DRS and DMD, the second with bilateral DRS and the only one with other neurologic features. DRS is the most common CCDD, and DMD is the most common muscular dystrophy in males, leaving open the possibility that these two disorders have occurred together at least three times by chance. Mutated *dystrophin* is present in extraocular muscles and in the central nervous system (CNS), and the co-occurrence of DRS with DMD may be the developmental result of the genetic muscle abnormality, the CNS effects of mutated *dystrophin*, other co-existent genetic abnormalities, or some combination of these factors.

References: None.

Keywords: Duchenne Muscular Dystrophy, Duane Retraction Syndrome, Congenital Cranial Dysinnervation Disorders, Dystrophin, Seizures

Financial Disclosures: The authors had no disclosures.

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Poster 132

Peribulbar Botulinum Toxin As A Treatment For Symptomatic Opsoclonus In Oculopalatal Myoclonus

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Introduction:
Oculopalatal myoclonus is the result of a lesion of the dento-rubro-olivary tract in the brainstem and is characterized by rhymical movements of the soft palate and pendular vertical nystagmus.[1] The acquired nystagmus results in debilitating oscillopsia. Various pharmacologic agents and surgical techniques have been employed to alleviate these symptoms with limited success. There have been very few reports of treatment with retrobulbar botulinum injection in the literature. [1,2] We describe a case of oculopalatal myoclonus in which peribulbar botulinum toxin injection was extremely successful in alleviating nystagmus and improving visual acuity.

Methods:
A 62 year old male with a history of left midbrain and pontine hypertensive hemorrhage 2 years prior presented to the ophthalmology clinic with complaint of “unsteady images.” His vision was 20/80 OU. Motility exam was significant for left gaze palsy and upbeating nystagmus OU. Nystagmus decreased with convergence however attempts to induce convergence with prism did not result in any symptomatic relief. The decision was made to try a peribulbar injection of 25 units of botulinum toxin to the left orbit.

Results:
The patient returned 2 weeks later with dramatic reduction in nystagmus OS and visual acuity of 20/30 in that eye. The patient noted significant improvement in his quality of life and is now pursuing peribulbar botulinum toxin injection in the right eye.

Conclusions:
Patients with acquired nystagmus suffer from incapacitating oscillopsia, a condition that has historically had few successful treatment options. Peribulbar botulinum toxin injection represents a safe and efficacious treatment that results in significant improvement in visual acuity as well as quality of life for these patients.

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Keywords: Nystagmus, Oscillopsia, Opsoclonus, Botulinum Toxin, Oculopalatal Myoclonus

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 133

Thalamic Stroke In A Young Patient Presenting With Sudden Onset Large Skew Deviation

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Introduction:
Introduction: Skew deviation usually localizes to the utriculo-ocular and brainstem pathways. Rare literature reports based largely on imaging findings suggested medial thalamic implication in the supranuclear vertical gaze control.

Methods:
Case Report: A 26-year-old male without any past medical history presented 1.5 hours after abrupt onset of blurry and tilted vision, vertical binocular diplopia, as well as postural and gait instability during defecation. On exam, his right eye was hypertropic and slightly incyclotorted, with no change in the large prismatic deviation in different gaze positions or head tilt. The upright-supine test was positive. Direction changing eccentric nystagmus and truncal ataxia accompanied. Noncontrast head CT and CT angiogram of head and neck were unremarkable. Clinical presentation was concerning for an acute ischemic stroke localizing to the brainstem. Given his severely disabling symptoms, a decision was made to treat with intravenous tissue plasminogen activator per acute stroke protocol. One hour later visual symptoms and imbalance were resolved, and normal ocular alignment was noted on the examination. Brain magnetic resonance imaging revealed an isolated area of restricted diffusion in involving the mid portion of the right thalamus consistent with an acute ischemic stroke. There was no evidence of any other previous fluid attenuated inversion recovery (FLAIR) sequence hyperintensities suggestive of older lesions. Both transcranial Doppler ultrasound and transthoracic echocardiogram verified the presence of a large patent foramen ovale (PFO). Further complete stroke work up including full hypercoagulable panel was negative. Patient was discharged home asymptomatic, on daily aspirin and enrolled in a clinical trial for the PFO closure.

Conclusions:
Conclusions: Isolated thalamic infarct can present with sudden onset vertical diplopia and skew deviation. The acute clinical presentation must raise the suspicion for the appropriate and emergent management of stroke. More clinico-pathological correlation and functional imaging studies are needed to characterize the involved pathways.

References: None.

Keywords: Skew Deviation, Vascular Disorders, Neuroimaging, Stroke

Financial Disclosures: The authors had no disclosures.

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Poster 134

Ophthalmological Spectrum of Locked-In Syndrome

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Introduction:
Although a few authors have reported abnormal eye movements in Locked in syndrome (LIS), there is no study focusing on the large spectrum of ophthalmological manifestations of LIS and their consequences on the visual function. The aim of this study is to describe the range of ophthalmological manifestations observed in patients with LIS, and to evaluate their visual impairment.

Methods:
Thirteen cases of LIS seen in a single tertiary center between 1997 and 2013 were retrospectively reviewed. For each patient, a neuro-ophthalmological evaluation was performed, including whenever possible, refraction, visual acuity, eye movements, slit lamp examination (portable device), pupils, visual field (confrontational) and fundus examination. For each evaluation, the environmental parameters (luminosity, contrasts, head position, distance of examination) were modified in order to achieve the best evaluation of the visual function.

Results:
Mean visual acuity was 20/80. Diplopia was reported by 46 % of patients. Visual field was impaired in 23% of patients. Ocular movements were impaired in 77% of patients: 69% presented unilateral or bilateral VIth nerve palsy, 8% had a complete ophtalmoplegia, 61% had a nystagmus with oscillopsia, and 38% had oculopalatal tremor. Bilateral mydriasis was observed in 22% of patients. Lagophthalmia, keratitis and dry eye manifestations were observed in most patients and constituted the main complaint of the patients.

Conclusions:
Eventhough it is usually admitted that the visual function is preserved in locked-in syndrome, we demonstrated that most of the patients suffer from visual impairement from several origin. Visual acuity is poor, nearly half of the patients suffer from disabling diplopia or oscillopsia and most of them suffer from dry eye syndrome. However, visual field seems to be more preserved than expected. A specialised ophtalmological work-up should be performed for every patient with LIS in order to optimize their visual function, to improve their quality of life and to evaluate their ability to communicate.

References: None.

Keywords: Locked-In Syndrome, Opsoclonus, VI Nerve Palsy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 135

Cigarette Smoking and Activities of Daily Living in Ocular Myasthenia Gravis

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Introduction:
Myasthenia Gravis (MG) is an autoimmune disorder of the neuromuscular junction most often caused by autoantibodies targeting the acetylcholine receptor (AChR). Cigarette smoking is known to affect neuronal AChRs and it has been shown to influence other autoimmune diseases, but the effect of cigarette smoking on MG has not been thoroughly investigated.

Methods:
Cigarette smoking status and MG disease activity were assessed by a prospective telephone survey administered to patients with MG encountered from 2006-2014 in a single neuro-ophthalmology practice. MG disease activity was evaluated by calculating the Myasthenia Gravis-specific Activities of Daily Living (MG-ADL) score, and cigarette smoking status was determined by administering questions adapted from the National Health Interview Survey.

Results:
84 patients with MG were identified during the study period; 40 were excluded due to an uncertain diagnosis or an inability to obtain correct contact information. In all, surveys were administered to 44 patients. Comparison of MG-ADL scores between current smokers (5.6±4.5), former smokers (2.9±3.1), and never smokers (1.4±2.5) revealed a statistically significant relationship ($p=0.003$, one way analysis of variance) where current smokers had the highest MG-ADL scores and never smokers the lowest. Comparison of the MG-ADL ocular subscore revealed the same relationship (current 3.4±2.6, former 1.8±2.1, never 1.1±1.5, $p=0.031$, table 2 and figure 4). There were borderline significant correlations of pack-years with MG-ADL score ($r=0.30$, $p=0.051$) and MG-ADL ocular subscore ($r=0.27$, $p=0.074$).

Conclusions:
Our study reveals a significant association between cigarette smoking and disease activity in MG. In light of these results, we urge clinicians to strongly recommend smoking cessation to myasthenic patients in the hopes that successful smoking cessation may lead to improved MG disease activity. Even though this study does not specifically address whether MG disease activity may improve after smoking cessation, the overwhelming health benefits from smoking cessation make this recommendation fairly uncontroversial.

References: None.

Keywords: Myasthenia Gravis, Neuroophthalmology & Systemic Disease

Financial Disclosures: The authors had no disclosures.

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Poster 136

An Evaluation Of Educational Neurological Eye Movement Disorder Videos Posted On Internet Video Sharing Sites

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Introduction:
Internet video sharing sites allow the free dissemination of educational material. This study investigated the quality and educational content of videos of eye movement disorders posted on such sites.

Methods:
Videos were identified by searching the title of the eye movement disorder of interest on the video sharing sites YouTube and Vimeo, and also by following the links suggested. The number of hits and the hits per day since the video was uploaded were recorded. The videos were then rated for the picture quality and also sound quality if there was a verbal commentary. Any errors in the title and content were noted. Lastly, the educational content of the videos were rated as to the presence of a description of the abnormality, whether the anatomical location of the lesion was identified and an appropriate diagnosis discussed.

Results:
130 videos were viewed. The mean number of hits was 14532 (range 5-249480) with a mean hit rate of 8.45/day (range 0.025-91.45). The mean picture quality was 1.93/3 and the mean sound quality was 2.67/3. 20 (15.4%) had errors and it was not possible in 3 (2.3%) to confirm the diagnosis from what was shown on the video. 48 (36.9%) had no commentary apart from the title. 26 (20%) had excellent educational value in that they included a commentary on the eye movement abnormality, the anatomical location of the lesion, if appropriate, and the pathological diagnosis, of which 5 (3.8% of total) combined these with excellent picture and sound quality.

Conclusions:
It is possible to view a wide range of eye movement abnormalities on these sites, however the lack of peer review means that there is a significant error rate. The educational value of a large proportion of the videos is limited by a lack of commentary on the abnormalities shown.

References: None.

Keywords: Nystagmus, Ocular Motility

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 137

How Do Patients with Strabismus Locate Visual Targets?

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Introduction:
In alternating strabismus, it is unknown which eye provides information about the location of the next visual target so that an accurate saccade can be made.

Methods:
Subjects with alternating exotropia and no amblyopia wore red/blue filter glasses for dichoptic stimulation while viewing stimuli rear-projected onto a tangent screen. Each trial began with a fixation cross, visible to either the right, left, or both eyes. After the subject fixated the cross, a peripheral stimulus appeared for 200 msec, visible to either the right, left, or both eyes. The subject's task was to look at it.

Results:
There were 3 main findings: 1) the eye to which the target was presented usually was the eye used to fixate the target; 2) when stimuli were presented in the far nasal field of the perceiving eye, subjects occasionally performed a "cross-over" saccade by placing the other eye on the target, to avoid having to make a large adducting saccade. In such cases, information about target location was obtained in one eye and used to program a saccade for the other eye. Cross-over saccades had a longer latency and were less accurate; 3) In a separate experiment, binocular sensory maps were compiled to delineate the portions of the visual field perceived with each eye. For each subject, the layout of suppression scotomas closely matched the map of target acquisition by eye. In other words, targets were fixated by the eye used to perceive them.

Conclusions:
By comparing maps of sensory perception and oculomotor behavior, these studies have shown how patients with strabismus are able to fixate accurately objects of interest in their visual environment, despite misalignment of the eyes. The deviated eye, rather than being completely suppressed, is engaged in locating targets that precede a fixation swap.

References: None.

Keywords: Diplopia, Exotropia, Saccade, Suppression, Strabismus

Financial Disclosures: The authors had no disclosures.

Grant Support: National Eye Institute

Poster 138

Superior Cerebellar Peduncle Demyelination Causing Geotropic Central Positional Nystagmus

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Introduction:
While the presence of spontaneous nystagmus in multiple sclerosis (MS) patients frequently constitutes a sign of disease relapse, the occurrence of positional nystagmus is more often due to a non-MS cause (e.g., benign paroxysmal positioning vertigo (BPPV)). Rarely, a strategic infratentorial lesion can cause central positional/positioning nystagmus (CPPN) and mimic BPPV. Apogeotropic and downbeat CPPN constitute the commonest forms. We describe a MS patient with geotropic CPPN caused by a superior cerebellar peduncle (SCP) demyelinating plaque.

Methods:
A 46-year old woman with a previous diagnosis of relapsing-remitting MS presented with disabling positional vertigo and vomiting exacerbated by head movements while lying down. Eye movements were filmed and subsequently recorded using Video-nystagmography (VNG). Brain magnetic resonance imaging (MRI) was performed.

Results:
Exam in the upright position demonstrated mild spontaneous right horizontal nystagmus with a vertical downbeating component. In the supine position with the head straight, nystagmus became more intense and accompanied by vertigo and vomiting; head rotations caused persistent and non-fatigable direction-changing geotropic horizontal nystagmus. Log-roll maneuver did not abate nystagmus. The reminder of the neurologic exam was normal, except for mild gait ataxia. VNG performed on the second day revealed right horizontal and downbeat nystagmus (3.1°/s; 0.3°/s) in the upright position that changed to right horizontal and upbeat nystagmus (5.2°/s; 4.4°/s) in the supine position; geotropic nystagmus was no longer evident. T2/FLAIR brain MRI showed a new demyelinating non-enhancing lesion in the inner part of the right SCP. Patient was treated with a 5-day course of 1 g/day intravenous methylprednisolone. After 4 days, nystagmus and vertigo had completely subsided.

Conclusions:
This is the first report of central positional geotropic nystagmus associated with focal superior cerebellar peduncle demyelination. Disruption of the central otolithic connections is hypothesized to be the mechanism underlying the presence of central positional nystagmus in this case.

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Keywords: Nystagmus, Demeylinating Disease, Ocular Manifestations of Vestibular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 139

Normative Database for the King-Devick Test in Adults and Adolescents

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Introduction:
The King-Devick(K-D) test, a <2-minute timed assessment of rapid number naming, has been studied as a rapid, quantitative screening tool for neurological dysfunction associated with concussion, hypoxia, Parkinson's disease, multiple sclerosis and extreme sleep deprivation. All studies to date have either compared within subjects against individual baselines or between affected subjects and age-matched neurologically-normal control subjects. A large normative database has not been previously established. The purpose of this study was to determine the distribution of K-D test performance in normal adults and adolescents and evaluate the effect of potential confounding variables.

Methods:
In this cross-sectional, multi-center study, subjects ≥15yrs old with binocular best-corrected near visual acuity better than 20/30 completed two trials of the K-D test protocol. Exclusion criteria included concussion within 3-months, post-concussion syndrome, dyslexia or neuro-degenerative disorders. History of concussion, amblyopia, strabismus as well as demographic variables of education, race/ethnicity, gender and age were assessed by subject interview. Analysis of Covariance was used to determine if age, education, or race affected performance while controlling other cofounders.

Results:
Subjects (n=691, age:39.8±17.7yrs,58%female) were enrolled in 5 sites. Best K-D times were 41.2±8.2s. Difference between K-D trials was 3.1±3.3s. Performance did not vary by history of concussion, gender, amblyopia, or strabismus. Younger age, higher education and Caucasian or Hispanic race/ethnicity had better K-D times($p \leq 0.001$). K-D times were stable in the subjects aged ≤39yrs and demonstrated worsening ≥40yrs.

Conclusions:
The K-D test requires visual processing, saccades, language, attention, and has been proposed as a marker of integrated neurological function. We report normative data in a large adolescent/adult cohort and report associations with age, education and race. Knowledge of these confounding variables is important for design and interpretation of future K-D studies. Our database will have application to future studies of K-D test performance in neurologically diseased populations and potential future application to clinical settings.

References: None.

Keywords: Diagnostic Tests, Ocular Motility

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Grant Support: Illinois Society for the Prevention of Blindness Research Grant

Poster 140

Marcus Gunn Jaw Winking with Electronegative Cone-Rod Dystrophy: Case Report

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Introduction:
Marcus Gunn jaw winking syndrome (MGJW) is due to aberrant innervation of the levator palpebrae superioris muscle by the trigeminal nerve. This has been reported with other ocular abnormalities like monocular elevation deficiency and Duane's syndrome[1]. We report a case associated with electronegative cone-rod dystrophy.To the best of my knowledge, this is the first report of MJGW with a retinal dystrophy. This report expands our knowledge of ocular disorders associate with MGJW and may assist in the understanding of the pathophysiology of this condition.

Methods:
Case Report

Results:
An Iranian boy was born with poor vision, nystagmus, colorblindness and MGJW. He was the product of consanguineous parents. His younger brother was normal and there was no family history of visual problems. Visual acuity was 6/120 colour vision was absent. He had fine vertical nystagmus and his retina appeared normal. Electroretinogram (ERG) revealed electronegative cone-rod dystrophy.

Conclusions:
The exact mechanism of MGJW and electronegative cone-rod dystrophy have yet to be elucidated. Electronegative ERG has been attributed to dysfunction of the ON-bipolar pathway[2]. Recently this has been reported in Phosphomannomutase Defiency, a congenital disorder of glycosylation. MGJW has been associated with the cranial dysinnervation syndromes. Genetic studies in to these disorders have enabled us to understand some aspects of the developing brain[4]. These two conditions coexisting in the same individual may further expand our understanding of these conditions.

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Keywords: Nystagmus, Cone-Rod Systrophy, Marcus Gunn Jaw Winking, Ptosis, Genetics

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 141

Levodopa-Induced Ocular Dyskinesias

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Introduction:
Levodopa-induced dyskinesias (LID) are commonly encountered in advanced Parkinson's disease (PD), and classically affect the limbs, trunk, and head. We present a patient with advanced PD who developed severe, disabling LID, with involvement of his oculomotor system.

Methods:
Case report.

Results:
A 62 year-old man with left-dominant PD diagnosed at age 37, and continuously on carbidopa-levodopa since age 38, developed dyskinesias of the head which were first documented at age 44, and were followed over the next several years by disabling foot cramping, athetoid/dystonic hand movements, facial grimacing, and prominent retrocollis. At age 48, he demonstrated abnormal involuntary eye movements (AIEMs), characterized by difficulty with visual fixation. Current examination found intermittent upward and rightward gaze deviation, however, he was able to make conta-versive voluntary saccades after prolonged saccadic latency. His AIEMs occur exclusively during ON periods, and are worsened by periods of emotional and physical stress. Brain MRI revealed no lesions accountable for his AIEMs.

Conclusions:
One recent review identified 5 from 32 advanced PD patients with AIEMs occurring exclusively in the ON state. AIEMs were characterized by repeated, stereotyped, upward and/or lateral gaze deviation, sometimes phasic, brief and jerky, sometimes tonic and sustained for several seconds. Gaze deviation typically was to the side more affected by Parkinsonism (in 4/5 patients). AIEMs are modulated by facilitation and inhibitory maneuvers as in other LID, e.g., temporarily suppressed by will and visual fixation and worsened by emotional and physical stress. The severity of AIEMs does not necessarily correlate with the severity of other concomitant LID. AIEMs never occur in isolation, and the onset is delayed by years with respect to the onset of other LID, suggesting that extensive dopaminergic denervation in the caudate nucleus may be a prerequisite for AIEMs, yet the exact pathophysiology remains elusive.

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Keywords: Levodopa-Induced Dyskinesias, Abnormal Involuntary Eye Movements

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 142

Clinical Features, Diagnostic Findings and Treatment of Adult-Onset Opsoclonus-Myoclonus Syndrome: A Case Series

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Introduction:
OMS consists of involuntary saccades with myoclonus, cerebellar ataxia, and/or encephalopathy. Saccadic movements are termed opsoclonus when multidirectional and ocular flutter when in horizontal plane. OMS is thought to be caused by immune-mediated injury to either pontine omnipause cells which inhibit gaze center burst neurons or cerebellar hemispheres which disinhibit the fastigial nucleus.Our goal is to discuss clinical features, diagnostic findings, and treatment of adult-onset opsoclonus-myoclonus syndrome (OMS).

Methods:
Retrospective review of six adults with OMS (ages 24-62 years, 3 women), diagnosed and treated at two tertiary care centers from 2011 to 2014. Clinical, laboratory, and imaging findings, including brain magnetic resonance imaging (MRI) and [^{18F}]fluoro-2-deoxyglucose positron emission tomography (FDG-PET), were analyzed.

Results:
Ocular flutter and ataxia were present in all, while opsoclonus was found in only two patients. Myoclonus and encephalopathy were present in four and two patients, respectively. Infectious pathogen was not found in anyone. CSF analysis showed lymphocytic pleocytosis in five patients. Neoplasms were diagnosed in three: one benign ovarian dermoid tumor and two malignancies – uterine carcinosarcoma and neuroblastoma. Neural-specific autoantibodies were detected in four patients: one with anti-Ri related to uterine-carcinosarcoma, one with anti-GQ1b, and two with anti-GAD65 (one associated with ovarian dermoid tumor). MRI showed T2 hyperintensity in inferior right cerebellum in one patient. FDG-PET of brain showed cerebellar hypometabolism in three (two bilateral and one unilateral). One of two patients with malignant neoplasms died (both treated with immunotherapy). In the three nonparaneoplastic cases, clinical progression occurred with intravenous corticosteroids until intravenous immunoglobulin (IVIg) was administered.

Conclusions:
In adults, ocular flutter and ataxia, rather than opsoclonus or myoclonus, are the characteristic clinical features. The syndrome is associated with diverse antibodies, which may be autoimmune or paraneoplastic. Selective cerebellar hypometabolism in three patients supports the hypothesis of cerebellar hemispheric dysfunction. Patients without malignancies may achieve complete remission with IVIg.

References: None.

Keywords: Opsoclonus-Myoclonus, Paraneoplastic

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Poster 143

Divergence Palsy due to Antiepileptic Drugs

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Introduction:
Diplopia is a potential side effect of many anti-epileptic drugs (AEDs). However, it is not always possible to examine the patient while they are symptomatic and thus the characteristics and the specific mechanisms of anti-epileptic drug-induced diplopia have not been well described.

Methods:
We describe two patients who had spells characterized by divergence palsy while receiving anticonvulsants.

Results:
We describe two cases of AED-associated diplopia, one attributable to oxcarbazepine and the other to divalproex. Both patients were found to have a divergence palsy only during their spells. In both cases, removal of the offending agent resulted in prompt resolution of symptom which has not recurred over the past 6 and 2 years, respectively. In our second case, divalproex was restarted to confirm our hypothesis of a causal relationship and the spells recurred within days only to resolve again after divalproex cessation.

Conclusions:
While diplopia is listed as a side effect of many AEDs, a literature search did not identify any detailed description of an examination during an episode of diplopia. To our knowledge, this is the first report where an association between antiepileptics and divergence palsy was confirmed by a rechallenge. Both patients underwent extensive testing for their episodes of diplopia before being diagnosed with episodic divergence palsy. Awareness of the association between antiepileptics and divergence palsy may change management of patients presenting with similar episodes, especially if patients can be examined while they are symptomatic. It is important to consider iatrogenic causes when patients present with intermittent diplopia.

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Keywords: Divergence Palsy, Diplopia, Antiepileptic Drugs, Ocular Motility

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Poster 144

Quantifying The Vestibulo-Ocular Reflex With Video-Oculography: Nature And Frequency Of Artifacts

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Introduction:
Little is known about the impact of disruptive phenomena (corrective saccades, nystagmus, fixation losses, eye-blinks) on quantitative vestibulo-ocular reflex (VOR) assessment. We sought to characterize the frequency, nature, and impact of abnormal physiologic findings and artifacts on quantitative head impulse test (HIT) VOR measures.

Methods:
From a prospective study of video-oculography (VOG) in 26 patients with acute vestibular syndrome (16 vestibular neuritis, 10 stroke), we classified 1358 HIT traces using a structured coding manual. All disruptive findings were coded based on morphologic similarity to known physiologic patterns or artifact type. HIT traces were classified by a single, masked rater. A second, independent rater re-coded a 10% subsample to assess inter-rater reliability. Outcomes were presence and type of intrusive eye movement or artifact, whether the intrusion rendered the trace difficult to interpret, and whether disruptive phenomena varied by underlying disease. We report descriptive statistics, Cohen's kappa (inter-rater reliability), and Chi2 p-values (comparisons across diseases).

Results:
Of all HIT traces, 72% had abnormal (but pathophysiologically-appropriate) intrusive saccades, 44% of traces had at least one artifact, and 42% of traces were deemed uninterpretable. The most common intrusions limiting VOR interpretation were fast-phase eye movements (saccades or nystagmus) occurring during VOR response. Inter-rater agreement on attributes varied (0.27-0.79) but was excellent for presence of a normal VOR (0.78) and very good for the presence of one or more artifacts (0.64) or an uninterpretable trace (0.66). Abnormal head impulses in patients with vestibular neuritis were more susceptible to artifacts (57% of ipsilesional neuritis traces uninterpretable vs. 31-34% of contralesional neuritis traces and stroke traces, Chi2 $p<0.001$).

Conclusions:
Physicians using quantitative recording devices to measure VOR responses to head impulses for clinical diagnosis should be aware of the potential impact of intrusive eye movements and measurement artifacts, especially in patients with an acutely abnormal HIT.

References: None.

Keywords: Eye Movement Measurements, Artifacts, Vertigo, Vestibular Neuritis, Stroke

Financial Disclosures: The authors had no disclosures.

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Poster 145

Neuroophthalmic Manifestations Of Intracranial Tumours In South India

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Introduction:
To study the clinical profile of patients with intracranial tumours presenting to the NeuroOphthalmology department and to correlate the ocular manifestations and site of the intracranial tumour.

Methods:
A prospective study of 192 consecutive patients including paediatric age group,who were proven to have Intracranial tumour clinically and radiologically from June 2011 to June 2013 for a period of 2 years,who presented to the Department of Neuro-Ophthalmology in a tertiary eye care centre in South India was conducted and followed up for 3months after treatment.All patients underwent thorough ophthalmological and neurological evaluation.

Results:
Of 192 patients, 104(54.2%) were men and 88(45.8%) women. Mean age was 41.97years,ranging from 3 to 75years. 156 patients(81.3%) had defective vision at presentation,25% headache,4.7% double vision. Bitemporal hemianopia was the commonest field defect followed by generalized constriction. Fundus examination showed papilledema in17.2%,Temporal pallor in 34.9%,primary optic atrophy in 27.6%.Sellar and suprasellar tumours presented with normal fundus or segmental,primary optic atrophy.Posterior fossa tumours presented with papilledema.Abducent nerve was paralysed in 11.5%,oculomotor nerve in 7.8%,Vesibulocochlear nerve in8.3%.There was a statistically significant association between best corrected visual acuity at presentation and follow up. ($p<0.001$).Thus the visual prognosis depends upon the vision at presentation. There was a significant association between type of tumour and age group($p<0.001$),but no association between gender and type of tumour ($p=0.096$) .Pituitary adenomas(46.9%),Meningiomas(24 %),Acoustic neuroma(8.3%)were the commonest tumours in adults and medulloblastoma in children.

Conclusions:
A simple case of double vision(32 patients in our study), might have an underlying brain tumour.One with a normal fundus(16.1%) can harbour a sellar,suprasellar tumour.So when a patient presents with ocular complaints, careful clinical examination,if arises a suspicion of brain tumour,has to be imaged immediately, which can reveal a life or vision threatening brain tumour.So, a neuroophthalmologist can save the life and vision of the patient by detecting it at an early stage.

References: None.

Keywords: Intracranial Tumour, Pituitary Macroadenoma, Headache, Papilledema, Optic Atrophy

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Poster 146

Sideline Testing in Youth and Collegiate Athletes: What Does Vision Add to the Concussion Puzzle?

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Introduction:
Identification of rapid yet simple diagnostic tests for sports-related concussion is critical. These tests must be age-appropriate and capture relevant aspects of brain function. Vision encompasses nearly 50% of the brain's pathways, yet is not represented in current sideline testing protocols. We examined the King-Devick (K-D) test, a vision-based measure of rapid number naming, as a complement to the Sport Concussion Assessment Tool, 3rd Edition (SCAT3/Child-SCAT3) in youth and collegiate athletes.

Methods:
Members of a youth ice hockey and football league and collegiate athletes from NYU and Long Island University (LIU) participated in a prospective study to examine sideline tests, including the K-D test, Standardized Assessment of Concussion, (SAC, cognitive component of SCAT3/Child-SCAT3) and timed-tandem-gait test (balance component of SCAT3/Child-SCAT3).

Results:
Youth and collegiate athletes (n=342, age 14.7±4.9 years, range 5-23) underwent pre-season baseline testing during the fall of 2014. Higher (worse) time scores for the vision-based K-D test were associated with lower (worse) scores for the SAC, particularly for the Orientation ($p=0.003$) and Immediate Memory components ($p=0.01$, linear regression accounting for age). K-D scores correlated significantly yet moderately with scores for balance ($p=0.003$). Athlete age was most strongly correlated with K-D scores ($r= -0.79$, $p<0.0001$) compared to SAC ($r= 0.51$, $p<0.0001$) and timed-tandem ($r= -0.49$, $p<0.0001$).

Conclusions:
The K-D test, a vision-based measure that requires saccades and other eye movements, captures aspects of brain function that are not entirely captured by current sideline testing for balance and cognition. At the same time, associations of K-D scores with working memory and orientation suggest that closely related anatomical structures, such as the dorsolateral prefrontal cortex, underlie saccades and memory. K-D scores showed the greatest associations with age in this young athlete cohort, suggesting that vision may a key domain for assessing developmental aspects of brain function.

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Keywords: Vision, Concussion, King-Devick (K-D) Test, Eye Movements

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Poster 147

Assessment of Recruitment Patterns in a Neuro-Ophthalmology Registry

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Introduction:
A challenge when studying rare diseases is adequate subject recruitment. Prospective research registries are a useful tool for studying rare diseases by forming observational cohorts with which to study disease(1) and serving as a source of subject recruitment for future studies(2). We developed a neuro-ophthalmic patient registry in June, 2014. The purpose of this study is to critically assess recruitment patterns three months after registry implementation.

Methods:
An IRB approved neuro-opthhalmology patient registry was implemented using REDcap(3). Inclusion criteria were age ≥21 years and ability to provide informed consent in English. All patients attending outpatient neuro-ophthalmology appointments were screened for inclusion. Age, gender, race, ethnicity, eligibility and enrollment were recorded for all patients. Demographic variables were compared between registry participants and non-participants during the first three months following implementation.

Results:
182 patients were screened. 29(15%) and 16(8%) were ineligible due to age and inability to provide informed consent, respectively. 23(13%) declined to participate. 114 patients enrolled (age 49+/-16 years, 65% female, 14% Hispanic ethnicity, 40% black race, 34% white race). Patients excluded due to inability to provide consent were more likely to be older (60+/-20 years, $p=0.01$ t-test) or of Hispanic ethnicity (69%, $p<0.0005$, chi square) than enrolled patients. Patients who declined to participate did not differ from enrolled patients by age, gender, ethnicity or race. .

Conclusions:
75% of adult patients were recruited into a new neuro-opthhalmology registry over three months. This registry forms a foundation for advancing human neuro-ophthalmic research at our institution by establishing an observational cohort and serving as a source from which to recruit subjects for future studies.. The consent requirements disproportionately excluded subjects who were older or of Hispanic ethnicity. Modifying the consent process to include non-English speaking patients will be important to achieve an adequate population sample and avoid recruitment bias.

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Keywords: Registry, Observational Cohort, Neuro-Ophthalmic Diseases

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Poster 148

Prediction of Eye Position During General Anesthesia Using Bispectral Index Monitoring

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Introduction:
The position of the eyes in general anesthesia is generally considered one of slight divergence and elevation, yet it has not been well characterized to date. We aimed to quantify eye position related to the depth of anesthesia using bispectral index (BIS), a derived electroencephalograph parameter.

Methods:
In this prospective blinded study, we investigated the relationship between BIS, hemodynamic parameters during anesthesia and eye positions in 32 healthy children, mean age 5.4 years, who were undergoing surgical correction for epiblepharon using a standardized anesthetic technique with sevoflurane. BIS and hemodynamic parameters were continuously recorded throughout the procedure: from induction to awakening. Eye positions were video-recorded during surgery and analyzed after surgery at one-minute intervals by the examiner blinded to results of BIS.

Results:
There was significant negative correlation between BIS and end-tidal sevoflurane concentrations ($p<0.001$), and positive correlation between BIS and elevation of the eyes (eye position=0.014xBIS+0.699, $p=0.011$). Elevation of the eyes (83%) mostly occurred when BIS values reached over 65, while down-shoot eye movement (2%) was seen at BIS values less than 35.

Conclusions:
A shallower level of anesthesia, indicated by a higher BIS values was associated with a higher position of the eyes, suggesting that BIS monitoring may be beneficial in predicting eye position. In ophthalmic surgery with particular attention to eye position, the anesthesia depth is recommended to be maintained by monitoring BIS values in range of 35-65.

References: None.

Keywords: Diagnostic Tests, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 149

Demographic Profile Of The Patients Presenting To A Neuro-Ophthalmology Clinic Of A Tertiary Eye Care Centre

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Introduction:
To evaluate the clinical profile of neuro-ophthalmic disease in patients presenting to Neuro-ophthalmology clinic of a tertiary care centre during one year.

Methods:
A cross-sectional hospital-based observational study was done at a tertiary level eye care centre during one year. All patients with neuro-ophthalmic disease were referred to the neuro-ophthalmic clinic where they were evaluated with a detailed clinical history and examination.

Results:
A total of 30111 patients were evaluated of which 1597 (5%) were referred to neuro-ophthalmic clinic. The mean age of the referred patients was 31 years (31±19.53) with male predominance. Among 1597 patients, optic nerve disorders were noted in 63.8% (n=1020), cranial nerve palsy in 7% (n=114), cortical visual impairment in 6.5% (n=105) and others (disc hypoplasia, blepharospasm, optic nerve head drusen etc) were 6% (n=96). Among the patients with optic nerve disorders, primary optic neuropathy (traumatic optic neuropathy, hereditary, tumor related, retro bulbar neuritis, toxic neuropathy & idiopathic) was noted in 42.8% (n=685) and secondary optic neuropathy (Ischemic optic neuropathy, post papilledema optic neuropathy, post-papillitis, neuroretinitis, inflammatory optic neuropathy) were 20.9 % (n=335). 16.4% (n=263) patients were wrongly referrals.

Conclusions:
Neuro-ophthalmic clinic constitutes a significant referral unit in a tertiary eye care centre. Traumatic and Ischemic optic neuropathies are common and most important preventable forms of neuro-ophthalmic diseases.

References: None.

Keywords: Demography, Optic Neuropathy, Cortical Blindness, Trauma, Ischemia

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Poster 150

Botulinum Toxin-Augmented Strabismus Surgery versus Conventional Surgery in the Treatment of Large-Angle Infantile Esotropia

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Introduction:
The treatment of large-angle infantile esotropia remains a challenge. Surgical treatment traditionally has involved either three-muscle surgery or supra-maximal medial rectus recessions, but both methods have significant drawbacks including risk of over- or undercorrection. An alternative is to use botulinum toxin to weaken the medial rectus muscles, but multiple treatments are often required and the success rate for large deviations is poor. It has been suggested that the best approach may be to combine these treatments. No previous study has directly compared botulinum toxin-augmented surgery to conventional surgery alone.

Methods:
A retrospective, comparative study was completed evaluating baseline characteristics and outcomes of consecutive patients with large-angle infantile esotropia (55 prism diopters($^{\Delta}$) or greater) who underwent either conventional or botulinum toxin-augmented strabismus surgery. The primary outcome measure was post-op deviation and need for retreatment within one year of initial intervention. Success was defined as a deviation <10$^{\Delta}$ and no retreatment at 1 year after the initial intervention.

Results:
The record review identified 38 patients meeting inclusion criteria, of whom 14 had been treated with botulinum toxin-augmented surgery and 24 with bilateral medial rectus recessions. Prior to surgery, the augmented group had a larger median angle of deviation (65 versus 60$^{\Delta}$, p = 0.006) and less recession of the medial rectus muscles was performed (5.5 versus 6.0 mm, p = 0.005). The augmented group had greater success at 1 year (70% versus 30%, p = 0.035). The augmented group also had a significantly smaller median angle of deviation at 1 year (0 versus 18$^{\Delta}$, p = 0.026). There were no serious complications in either group.

Conclusions:
Botulinum toxin can significantly augment the effect of medial rectus recessions and improve the success of strabismus surgery in patients with large-angle infantile esotropia.

References: None.

Keywords: Pediatric Neuro-Ophthalmology, Botulinum Toxin, Strabismus, Infantile Esotropia, Bimedial Recession

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Poster 151

Heidenhain Variant Of Creutzfeldt Jakob's Disease (CJD), In A Patient Who Had Bovine Bioprosthetic Valve Implantation

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Introduction:
82year old woman, referred to neuroophthalmology clinic for unexplained visual loss. One month earlier she started to complain about blurred vision that deteriorated significantly in the last week. The patient and her son denied any behavioral changes or memory impairment. Her past medical history included: hypertension, hypercholesterolemia, peptic disease, and aortic valve replacement using a bovine bioprosthetic valve- 19-mm carpentier-Edwards Perimount

Methods:
On examination: Full ocular movements, visual acuity finger count in both eyes, normal anterior segment, RAPD negative, and normal fundus examination. Humphrey visual fields demonstrated complete absolute right homonymus hemianopsia. In her MRI review, performed two weeks earlier, there were nonspecific white matter changes. Extended evaluation was recommended

Results:
One week later the patient was admitted due to memory impairment "loosing words" and "unable to complete sentences". The repeated MRI showed no new pathology, total body CT was normal, EEG was compatible with CJD, cerebrospinal fluid was normal but TAU was extremely elevated. Patient developed rapid loss of short and long term memory, disorientation, incontinence, brisk reflexes. She eventually was discharged to hospice facility and died three weeks later. Unfortunately autopsy was not performed

Conclusions:
We believe our patient had CJD-the heidenhain variant that first presents with visual disturbances. Ophthalmologists being first to see these patients should be aware of this diagnosis possibility especially when there is a history of major surgery or tissue transplantation. In literature review, no reports of iatrogenic transmission of CJD through bovine valves were found

References: None.

Keywords: Neuro-Ophth & Infectious Disease (Eg, AIDS, Prion)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 152

The Effects of Pediatric Primary Brain Tumors on Vision and Quality of Life

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Introduction:
Brain tumors are the leading cause of death from childhood cancer. Overall survival has improved due to earlier detection, better therapies, and improved surveillance. Permanent sequelae of the tumor and its treatment may cause severe impairment and decreased quality of life (QOL). Visual dysfunction and impaired vision-related QOL (VR-QOL) are often not recognized in children because of examination difficulty and lack of awareness. We reviewed the literature and evaluated visual impairment and its effects on QOL in an ongoing quality improvement project.

Methods:
Patients ≤18 yo, ≥6 months from diagnosis of primary brain tumor (PBT), excluding primary intrinsic anterior visual pathway tumors, underwent neuro-ophthalmologic examination. Health-related QOL (HR-QOL) questionnaires, using PedsQL Brain Tumor Module,[1] were obtained from patients and parents. VR-QOL questionnaires, using CVFQ (Children's visual function questionnaire)[2] in children <8yo, and EYE-Q[3] in children 8-18yo, were obtained. Demographic data, driving status, schooling, and use of low-vision aids were recorded. We reviewed recent studies (2000-2014) of ophthalmologic sequelae, long-term disability, and HR-QOL in pediatric PBT patients.

Results:
26 patients were evaluated (18 supratentorial, 8 infratentorial tumors). 3/26 patients (11.54%) were legally blind (primarily suprasellar tumors); 12/26(46.15%) had visual impairment; 13/26(50%) had significant visual field defects. 15/26(57.69%) patients had strabismus, cranial nerve palsies, or nystagmus. HR-QOL median score was 68.6(range 28.1-95.8). VR-QOL median score was 3.27(range 0.38-4.0). Twelve studies met our inclusion criteria for review. Prevalence of visual dysfunction ranged from 8% to 79%. 3/12 studies reported the rate of bilateral blindness (3.3% to 16%). Most HR-QOL evaluations showed significantly lower scores in patients compared to normal control/range. VR-QOL was not previously addressed in pediatric PBT studies.

Conclusions:
Pediatric PBT patients' vision, HR-QOL, and VR-QOL are often severely affected, even when the PBT is considered "cured". Systematic neuro-ophthalmologic examinations in pediatric PBT patients may improve long-term visual outcomes and QOL through earlier interventions.

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Keywords: Brain Tumor, Quality Of Life, Visual Loss

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Poster 153

A Method for Quantifying Off Chart Visual Acuities

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Introduction:
Retrospective chart reviews can provide data to test and generate hypotheses, however, they are limited to the data collected, which in some instances is not sufficiently quantitative. Visual acuity for instance would ideally be collected by ETDRS methods for prospective clinical trials. This is often not the case with retrospective studies, where off chart visual acuities (typically <20/400) are recorded as count fingers (CF) at a set distance, hand motion or light perception. The purpose of this study was to determine by geometric optics the Snellen equivalent visual acuities for count fingers at different distances.

Methods:
A random sampling of the finger size and inter-digit distance of dominant hand of 50 males and 50 females was collected from volunteers in an academic center. The average finger size was calculated and the mean total size of the index, middle and ring finger was determined. This distance was used to determine a decimal acuity by calculating the numbers of minutes of arc subtended by 3 fingers, which would represent the letter E. This was converted to Snellen equivalent (x) as follows: 20/x = 8.75 mm/y (y=3 fingers with spaces).

Results:
The average size of the index (15.9±1.5mm male 13.8±1.9mm female), middle (16.2±1.3mm male 14.2±2.0mm female) and ring finger (15.1±1.2mm male 13.3±2.2mm female) was used with the average inter-digit distance (21.8±7.2 male, 19.9±6.1 female) to calculate the Snellen equivalent acuity for count finger distances from 1 to 6 feet. For example CF@6ft = 0.029, 20/560 for males. Similar data was generated for females.

Conclusions:
It is possible to generate an approximate Snellen equivalent visual acuity for count finger acuities using geometric optics. A website was developed to allow other researchers to input their own finger widths and determine a custom table for use in future retrospective chart reviews.

References: None.

Keywords: Diagnostic Testing

Financial Disclosures: The authors had no disclosures.

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Poster 154

Differential Functions Mediated By Melanopsin Assessed In Subjects With Healthy And Diseased Eyes

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Introduction:
Two central monosynaptic tracts originating from melanopsin-expressing retinal ganglion cells (MGCs) are the retinotectal tract (pupil light reflex) and the retinohypothalamic tract (entrainment of circadian rhythm).This study aims to assess the function of these two non-visual, light-dependent systems in patients who have optic atrophy and visual loss.

Methods:
Patients with bilateral optic atrophy due to hereditary optic neuropathy (HON; n=11) or open-angle glaucoma (GL; n=11) underwent testing with chromatic pupillometry, light-induced suppression of nocturnal melatonin, visual analogue scale for subjective sleepiness and reaction time at night. Main outcome parameters were the post-illumination pupil response (PIPR) to a blue light stimulus (a marker for intrinsic MGC signalling throught the retinotectal tract) and nocturnal melatonin suppression to acute light exposure (a marker of retinohypothalamic integrity). Secondary measures were subjective sleepiness and reaction times. Results were compared to age-matched controls (n=22).

Results:
The PIPR and nocturnal melatonin suppression were positively correlated in patients and controls ($p<0.05$). Patients (HON and GL) showed similar nocturnal melatonin suppression to controls. The PIPR was significantly reduced in the GL group but not HON group, compared to their controls ($p<0.05$). Light exposure at nighttime acutely reduced subjective sleepiness in patients with HON but not GL, when compared to controls. In addition, GL patients showed slower reaction times during and after nocturnal light exposure.

Conclusions:
Glaucomatous, but not hereditary, type of optic atrophy is associated with reduced acute light effects mediated mainly via MGCs. This is detected in the pupil but not hormonal marker of the melanopsin light input pathway. This may indicate differential involvement of MGCs subtypes or MGC photoreceptive sensitivity from certain types of ganglion cell pathology. In addition, such changes in MGC function can influence other cognitive functions.

References: None.

Keywords: Melanopsin Ganglion Cells, Melanopsin, Pupil, Melatonin, Circadian Rhythm

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Poster 155

Familial Papillitis And Macular Cystoid Edema: A Genetic Autoimmune Disorder?

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Introduction:
To describe the phenotype, the diagnostic challenge and the therapeutic options of a rare familial neuro-ophthalmological disorder, characterized by papillitis and macular cystoid edema.

Methods:
Two case reports are reported.

Results:
The proband is a 18-year-old female, who presented at 13 years with progressive loss of vision OS, with occasional eye pain. Ophthalmological evaluation at onset revealed visual acuities OD 20/20; OS 20/60, mild disc edema OD and moderate OS and cystoid macular edema (CME) OS. IV corticosteroids led to partial visual recovery OS to 20/60. After steroid withdrawal vision worsened OS to 20/200. Autoimmune panel including aquaporin4 antibodies was negative except for elevated immune-complexes and positive GM1 antibodies. Cerebrospinal fluid (CSF) examination demonstrated increased proteins and abnormal brain barrier index without oligoclonal bands . HLA revealed DRB1*15 haplotype. Screening for sarcoidosis, lyme disease and tuberculosis was negative. LHON mutations were absent. Brain MRI failed to reveal demyelinating lesions. The patient was treated with Acetazolamide, oral steroids and three iv Immunoglobulin courses and adalimumab without benefit. Intravitreal triamcinolone injection was effective in resolving CME for 2 and 8 months respectively.The mother (59 years) presented at 18 years with bilateral progressive loss of vision with occasional eye pain and bilateral disc edema with CME, completely resolved after steroids. VA worsened after steroid discontinuation evolving to severe optic atrophy OD with persistent disc edema and CME OS. Autoimmune screening disclosed GM1 antibodies. CSF exam showed high protein levels (88 mg/dl) with abnormal brain barrier index.

Conclusions:
We here present two familial papillitis cases, associated with CME responsive to steroid treatment. The strict resemblance of the phenotype points to a genetic basis of the disorder. The positivity of GM1 antibodies, the elevated immune complexes levels, the HLA haplotype and the steroid response suggest an autoimmune disorder. Exome sequencing is ongoing.

References: None.

Keywords: Genetic Disease, Optic Neuropathy, Neuro-Ophth & Systyemic Disease (Eg. MS, MG, Thyroid), Retina

Financial Disclosures: The authors had no disclosures.

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Poster 156

New Daily Persistent Headache Triggered by Cataract Extraction?

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Introduction:

New daily persistent headache (NDPH) was first described by Vanast (1986), who characterized it as a benign headache syndrome that typically remits without treatment.[1] Subsequently, however, it has been found to be a bilateral headache syndrome that is often persistent. Patients are able to identify the exact time their headache began.[2]
NDPH may be responsive to intravenous migraine medications, high dose corticosteroids, doxycycline, gabapentin, intravenous acyclovir or physical therapy.[2,3] Studies have identified such triggers for NDPH including infection, chemical exposure, stressful life event and surgery involving intubation.[2, 4-7] We introduce a patient whose bilateral cataract extraction appears to have triggered her NDPH.

Methods:

Case report.

Results:

An 82 year-old white female presented with a constant, bilateral, supraorbital, pressure-like headache of 5 months' duration. Pain began seven days after the second of two sequential cataract extractions that she found stressful. It never subsided, and periodically extended from the vertex down the back of her head. She denied diplopia, photophobia, phonophobia, nausea, autonomic symptoms and positional influence. Her only medication was valsartan for mild hypertension, and she denied illicit drugs and chronic analgesics. She had no viral infections, toxic exposures, other psychological stressors or other surgeries prior to the onset of headache. Initial exam was entirely unremarkable including CT, MRI and exam of neck movement.
The 2014 International Classification of Headache Disorders (ICHD-III-beta) diagnostic criteria defines NDPH as headache having a distinct onset with pain that becomes unremitting within 24 hours and persists for more than 3 months. Furthermore, the headache must not be better explained by another ICHD-III-beta diagnosis.[8]

Conclusions:

This case suggests that cataract surgery may be a possible trigger for NPDH. Neuro-ophthalmologists should keep this in mind when evaluating patients with headache following cataract surgery.

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Keywords: Headache

Financial Disclosures: The authors had no disclosures.

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Poster 157

Ten Years Of Temporal Artery Biopsies In Ontario, Canada: A Population-Based Study On Practice Patterns And The Incidence Of Giant Cell Arteritis

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Introduction:
The goal of this study was to determine the incidence of giant cell arteritis (GCA) in Ontario, Canada and determine the factors influencing which surgical specialists perform temporal artery biopsies (TABs). Significant geographic variability in referral patterns may lead to residents in surgical specialties such as ophthalmology with inadequate exposure to this procedure.

Methods:
This was a population-based study including all physicians in Ontario from 2002 to 2013. Using comprehensive physician services billing data from the Intellihealth Medical Services database, physicians performing TABs were categorized by specialty and geographic Local Health Integration Unit. The rate of positive TABs was retrieved from the literature from an Ontario sample during the study period.

Results:
The number of TABs was declining over the 10-year study period and the incidence of GCA was determined to be 3.0 per 100,000 people over 50 years of age. Of the 9,958 TABs performed over 10 years, most were performed by general surgeons (38%) followed by ophthalmologists (31%) and plastic surgeons (23%). Ophthalmologists performed significantly more TABs per person compared to general surgeons but significantly more general surgeons performed at least one biopsy. There was significant variation based on geographic location with plastic surgeons performing the most biopsies in regions with more than 1 million people and general surgeons performing most biopsies in rural areas. Among areas with residency training programs there was substantial variation to TAB exposure with many programs in plastics, general surgery and ophthalmology not performing enough procedures to attain competency in this area.

Conclusions:
The incidence of GCA in Ontario is consistent with the demographics of this province. Geographic location influences which specialty is most likely to perform TABs and trainees in general surgery, ophthalmology and plastic surgery have variable exposure to TABs and may be unprepared to serve their future practice population.

References: None.

Keywords: Diagnostic Tests, Giant Cell Arteritis

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Grant Support: None.

Poster 158

A Method For Recognizing Colorblind Malingering

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Introduction:
Standard tests of colorblindness screen for organic disease. This new test attempts to recognize malingerers of colorblindness.

Methods:
An online survey was distributed to 48 self-reported and verified colorblind participants and 81 participants instructed to simulate colorblind malingering. The survey contained three sets of six color-adjusted versions of the standard Ishihara color plates, as well as one set of six unmodified plates. The color-adjusted set demonstrating the highest differences in mean accuracy and group modes between both groups became the basis for a diagnostic test. Statistical measures of the test (sensitivity, specificity, and Youden index) were assessed at each possible cut-off threshold, and a receiver operating characteristic (ROC) function with its area under the curve (AUC) charted.

Results:
The redshift-adjusted plate set had the highest mean difference between groups (-50%, CI: -42% to -58%) as well as the largest mode difference. Statistical measures showed an optimal cut-off of at least 2 missed redshift plates to identify a colorblind malingerer (Youden index: 0.71, sensitivity: 75.31%, specificity: 95.83%). A stricter cut-off of at least 4 missed redshift plates showed a sensitivity of 43.21% and specificity of 100% (Youden index: 0.43). The AUC of the ROC was 0.89.

Conclusions:
Our proposed test for recognizing colorblind malingering demonstrates a high degree of reliability. A cut-off threshold of 4 missed redshift plates identified a colorblind malingerer with 100% specificity.

References: None.

Keywords: Color Blindness, Malingering, Psychophysics, Diagnostic Tests, Pseudo-Isochromatic Plates

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Poster 159

Mycotic Aneurysms Of Intracavernous Internal Carotid Artery

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Introduction:
Mycotic aneurysms of intracavernous segment of internal carotid artery are extremely rare. Early diagnosis is important as they have propensity to rupture.

Methods:
Case I - is a ten year old boy who had a boil at the tip of the nose which was incised and drained. A week later he developed preseptal cellulitis, fever and headache. He was given systemic antibiotics, fever and headache subsided but was unable to open his left eye. Examination showed complete third and fourth nerve palsy on the left side. Haemogram showed leucocytosis with increased ESR & C–reactive protein. MRI revealed an aneurysm in the region of the left cavernous sinus. CT angiogram demonstrated a lobulated aneurysm arising from cavernous segment of the left ICA, there was another small aneurysm arising from left ICA at the petrous apex. Case II - A three years old boy had multiple boils in the scalp, following which he developed preseptal cellulitis in the both eyes. He was given a long course of antibiotics, later on he developed complete ophthalmoplegia in both eyes. Haemogram showed leucocytosis, raised ESR and C-reactive protein. MRI showed aneurysms in both the cavernous sinuses. DSA confirmed the bilateral ICA aneurysms in cavernous sinus.

Results:
Case I - The parent artery occlusion using coils was performed. After 3 months he had marked improvement in third nerve palsy. Case II - On antibiotics the ophthalmoplegia on right side improved completely while there was partial improvement in ophthalmoplegia on left side. Endovascular procedure is planned for left ICA aneurysm.

Conclusions:
Mycotic aneurysm of cavernous segment of ICA presents as cavernous sinus syndrome with features of underlying infection. It results from direct invasion of vascular wall from the nearby infection such as cavernous sinus thrombophlebitis.

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Keywords: Mycotic Aneurysms, Cavernous Cinus, Interal Carotid Artery, Third Nerve Palsy, Preseptal Cellulitis

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Poster 160

Platelet-Mediated Microvascular Ischemia Mimicking Migraine in Patients with Thrombocythemia

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Introduction:
Patients with essential thrombocythemia (ET) can present with migraine-like typical or atypical transient ischaemic cerebral attacks. We describe a case where migraine-like attacks of fortification spectra without headache were the presenting symptoms in a patient with essential thrombocythemia.

Methods:
Case report

Results:
A 63-year-old cab driver presented with a 4-month history of seeing zig-zag lines, each episode lasting 5-10 minutes. These visual phenomena were experienced in alternate visual fields, were not associated with headache and were unrelated to any identifiable triggers. He had no past history of migraine but suffered from motion sickness. The neuro-ophthalmic examination was completely normal; in particular, there was no visual field defect by confrontation visual field testing. A preliminary diagnosis of late onset migraine aura without headache was entertained; however, the patient declined investigations despite his atypical presentation.A month later, he was admitted with right sided headache, fortification spectra, nausea and giddiness. A complete blood count revealed an elevated platelet level at 904x 10^9 per litre. Bone marrow aspirate showed a hypercellular marrow with increased megakaryocytes, polyploidy and clustering. Molecular studies found a heterozygous mutation for *JAK2* but no t[9;22] mRNA transcript was detected. Treatment with aspirin and hydroxyurea resulted in immediate resolution of visual symptoms without recurrence.

Conclusions:
This rare but well recognized syndrome of atypical transient ischemic attacks in thrombocythemia is likely caused by hypersensitive platelet production leading to ischemic and thrombotic processes in cerebral end-arterial microvasculature. It is important that neuro-ophthalmologists, neurologists as well as haematologists consider this diagnosis in any patient presenting with migraine-like visual symptoms.

References: None.

Keywords: High Intracranial Pressure/Headache

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Poster 161

Ganglion Cell Damage And Functional Recovery After Optic Neuritis

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Introduction:
Optic neuritis (ON) is characterized by inflammation of the optic nerve and retrograde axonal and neuronal damage in the retina. In optical coherence tomography (OCT) the retinal nerve layer swells during the acute phase. In the post-acute phase RNFL and ganglion cell layer thin as a surrogate for axonal loss and neurodegeneration. During the acute phase, ON regularly leads to severe vision loss in the affected eye. Recovery from optic neuritis is defined as reconstitution of visual function after an acute ON. The objective was to describe ON recovery based on neuronal damage in the retina.

Methods:
Prospective study in patients with acute optic neuritis. 56 patients (46 female and 10 male, age 36±9 years) with acute ON were followed over median 371 (25 – 975) days. Spectral domain OCT was performed on each visit, usually a few weeks apart. Best-corrected visual acuity (BCVA) was measured monocularly by the means of Snellen charts. Neuronal damage was determined as ganglion cell and inner plexiform layer (GCIPL) loss.

Results:
26 patients showed no GCIPL loss after acute ON, defined as in the range of 2x the standard deviation of unaffected eyes. Eyes with GCIPL loss were divided by the median (-15 µm) in eyes with moderate (n=16) and eyes with severe GCIPL loss (n=14). Male sex was associated with a higher GCIPL loss, whereas there was no influence of age. During the acute phase, eyes with later severe GICPL loss had worse BCVA, but the BCVA between moderate and no-loss eyes was similar. Eyes with more severe ON tended towards higher residual reduction of visual function.

Conclusions:
Recovery of ON can be defined by objective measurement of GCIPL thickness in the retina. It will be important to define factors predicting ON severity based on this classification.

References: None.

Keywords: OCT, Optic Neuritis, Demyelinating Disease, Retina

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 162

To Evaluate The Retinal Nerve Fiber Layer Loss In Optic Neuritis Using Spectral Domain Optical Coherence Tomography

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Introduction:
To assess the Retinal nerve fibre layer(RNFL) loss in optic neuritis patients using Spectral Domain Optical Coherence Tomography (SDOCT- Heidelberg Engineering software version 5.4.6) and to compare the RNFL loss with the visual acuity and visual outcome after treatment and also to evaluate the quadrant wise retinal nerve fibre layer loss in optic neuritis.

Methods:
A Cross sectional Observational, prospective study of 20 patients (27 eyes) with optic neuritis, from January 2013 to May 2014,in the department of Neuroophthalmology in a tertiary care centre in South India was conducted. Optic neuritis from 3 months to one year,aged less than 60 years, both unilateral and bilateral were included.Recurrent optic neuritis, extreme ages were excluded. SDOCT imaging was done in all 27 eyes.It was done in both affected and unaffected eyes. Assessment was done in six quadrants Superotemporal, Superonasal, Inferotemporal, Inferonasal, Nasal, Temporal and average of all six quadrants was calculated. RNFL thickness of affected eye was compared with unaffected eye and normative data of device.

Results:
Average of RNFL thickness in 6 quadrants of affected eyes (80.77µm) with unaffected eyes (97.92µm) showed significant loss (p 0.031). Comparison of the unilaterally affected eye(80.77µm) with normative data (98.00µm), showed significant reduction in RNFL thickness (p 0.031).Bilaterally affected eyes (67.71µm), when compared with normative data (98.43µm), showed clinically significant reduction (p <0.001). Unilaterally affected eyes had less RNFL loss than bilaterally affected eyes. Presenting visual acuity was associated with average RNFL loss, but statistically significant results (beta coefficient = -10.00, p value = 0.357 using regression analysis) could not be obtained. Inferotemporal quadrant was more affected . Temporal sector had more RNFL loss .

Conclusions:
From our study, spectralis SDOCT is an effective and convenient tool in calculating theRNFL thickness. Reduced thickness correlates with the poor visual function.

References: None.

Keywords: Optic Neuritis, Retinal Nerve Fiber Layer, Spectral Domain Optical Coherence Tomography, Quadrants, Visual Acuity

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 163

Retinal Ganglion Cell Injury In Early Pediatric Onset MS

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Introduction:
We sought to document retinal ganglion cell injury in a pediatric onset multiple sclerosis (MS) cohort and evaluate if differences in neuronal levels of injury can be seen by sex in eyes with or without history of optic neuritis (ON).

Methods:
This is a retrospective study of consecutive subjects with pediatric onset MS (<18 years at first symptom) who presented for visual evaluation to a pediatric MS center. Spectral domain optical coherence tomography (OCT) was performed. Segmentation of retinal layers was performed using automated software algorithm (Heidelberg). Generalized estimating equations were used to measure associations of sex, optic neuritis and age with retinal nerve fiber layer (RNFL) thickness and ganglion cell layer (GCL) volumes.

Results:
Fifty-five subjects (65% female; n=108 eyes) were included. Mean age of MS onset was 12.9 years (SD 3.9); mean age at time of exam was 15.1 years (SD 3.5) with average disease duration of 1.9 years (SD 2.7). In multivariable analyses, history of ON was associated with both reduced RNFL thickness (-16.2 µm, 95% CI -25.3, -7.0, p=0.001) and 24% lower ganglion cell layer volumes (-0.097 mm^3, 95% CI -0.13, -0.065, p<0.001). Older age at time of scan was associated with 2-µm thicker measurement of RNFL per year (95% CI 0.68, 3.43, p=0.001). In eyes with history of ON (n=28), males had 12µm lower RNFL thickness, though this did not reach statistical significance (95% CI -29.4, 4.62, p=0.15).

Conclusions:
Substantial cell soma loss occurs after optic neuritis even in pediatric onset MS. The observed trend towards greater neuroaxonal loss in males in early MS should be confirmed in larger studies.

References: None.

Keywords: Pediatric Neuro-Ophthalmology, Demyelinating Disease, Diagnostic Testing (OCT), Optic Neuropathy

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Poster 164

The Correlation of Critical Flicker Fusion Function and P100 latency of Visual Evoked Potential with Luminance

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Introduction:
Two frequent manifestations of optic nerve disease are loss of the sensation of brightness and blurred vision. Here we study the relationship between several measures of optic nerve function, Critical Flicker Fusion (CFF) function, implicit time of the P100 of Pattern Reversal Visual Evoked Potential (PRVEP), log MAR acuity and color function in subjects with visual dysfunction simulated by neutral density filters.

Methods:
Four healthy adult subjects underwent PRVEP, CFF, color vision (Ishihara plates), and log MAR acuity testing under various levels of luminance. Neutral density filters of 0.6 to 3.0 log unit were used to control stimulus luminance. CFF thresholds, log MAR acuity, Ishihara color plate measurements and P100 latencies and amplitudes of VEP responses were plotted as a function of luminance.

Results:
CFF decreased and P100 latency increased linearly with the logarithm of stimulus luminance in each of the 4 subjects. P100 latency increased by 9-22 ms, and CFF decreased by 4.7 Hz per log unit decrement in stimulus luminance. Color vision was least affected by changes in log stimulus luminance, and log MAR acuity decreased minimally as luminance increased up to 1.2 log, above which acuity declines precipitously.

Conclusions:
CFF and P100 implicit time are linearly related to log luminance. The slopes of the linear regression are similar across individuals despite having different baseline thresholds or latencies. The rate of change in CFF or P100 with luminance thus may be useful as a clinical test of optic nerve function. CFF is faster to administer and has low variability on repeat testing.

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Keywords: Critical Flicker Fusion Function, Visual Evoked Potential, Neutral Density Filter, Optic Nerve Function

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Poster 165

The Effects of Amblyopia on Visual Evoked Potentials

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Introduction:
Amblyopia is attributed to cortical changes, therefore Visual Evoked Potentials (VEP) testing is well positioned in the diagnosis, prognosis and management of this condition

Methods:
In this retrospective study we investigate how useful VEP can be for amblyopia management. We analyzed the amplitude, latency and morphology of VEP on the amblyopic eye compared to the fellow eye and the presence of changes in the normal eye due to patching. Pattern reversal VEP with 3 channels was used.

Results:
We retrospectively analyzed 25 VEP studies of pediatric patients with unilateral amblyopia (refractive and strabismic). Age ranged from 5 to 17 years. Visual acuity in the amblyopic eye ranged from 20/30 to 20/400. In the nonamblyopic eye the patch effect (prolonged implicit time) was rarely seen. In the amblyopic eye the majority of the patients had abnormal VEP in all area analyzed: implicit time, amplitude and morphology compared with the sound eye. Majority of patients had P100 prolonged less than 130ms. Only a minority of patients had P100 prolonged over 130ms. For the latest group, only maintenance patching was indicated.

Conclusions:
VEP is a helpful tool for the management as well as the understanding of the pathophysiology of amblyopia.

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Keywords: Amblyopia, VEP

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Poster 166

Doubling Method for Papilledema and Pseudopapilledema

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Introduction:
To demonstrate clinical usefulness of doubling method for distinguishing low grade papilledema (Modified Frisen Scale (MFS) grade 1 or 2), pseudopapilledema and normal optic disc by spectral-domain optical coherence tomography (SD-OCT).

Methods:
The databases were reviewed for patients with papilledema (Modified Frisen Scale grade 1 or 2), patients with pseudopapilledema and patient with normal optic disc (control) who undergone for SD-OCT and stereoscopic optic disc color photography. The doubled thickness of temporal quadrant (Tdt) and the doubled average of temporal and nasal quadrants, which was the sum of them, (Ttn) were calculated and compared to the thickness of inferior quadrant (Ti) in each group. Statistical significance was analyzed.

Results:
The data were obtained from 37 cases of papilledema, 37 cases of pseudopapilledema and 23 cases of control. In group of papilledema (MFS grade 1 or 2), the average thickness was 126.7μm, Tdt was 170.2μm, Ttn was 179.3μm and Ti was 190.5μm. In group of pseudopapilledema, the average thickness was 113.8μm, Tdt was 157.2μm, Ttn was 165.0μm and Ti was 146.8μm. In control group, the average thickness was 86.1μm, Tdt was 120.2μm, Ttn was 125.0μm and Ti was 117.9μm. In 81% of papilledema, 23% of pseudopapilledema and 37% of control group, Ti was greater than Tdt and Ttn. The difference between group of papilledema and pseudopapilledema and the difference between group of papilledema and control group were statistically significant ($p<0.05$). (Further data collection and final analysis are pending at the time of submission.)

Conclusions:
The differentiation of low grade papilledema and pseudopapilledema needs to be determined based on clinical setting. As an adjunct method, the doubling method by SD-OCT is a simple way to help to distinguish between low grade papilledema and pseudopapilledema. During the early stage of papilledema, swelling occurs more in inferior quadrant than temporal or nasal quadrants.

References: None.

Keywords: OCT, Pseudotumor cerebri, Papilledema, Pseudopapilledema

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Poster 167

Correlation Between Structural And Functional Changes In Retina In Parkinson's Disease

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Introduction:
To evaluate structural changes in retina and correlate those with visual function changes in Parkinson's disease (PD).

Methods:
A cross-sectional comparative study with 20 cases of PD and 20 age matched healthy controls was conducted. Visual acuity, color vision, contrast sensitivity, visual fields, pattern VER and multifocal ERG were recorded to determine functional change, while structural changes were evaluated as retinal nerve fibre layer (RNFL) thickness, macular thickness, macular volume and ganglion cell-inner plexiform layer complex (GCL-IPL) thickness using SD-OCT.

Results:
PD patients were in stage 2 (H&Y stage) of disease (range 1-3), with mean UPDRS III score of 19 ± 10.42, having average disease duration of 5.8 ± 2.78 years. Visual acuity, color vision and visual fields were unaffected but contrast sensitivity was significantly worse than controls ($p < 0.001$). Multifocal ERG values in the central 2◦ field revealed decreased foveal electrical activity, with increased pattern VER amplitude and latency. Significant RNFL thinning was observed in the average RNFL ($p=0.033$), superior ($p=0.018$) and temporal ($p=0.036$) quadrants. Significant ganglion cell layer loss was captured on OCT with average, minimum GCL-IPL and all six sectors showing thinning (p value≤ 0.003). The functional changes correlated significantly with structural changes, disease duration and severity. No correlation was seen between structural alterations in retina and disease duration or severity.

Conclusions:
Subclinical visual dysfunction was observed in PD patients with good structural-functional correlation. GCL-IPL thinning may be a more reliable parameter than RNFL thickness for structural alterations in retina.

References: None.

Keywords: Parkinson's Disease, Retinal Nerve Fibre Layer, Ganglion Cell Layer, Multifocal ERG, Optical Coherence Tomography

Financial Disclosures: The authors had no disclosures.

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Poster 168

Relationship Between Visual Acuity And Retinal Nerve Fiber Layer Thickness Measured By Spectral Domain Optical Coherence Tomography In Patients With Optic Neuropathy

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Introduction:
The structural axonal loss in the optic nerve can be quantified by measuring the peripapillary retinal nerve fiber(RNFL) thickness using optical coherence tomography(OCT). Measuring the RNFL thickness in optic neuropathy provides a structural assessment of the optic nerve, enables prognostic evaluations. We assessed the relationship between RNFL measured by spectral domain optical coherence tomography (SD-OCT) and visual acuity in optic neuritis and traumatic optic neuropathy.

Methods:
In this cross-sectional observational study, 40 patients were included. RNFL thickness and visual acuity (VA) in both optic neuritis and traumatic optic neuropathy were measured at least 6 months of the event. The correlations between best-corrected visual acuity (BCVA) and OCT parameters were evaluated using regression analysis. (GraphPad Software, San Diego, CA)

Results:
40 subjects received systemic steroids. After at least 6 months, the attack eye had significant RNFL thinning in 4 (superior, inferior, temporal, nasal) quadrants (푝 ≤ 0.05) compared to fellow normal eye. When logMAR BCVA was plotted against RNFL thickness, Pearson's correlation tests showed superior (p=0.033), temporal(p=0.9272), inferior(p=0.0035), and nasal(p=0.5972) quadrant. Linear regression analysis of logMAR BCVA and RNFL thickness in optic neuropathy patients indicated a relationship of y = -33.05X + 111.2 in superior quadrant, and Y = -56.04X + 115.1(x: logMAR VA, y: RNFL thickness) in inferior quadrant, which was statistically significant.

Conclusions:
The relationship between BCVA and SD-OCT parameters were significantly noted in superior and inferior quadrant of eyes with optic neuritis and traumatic optic neuropathy. The lower and superior RNFL thickness may predict visual acuity after optic neuropathy, and correlate with impaired visual function.

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retinal structures measured by spectral domain optical coherencetomography in patients with open-angle glaucoma. Invest Ophthalmol Vis Sci. Jul 17; 55(8):4801-11, 2014

Keywords: Visual Acuity, Optical Coherence Tomography, Retinal Nerve Fiber Layer Thickness

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 169

Ganglion Cell Layer Thinning Detected By Optical Coherence Tomography As A Sign Of Early Optic Atrophy In Pediatric Papilledema

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Introduction:
Recent Spectralis (Heidelberg, Germany) spectral domain optical coherence tomography (OCT) research software can quantify the thickness of each individual retinal layer. Analyzing the macula may give clues to differentiate resolution of papilledema from superimposed atrophy. We sought to characterize and compare the thickness of each macular layer in children with resolved papilledema versus normals.

Methods:
Data was obtained in an ongoing retrospective, IRB-approved observational study including eyes of children with resolved papilledema due to idiopathic intracranial hypertension (IIH) and normals who had optic nerve and macular imaging with Spectralis OCT. The average thickness of each of the seven retinal layers in the macula (central 6 mm) and peripapillary retinal nerve fiber layer (pRNFL) were compared between these groups using a two-sided t-test with Bonferroni correction applied as necessary.

Results:
Included were 68 eyes from 68 children: 25 with resolved papilledema due to IIH and 43 normals. Eyes with papilledema had significantly thinner ganglion cell layer (GCL) and inner plexiform layer (IPL) than normals: (mean±SD (mm^3)): 0.99±0.18 vs. 1.13±0.10, $p_{Bonferroni}$=0.0091; and 0.83±0.12 vs. 0.91±0.07, $p_{Bonferroni}$=0.0329, respectively. Area under receiver operating curve (ROC-AUC) showed higher discrimination ability of papilledema vs. normal for GCL and IPL than pRNFL (AUC=0.72, 0.67, and 0.50 respectively). The pRNFL was not different between eyes with pediatric papilledema and normals (mean±SD (microns)): 102.96±28.16 vs. 102.71±10.01, p=0.9667.

Conclusions:
In pediatric eyes with resolved papilledema, the macular GCL and IPL may be more sensitive than pRNFL for the detection of early optic atrophy. This finding may help distinguish the resolution of papilledema from superimposed early optic atrophy.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, Mferg, Etc), Pseudotumor Cerebri, Pediatric Neuro-Ophthalmology, Retina, High Intracranial Pressure/Headache

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Poster 170

Peripapillary Retinal Nerve Fiber Layer Thickness Corresponds To Drusen Location And Extent Of Visual Field Defects In Patients With Optic Disc Drusen

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Introduction:
Optic disc drusen (ODD) are hyaline deposits located within the optic nerve head. While a minority of ODD patients are affected by complications such as anterior ischemic optic neuropathy and retinal hemorrhages, optic coherence tomography (OCT) reveals thinning of the peripapillary retinal nerve fiber layer (RNFL) in most patients. Peripapillary RNFL thinning is thought to be associated with the high frequency of visual field defects seen in these patients.The goal of this study was to investigate the basic characteristics of patients with ODD and to compare the peripapillary RNFL thickness to the anatomic location of ODD, the risk of complications and the extent of visual field defects.

Methods:
Records from patients, that in the period from January 2014 until October 2014 were either diagnosed with ODD or visited the hospital because of previously identified ODD, were reviewed in this retrospective study.

Results:
155 eyes of 86 ODD patients were evaluated. 65 % were female and 75 % had bilateral ODD. Presenting complications were seen in 22 % of all inquiries including anterior ischemic optic neuropathy (10,5 %), optic neuritis (5,8%), retinal hemorrhage (4,7%) and central retinal artery occlusion (1,2%). Peripapillary RNFL thinning was seen in 83,6 % of eyes with OCT performed (n =61). Patients with superficial ODD had greater mean peripapillary RNFL thinning than patients with buried ODD (P=<0.0001). There was a correlation between mean RNFL thinning and visual field defects as measured by perimetric mean deviation (R= -0,72; P<0.0001). No significantly reduced mean peripapillary RNFL thickness was seen in patients with one or more complications compared to patients without complications.

Conclusions:
Basic characteristics for ODD patients correspond well with the previously reported. Anterior ischemic optic neuropathy is the most frequent severe complication of ODD. Peripapillary RNFL thickness correlates with the anatomic drusen location and the extent of visual field defects in ODD patients.

References: None.

Keywords: Optic Disc Drusen, Retinal Nerve Fiber Layer, Visual Fields, Perimetry

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Poster 171

Progressive Retinal Structure Abnormalities in Multiple System Atrophy

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Introduction:
To study the retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness in patients with MSA, assess changes over time, and determine whether these measurements could be used as biomarker of disease severity.

Methods:
We studied 31 eyes from 16 patients with MSA, 24 eyes from 12 Parkinson disease (PD) patients and 44 eyes from 22 controls. Subjects underwent complete ophthalmological evaluation including high definition-optic coherence tomography (HD-OCT) to measure RNFL and GCC thickness. The Unified Multiple System Atrophy Rating Scale (UMSARS) was used to evaluate disease severity and progression.

Results:
All MSA and control subjects had normal visual acuity and color discrimination. Average RNFL and GCC thickness were significantly reduced in MSA ($p=0.029$, $p=0.002$) and PD ($p=0.004$ $p<0.001$) when compared to controls. In 11 MSA patients, prospective measurements were available. There was a significant reduction of the global RNFL and global GCC thicknesses between the initial and the follow-up measurements (10±7 months). Significant inverse correlations were found between the inferior RNFL thickness and disease duration, and between nasal and inferior RNFL thicknesses and UMSARS scores. From these results, we defined regression equations that predict clinical impairment (*UMSARS-I= 0.11*Disease duration+0.828*age-0.356*inferior RNFL+ 0.537* global RNFL– 9.5*; U*MSARS-II= -0.702*nasal RNFL + 0.837 global RNFL– 0.28*inferior RNFL + 30.6*)

Conclusions:
There is a progressive reduction in the RNFL thickness in visually asymptomatic MSA patients. This abnormality can be detected by HD-OCT, a non-invasive, easy-to-perform technique.

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Keywords: OCT, RNFL, MSA, Parkinson

Financial Disclosures: The authors had no disclosures.

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Poster 172

OCT shows Consistent Relationships between Macular Layers and Peripapillary RNFL in Chronic Demyelinating and Compressive Optic Neuropathies

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Introduction:
Optical coherence tomography (OCT) demonstrates thinning of the peripapillary retinal nerve fiber layer (P-RNFL) and inner macular layers in patients with chronic optic neuropathy, including those with multiple sclerosis (MS) and a history of optic neuritis (ON). We sought relationships between each layer of the macula and the P-RNFL in demyelinating and compressive optic neuropathy.

Methods:
We analyzed spectral-domain OCT results from chronic patients with MS or neuromyelitis optica (NMO) with and without a history of ON (128 MS eyes and 10 NMO eyes), idiopathic ON (13 eyes) and compressive optic neuropathy (14 eyes). No patient had a history of significant visual change within the past 6 months and none had additional eye pathology. We performed regression analysis for each patient group, comparing P-RNFL and individual macular layer values.

Results:
There were highly significant positive correlations between mean P-RNFL thickness and the volumes of each of the three inner retinal layers (RNFL, GCL and IPL); these layers in turn correlated closely with each other. Similar relationships existed with the temporal quadrant of P-RNFL. These linear correlations were virtually superimposable between any of the demyelinating or compressive neuropathy groups. In contrast, the P-RNFL did not correlate, or demonstrated a weak negative correlation, with the retinal layers from the INL outward.

Conclusions:
Chronic optic atrophy induces a predictable degree of retrograde degeneration that includes the axons, cell bodies and dendrites of the retinal ganglion cell, regardless of its cause. We found no evidence of trans-synaptic degeneration involving the outer retinal layers; if anything, there was a slight thickening of these layers as the inner retinal layers thinned.

References: None.

Keywords: Diagnostic Tests (OCT), Optic Neuropathy, Demyelinating Diseases, Tumors

Financial Disclosures: The authors had no disclosures.

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Poster 173

OCT Shows Different Relationships Between Macular Layers And Peripapillary RNFL In Acute Versus Chronic Papillitis And Papilledema

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Introduction:
Optical coherence tomography (OCT) demonstrates swelling of the optic nerve head (ONH) and peripapillary retinal nerve fiber layer (P-RNFL) in patients with acute papilledema due to intracranial hypertension and in anterior optic neuritis (papillitis). As these conditions become chronic, atrophy of retinal ganglion cell (RGC) axons develops. We sought relationships between the P-RNFL and each layer of the macula in acute and chronic papillitis and compared them to eyes with papilledema.

Methods:
We analyzed spectral-domain OCT in eyes with papillitis during the acute and chronic phases (13 eyes) and compared results to a large cohort of eyes with papilledema associated with intracranial hypertension (88 eyes). We performed regression analysis for each patient group, comparing P-RNFL and individual macular layer values.

Results:
There were highly significant positive correlations between mean P-RNFL thickness and the volumes of each of the three inner retinal layers (RNFL, GCL and IPL) in chronic eyes with normal or thinned P-RNFLs, but not in eyes with acute ONH swelling. In the latter, there were trends toward positive correlation only with the macular RNFL, which was weakly significant only in the larger papilledema group. In both papillitis and papilledema, there was no correlation between P-RNFL and the outer retinal layers. Relationships of P-RNFL and retinal layer volumes were very similar in papillitis and papilledema eyes.

Conclusions:
Conditions that cause swelling of RGC axons at the ONH may induce slight thickening of the macular RNFL, but not of the underlying GCL and IPL that contain RGC cell bodies and dendrites, nor of the outer retinal layers. In contrast, loss of RGC axons associated with chronic papilledema or papillitis causes retrograde degeneration in the macular RNFL, GCL and IPL. Recognition of the normal, close relationship between the P-RNFL and inner retinal layers may allow early detection of RGC swelling.

References: None.

Keywords: Diagnostic Tests (OCT), Optic Neuropathy, Demyelinating Diseases, High Intracranial Pressure

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Poster 174

The Photopic Negative Response In Idiopathic Intracranial Hypertension

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Introduction:
There is a need for non-invasive biomarkers that will improve diagnosis and management of idiopathic intracranial hypertension (IIH). The photopic negative response (PhNR) is a slow negative component of the full-field electroretinogram with specificity for inner retinal dysfunction associated with retinal ganglion cell injury. It is abnormal in other optic neuropathies and has not been previously studied in IIH or papilledema. Our purpose was to evaluate the PhNR as an index of visual function in IIH.

Methods:
The PhNR of the photopic full-field, brief flash electroretinogram was recorded in ten subjects with IIH using standard stimulation and recording techniques. PhNR amplitude in IIH subjects was compared 15 visually normal control subjects. In IIH subjects, visual function was assessed using standard automated perimetry mean deviation (SAP-MD) scores and current and prior optic nerve structures were evaluated using the Frisén papilledema grading scale. Associations between PhNR amplitude, SAP-MD and papilledema grade were evaluated.

Results:
The mean PhNR amplitude was significantly lower in IIH subjects compared with control subjects($p = 0.015$ Mann-Whitney rank sum). Log PhNR amplitude and SAP-MD were correlated significantly (pearson correlation, $r = 0.8$, $p= 0.01$). All IIH subjects with reduced PhNR amplitude (n=6) had optic atrophy or history of high-grade papilledema, while those with normal PhNR (n=4) did not have history of high-grade papilledema ($p=0.0005$ Fisher's exact). SAP-MD severity was not associated with history of high-grade papilledema ($p=0.52$ Fisher's exact).

Conclusions:
We demonstrate that the PhNR amplitude can be decreased in IIH subjects and that the decrease correlates with compromise in a clinical measure of visual function (SAP-MD). The observation that high-grade papilledema is associated with PhNR abnormalities but not SAP-MD severity supports literature implicating PhNR association with pre-perimetric optic nerve injury. Further studies are needed to determine the clinical utility of PhNR as a marker for diagnosis and monitoring of IIH.

References: None.

Keywords: Diagnostic Tests, High Intracranial Pressure, Optic Neuropathy, Pseudotumor Cerebri, Perimetry

Financial Disclosures: The authors had no disclosures.

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Poster 175

Attenuated Hunter Syndrome: A Rare Cause of Simultaneous Retinal and Optic Nerve Disease

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Introduction:
Hunter Syndrome (HS) is a multisystemic disorder characterized by glycosaminoglycan (GAG) accumulation due to enzyme deficiency of iduronate 2-sulfatase. This case report characterizes visual pathway involvement in HS.

Methods:
Case report.

Results:
A 44-year-old man with HS presented with headaches, nausea, and peripheral vision loss. Visual acuities were 20/25 OU with normal color vision. There was no APD; bilateral optic disc edema was noted. Humphrey visual fields (VF) showed pericentric ring scotomas. Full field ERG was normal. Intracranial pressure monitoring was normal. Orbital MRI demonstrated bilateral scleral thickening with a suggestion of scleral canal crowding. Over the next 16 months, VF defects mildly progressed, despite stable acuities and disc appearance. OCT demonstrated microcystic macular edema, thinning of the retinal nerve fiber layer (RNFL: OD 100 / OS 129 microns), ganglion cell layer (GCL), outer nuclear and photoreceptor layers. At 15 months, RNFL thickness declined in OD (by 13 microns), increased in OS (by 9 microns), while macular and retinal changes were stable.

Conclusions:
This patient illustrates the complex mechanisms of visual impairment in HS. We hypothesize that the retinal changes and scleral canal crowding with optic disc edema both resulted from GAG deposition. Likewise, the ring scotomas of our patient were pericentral and a full field ERG was normal. Segmentation of the GCL demonstrated a pattern of loss consistent with the field defect. GCL loss could have resulted from trans-synaptic degeneration of the photoreceptor layer, but we think primary injury to the GCL is most likely. The visual acuity preservation and symmetrical pattern of VF loss make a primary optic nerve mechanism unlikely. These findings demonstrate that a combination of retinal and optic nerve changes, including optic disc swelling, optic atrophy and retinopathy, occur in HS. This case emphasizes the potential role for OCT to help delineate the areas of visual pathway involvment.

References: None.

Keywords: Optical Coherence Tomography (OCT), Hunter Syndrome, Disc edema, Retina, Eye Abnormalities

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Poster 176

Ganglion cell and retinal nerve fiber layer analysis in a case of PION

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Introduction:
Posterior Ischemic Optic Neuropathy (PION) is a retro bulbar optic nerve ischemia presenting with sudden, painless visual loss with the presence of decreased vision, visual field defect, an afferent pupillary defect, yet the retina and optic nerve appear normal initially. PION can be seen in isolation, as part of giant cell arteritis, or post surgical. A PubMed search does not reveal any cases of OCT in the phases of PION. Ganglion cell OCT can help determine when ganglion cell thinning occurs in ischemic optic neuropathy. A case of PION and OCT is presented.

Methods:
Single case study of a 64-year-old woman with sudden, painless loss of vision in the right eye. She had no symptoms of GCA and there was no recent surgical history. The visual acuity showed count fingers at 3 feet in the right eye and 20/20 left eye. HVF right eye (Figure 1) showed a superior altitudinal defect. There was a large right afferent pupillary defect. The optic nerve, macula and peripheral retina appeared normal (Figure 2). Initial OCT of the GCL and RNFL were normal (Figure 3). MRI of the orbits showed no optic nerve enhancement (Figure 4). Numerous blood tests were normal including ESR and CRP. Three days of IV methylprednisolone followed by oral prednisone taper were given. Follow up GCL and RNFL OCT were obtained 4 weeks (Figure 5) and 9 weeks (Figure 6) after initial visit.

Results:
RNFL OCT is initially normal in PION followed by later thickening likely due to axoplasmic stasis. RNFL thins in the later phase of optic nerve ischemia. GCL OCT is initially normal in PION and shows thinning at 4 weeks and 9 weeks in this case.

Conclusions:
GCL OCT thins rapidly following PION suggestive of rapid loss of ganglion cells. There is a short time window in preventing ganglion cell death in potential optic nerve ischemia treatment.

References: None.

Keywords: optic neuropathy, OCT

Financial Disclosures: The authors had no disclosures.

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Poster 177

Perimacular Ganglion Cell Complex Thinning Detected By Spectral-Domain OCT Useful In Detecting Optic Tract Syndrome

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Introduction:
Unilateral lesions to the optic tract lead to optic nerve atrophy (bow-tie atrophy) and concurrent macular ganglion cell complex (GCC) thickness reduction in a reproducible pattern in both eyes. This is called optic tract syndrome and it is reflected clinically as an incongruous homonymous hemianopia and a contralateral relative afferent pupillary defect (RAPD).

Methods:
Case report description of a patient with an optic tract lesion and its characteristic findings at the Spectral-Domain OCT (SD OCT) using the OD-OS asymmetry analysis.

Results:
The OD-OS asymmetry analysis can be very useful to detect ipsilateral peri-macular temporal thinning and a contralateral peri-macular nasal thinning of the GCC which are characteristic signs of this syndrome. It compares the thickness of cells between eyes by highlighting in grayscale cells that are thinner than corresponding cell in the opposing eye. The grayscale of this analysis, by enhancing the pattern resembling the homonymous hemianopia, makes it easier to detect optic tract lesions and to differentiate them from glaucoma.

Conclusions:
It is very useful clinically when a patient is erroneously first referred for suspicion of glaucoma and when bow-tie atrophy is not evident.

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Keywords: Spectral-Domain Optical Coherence Tomography, Macular Ganglion Cell Complex, Homonymous Hemianopsia, Optic Tract Syndrome

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 178

To Evaluate Changes In Retinal Nerve Fiber Layer And Ganglion Cell Layer On Cirrus HD-OCT In Cases Of Multiple Sclerosis (With And Without Optic Neuritis) And Optic Neuritis

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Introduction:
Purpose: To prospectively examine relation of visual functions to retinal nerve fibre layer(RNFL) thickness and ganglion cell layer(GCL) complex changes over 6 months as a structural biomarker for axonal loss in multiple sclerosis and optic neuritis patients.

Methods:
Patient with Multiple sclerosis without optic neuritis (MS) (n=20; 40 eyes), Optic neuritis (ON) (n=26; 58 eyes), Multiple sclerosis with optic neuritis (MS+ON) (n=24; 48), and disease-free controls (n=20; 40 eyes).Visual testing was performed for each eye at baseline and 6 months which included Snellens visual acuity (in Log MAR units), Pelli-Robsons contrast sensitivity, Ishiharas colour vision, visual evoked response, Retinal nerve fibre layer and ganglion cell layer complex thickness was measured using Cirrus HD-OCT. EDSS score was calculated for multiple sclerosis patients.

Results:
Average RNFL thickness was reduced significantly [with respect to controls (86.1µm)] among the eyes of patients with MS+ON (56.8µm) (P<0.005) as well the unaffected fellow eye (67.3µm) (P<0.005) and ON (52.8µm) (P<0.005) but no significant difference was found in MS patients (80.6µm) (P=1). GCL complex thickness was reduced significantly [with respect to controls (84.3µm)] among eyes of MS+ON (56.1µm) (P<0.005), the fellow unaffected eye of this group(66.2µm) (P<0.005), ON (54µm) (P<0.005) as well as MS patients (65.8µm) (P<0.005).GCL complex thickness significantly correlated clinically with visual acuity (P=0.0032), colour (P<0.001), EDSS (P=0.0047), VER amplitude (P=0.0078) and latency (P=0.0001) in MS patients and significantly clinically correlated with visual acuity (P=0.0042), colour vision (<0.001) and contrast (p=0.02)in ON patients.

Conclusions:
Ganglion cell layer complex thickness measurement is a better clinical marker than retinal nerve fibre layer thickness (Cirrus HD-OCT) in Multiple sclerosis and optic neuritis patients. Although eyes with history of optic neuritis demonstrate the greatest reduction in GCL complex thickness, MS non-ON eyes have less GCL complex thickness than controls, suggesting the occurrence of chronic axonal loss separate from acute attacks in MS patients.

References: None.

Keywords: Demyelinating Disease, Optic Neuropathy, Diagnostic Tests, Neuro-Ophth & Systyemic Disease, Higher Visual Functions

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Poster 179

Examination of Visual Evoked Potential (VEP) in a Pediatric Population with Newly Diagnosed Elevated Intracranial Hypertension

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Introduction:
Pattern VEP has been demonstrated in adults (>16 years of age) to have severely delayed latencies demonstrating a significant correlation between the affects of intracranial pressure and subsequent health of the visual system. Most studies involve adult populations, with pediatric populations uninvestigated. We hypothesize that VEP, similar to adult populations, can be used to predict dysfunction of the visual pathway from elevated ICP.

Methods:
32 children (12.08 years, SD 4.40) diagnosed with IIH (37.41 mmHg±7.16) using the Modified Dandy Criteria were examined. Pattern VEPs were recorded monocularly. Va LogMar (Mean 0.1291±0.252), OCT average RNFL (Mean 131.08uM±4.56) will be compared and associated with opening intracranial pressure were recorded at presentation. These parameters were used to compare outcomes of VEP Latency and Amplitude compared with an age matched control population obtained within 4 months of documented elevated opening pressure.

Results:
The average age (male 9.696±0.8396; female 13.914±1.0423, p=0.002) and BMI (male 23.323±2.14; female 34.646±2.34, p=0.003) differed significantly between the population of pediatric patients evaluated. The presence of optic disc edema showed no association with elevated ICP. Average RNFL was positively correlated with elevated intracranial pressure, while RNFL (131.08±4.56, r2=1.676, p=0.04).
VEP was analyzed in this population. Total p100 latency was significantly reduced in patients presenting with elevated ICP (101±1.31, p=0.03), while amplitude was elevated (25.16±2.32, p=0.02). While latency was not associated with elevations in intracranial pressure (r2=0.01), elevation in amplitude was found to be positively correlated (r2=0.84, p=0.02).

Conclusions:
Age, BMI, Visual acuity, color vision, and the presence of optic disc edema are inaccurate measures to be used to determine visual pathway dysfunction elevated ICP. Optical Coherence Tomography and Visual fields obtained can indicate pathology. VEP can be used to determine elevation in ICP, and might represent a easily obtainable and reliable method of monitoring changes in intracranial pressure.

References: None.

Keywords: Pediatric IIH, Idiopathic Intracranial Hypertension, Visual Evoked Potential

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Grant Support: None.

Poster 180

Retinal Nerve Fiber Layer Thickness in a Population-Based Study of Elderly Subjects: The Alienor Study

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Introduction:
To establish normative data of retinal nerve fiber layer (RNFL) thickness in the elderly and to determine the factors influencing its thickness.

Methods:
Peripapillary RNFL thickness was measured with spectral domain OCT (SD-OCT) in 210 elderly participants from the Alienor population-based study who were aged 75 years or older. The measure was assessed in 6 segments. RNFL data were analyzed across age and sex strata in non-glaucoma participants. Mixed linear models were used to evaluate the associations of RNFL thickness with age, sex, ocular parameters (axial length, cataract), and vascular risk factors (blood pressure, diabetes, body mass index, smoking status, heart disease and stroke).

Results:
The mean global RNFL thickness was 91.4 µm (SD: 12.6), ranging from 55 to 122; the highest values were found in the inferotemporal and superotemporal segments. After adjustment for sex and ocular parameters, including axial length, increasing age was significantly associated with lower thickness globally (mean thinning per decade = 5.6 µm, p=0.003), in the superotemporal (-12.7 µm per decade, p<0.0001) and inferotemporal (-8.1 µm per decade, p=0.022) segments. RNFL thickness tended to be higher in women than in men, but this trend was significant only in the inferotemporal segment (+6.6 µm for women, p=0.012). The axial length was associated with RNFL thickness globally and in most segments. RNFL thickness did not differ according to cataract extraction. There were no association between vascular factors and RNFL thickness.

Conclusions:
In concordance with previous studies in adult population, we found a decrease of RNFL thickness with age, even after 75 years. The decrease was stronger in the supero and inferotemporal segments. Moreover, the study demonstrated that RNFL tended to be higher in women, particularly in the inferotemporal segment. Finally, as RNFL thickness did not differ according to cataract extraction, it can be used in both people with and without cataract extraction.

References: None.

Keywords: OCT, Retinal Nerve Fiber Layer, Epidemiology

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Poster 181

OCT-Derived Retinal Capillary Density is Decreased in Corresponding Areas of Retinal Neuron Loss in Optic Neuropathy

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Introduction:
To evaluate the chronic effect of optic neuropathy on retinal capillary density using a new OCT-based method of angiography that does not require dye injection. We hypothesized that loss of retinal ganglion cells and their axons would reduce metabolic demand of the inner retina, causing loss of capillary blood flow.

Methods:
Retinal capillaries were visualized using en face OCT angiography, based upon the detection of intravascular movement of light-scattering particles. Fourteen eyes were studied from 8 patients with optic neuritis (ON; n=2), neuromyelitis optica (NMO; n=1), nonarteritic anterior ischemic optic neuropathy (NAION; n=2), Leber hereditary optic neuropathy (LHON; n=2) and compressive optic neuropathy (pituitary adenoma; n=1).

Results:
In ON and NMO patients, retinal capillary density derived from blood flow was decreased significantly in the macula and around the optic disc that corresponded to the areas with loss of retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform complex (GCC). Following resolution of disc edema, NAION eyes demonstrated lack of retinal capillary filling in altitudinal sectors corresponding to the same areas with loss of RNFL, GCC, and visual field. In LHON patients, maculo-papillary bundle defects and macula areas of GCC loss were observed using en face SD-OCT and retinal capillary flow was absent in the corresponding macula and retinal areas. In one patient with compressive optic neuropathy from a pituitary adenoma the structural loss in the maculo-papillary bundle, nasal RNFL and GCC was associated with lack of corresponding retinal capillaries rendered by OCT angiography.

Conclusions:
Loss of retinal ganglion cells and their axons appears to result in sufficient reduction in metabolic requirements of the retina to result in significant loss of capillary blood flow in corresponding locations. OCT angiography may help in understanding the link between metabolic demand and blood flow in eyes with optic neuropathy.

References: None.

Keywords: Diagnostic Tests, Optic Neuropathy, Retina, Capillary Blood Flow, Ganglion Cell Complex

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Poster 182

Adaptive Optics Imaging With Histopathologic Correlation in Cancer-Associated Retinopathy

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Introduction:
We describe the first report of in vivo adaptive optics imaging in cancer-associated retinopathy as correlated with histopathology.

Methods:
A patient with cancer-associated retinopathy (positive anti-retinal autoantibody testing and markedly diminished ERG) was imaged with fundus photography, confocal scanning laser ophthalmoscopy (cSLO) and high-density spectral domain OCT. cSLO images were obtained using infrared (IR) reflectance, blue light fundus autofluorescence (FAF) and IR FAF imaging modes. Adaptive optics scanning light ophthalmoscopy (AOSLO) images were obtained of a ~900 μm^2 region centered on the foveola, and strips extending ~2.5 mm nasally, 2.4 mm temporally, 2.4 mm superiorly and 2 mm inferiorly. One month later, images were acquired of a ~1.3 mm^2 region centered on the foveola. Post-mortem PO sections of formalin-fixed globe were obtained and processed for H&E.

Results:
Relatively normal cone photoreceptors were visible in an elliptical area within the foveola. A narrow band of hypo-reflectivity containing sparse cones separated this central region from a surrounding annular area that contained both normal and abnormal appearing cones. Cone structure was extremely abnormal at 300 µm, with large areas of hypo-reflective cones interspersed with hyper-reflective cones exhibiting irregular morphology. The surrounding retina was relatively hypo-reflective with very few identifiable cones, and clumps of hyper-reflective material extending into the inner retina. Histopathology revealed complete loss of photoreceptor cell nuclei except at the fovea where a single layer of nuclei was seen in the outer nuclear layer with attached cone inner segments. There were migrated RPE cells and melanophages in the atrophic inner nuclear layer.

Conclusions:
This is the first report of in vivo adaptive optics imaging with histopathologic correlation in any disease entity. Our findings validate the ability of AOSLO to identify cone photoreceptor loss in vivo in patients with cancer associated retinopathy.

References: None.

Keywords: Adaptive Optics Imaging, Cancer Associated Retinopathy, Histopathology

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Poster 183

Robust Optic Nerve Head Analysis Based On 3D Optical Coherence Tomography

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Introduction:
Many conditions such as glaucoma (GD), optic neuritis (ON), multiple sclerosis (MS) or idiopathic intracranial hypertension (IIH) affect the optic nerve head (ONH). Optical coherence tomography (OCT) allows 3D ONH imaging. However, current ONH analysis methods work in only atrophic or in swollen ONH but not both. Manual steps for masking Bruch's membrane opening (BMO) or ONH center are regularly required. Our objective was to develop a robust and fully automatic ONH quantification algorithm applicable in atrophic, normal and swollen conditions.

Methods:
Algorithm development based on the following steps. Motion artifacts were corrected. The region of the retinal pigment epithelium (RPE) as leading structure to detect BMO was estimated. The RPE was enhanced and blood vessels suppressed during a filtering sequence. The ONH centroid was then established from the BMO. The optic nerve head volume (ONHV) was derived from the borders of RPE, BMO and inner limiting membrane (ILM) within a 3.4 mm diameter circle around the ONH centroid. The algorithm was tested on ONH volume scans acquired with a Spectralis HD-OCT.

Results:
Scans from 148 eyes of healthy controls, GD patients, MS patients with and without previous ON and IIH patients were processed. The algorithm failed in 4 eyes (2.7%) due to unpropitious position of blood vessels. ONHV showed excellent test-retest reliability in a sub-study including 3 repeated measurements of 11 healthy eyes (intra-class correlation coefficient: 0.984). Finally, ONHV correlated well to the retinal nerve fiber layer thickness provided by the device ($p<0.001$).

Conclusions:
Our algorithm was able to reliably determine BMO dimensions and estimate the ONH centroid. ONHV estimations were robust in both atrophic and swollen ONH conditions. The presented method should therefore serve as a source for several ONH parameters and as a reliable tool to follow-up ONH changes in diseases involving papilledema and ONH atrophy.

References: None.

Keywords: Optical coherence tomography, Optic nerve head, Multiple sclerosis, idiopathic intracranial hypertension, Glaucoma

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Poster 184

Ocular Motility Defects with Concordance Neuroimaging

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Introduction:
Ocular motility defects (OMDs) have various etiologies and comprise one of the most comprehensive differential diagnoses in neuro-ophthalmology. The differential diagnosis of (OMDs) ranges from a benign to a life-threatening cause. MRI or CT of orbit/brain are complimentary to each other and play a significant role in neuro-ophthalmology and neurology evaluation. Typically, MRI is considered the imaging of choice for neuro-ophthalmological assessment, with CT being reserved for disorders involving bone, calcification or those conditions requiring a surgical approach to the bone. We herein present a retrospective review of a series of patients with (OMDs) with concomitant neuro-imaging findings.

Methods:
This is a retrospective review of neuro-imaging studies of patients with (OMDs) seen in our institution and reviewed by a single neuro-radiologist. Patients with (OMDs) secondary to myasthenia gravis, intraocular pathology, functional vision loss and thyroid orbitopathy were excluded.

Results:
Sixty-five patients with (OMDs) with abnormal neuroimaging were identified. Of the 65 patients, 23 (35.4 %) patients had involvement of a single cranial nerve. There were 6 patients (9.2 %) with isolated third nerve palsy due to *Guillain-Barré syndrome* (*GBS*) variant, acute cerebrovascular accident (CVA) *and B-cell lymphoma* . Two patients (3.07%) had isolated fourth nerve palsy due to metastatic renal cell carcinoma and trauma. Fifteen patients (23.07 %) had isolated sixth nerve palsy from CVA, *B-cell lymphoma, leptomeningeal* carcinomatosis (LC), metastasis, glioblastoma multiforme (GBM), Chiari I malformation, multiple sclerosis and neurosarcoidosis. Twenty-six patients (40%) had multiple cranial nerve involvement due to CVA, trauma, cavernous meningioma, *lymphoma, LC*, metastasis, and GBM. Seven patients (10.76%) had nystagmus and 6 patients (9.23%) had gaze palsies due to CVA, trauma, and pineoblastoma. There were 3 patients (4.61%) with idiopathic muscle atrophy associated with trauma.

Conclusions:
Our findings highlight the value of advanced neuro-imaging in the early diagnosis and localization of the various causes of (OMDs).

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Keywords: Neuro-Imaging, Ocular Motility Deficit, Neuro-Rdiology And Neuro-Ophthalmology, Concordance Neuroimaging, Diplopia And Neuro-Imaging

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Poster 185

Mural Enhancement of the Intracranial Internal Carotid Artery in Giant Cell Arteritis

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Introduction:
While autopsy studies of patients with giant cell arteritis (GCA) have demonstrated inflammatory involvement of the internal carotid artery (ICA), radiologic signs of ICA inflammation have not been a prominent feature in the published literature. We present three patients with biopsy-proven GCA who demonstrated evidence of mural enhancement of the intracranial ICAs by magnetic resonance imaging (MRI).

Methods:
Retrospective review of 64 patients with biopsy-proven GCA. Contrast-enhanced cranial MRI was performed in 11 of these patients. The appearance of the ICAs was compared to normal controls.

Results:
Three GCA patients demonstrated bilateral mural enhancement of the cavernous portion of the ICA. Patient 1 was a 64-year-old woman who presented with jaw pain and headaches, followed by vision loss to no light perception (NLP) in the left eye due to anterior ischemic optic neuropathy (ION) and visual field loss in the right eye due to posterior ION. She concurrently suffered a myocardial infarction, likely related to GCA. Patient 2 was a 79-year-old female who suffered anterior ION of the left eye and subsequently developed anterior and posterior ION of the right eye several days after initiation of high-dose steroid treatment, resulting in bilateral NLP vision. Patient 3 was a 75-year-old male who presented with bilateral sixth nerve palsies and headaches. In addition to the abnormal ICA findings, all patients demonstrated bilateral enhancement of the orbital fat or optic nerve sheaths.

Conclusions:
Mural ICA enhancement on MRI is not a typical finding in GCA, but its presence may portend a more severe disease course and warrant aggressive treatment.

References: None.

Keywords: Vascular Disorders, Neuroimaging, Neuro-Ophth & Systemic Disease, Optic Neuropathy

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Poster 186

Morning Glory Disk Anomaly Associated with Absence of Intracranial Internal Carotid Artery

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Introduction:
Morning glory disk anomaly (MGDA) has been associated with numerous other congenital malformations including intracranial vascular abnormalities(1). The latest have been noticed in as many as 45% of cases (2), ranging from segmental narrowing of the Circle of Willis to complete stenosis of the internal carotid artery. We report a case of MGDA associated with agenesis of the intracranial internal carotid artery (ICA).

Methods:
A13 year old female presented for progressive visual loss in the left eye. Her vison was best corrected to 20/20 OD and 20/25 OS (-1.25D OU). She had +1 RAPD OS with full color vision and normal, symmetrical anterior segment examinations. Fundus examination was normal except for an anomalous optic disk OS, funnel shaped with peripapillary atrophy and central gliosis overlying the central retinal vessels. The visual field was full OD and had an enlarged blind spot OS. A diagnosis of morning glory disk anomaly (MGDA) OS was made and MRI/MRA was ordered.

Results:
MRI/MRA demonstrated complete absence of the right intracranial ICA with the right middle cerebral artery receiving flow directly from the basilar artery and the right anterior cerebral artery from the left anterior circulation. The rest of the circulation was normal without evidence of vascular stenosis or hypertrophied lenticulostriate vessels to suggest moyamoya.

Conclusions:
To our knowledge this is the first case report of a congenitally absent intracranial portion of ICA associated with MGDA. Due to the high risk of vascular and structural brain anomalies and risk of stroke, bleeding and seizures, all patients with MGDA should undergo MRI/MRA or computerized tomographic angiography.

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Keywords: Congenital Disk Anomaly, Intracranial Vascular Malformation

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Poster 187

Measurement of Optic Nerve Sheath Diameter by CT, MRI and Ultrasound

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Introduction:
Quantification of the optic nerve sheath diameter (ONSD) is a promising approach for detection of elevated intracranial pressure. The comparability of current methods is unclear. The objective of this study was to assess the relationship between ONSD as measured with CT, MRI and ultrasound (US) in patients without known optic nerve disease or increased intracranial pressure.

Methods:
15 patients (60.8 [y] ±16.73 SD; 7 female) with paranasal sinus pathology in whom CT and MRI were performed underwent ONSD measurements by US, as well as an ophthalmological examination. US-, CT- and MRI-derived maximal ONSD values 3mm behind the globe were compared.

Results:
ONSD measured (n=30) by US (mean 6.2 [mm] ±0.84 SD) were significantly ($p<0.01$) higher than ONSD in CT (5.2 ±1.11) or MRI (5.3 ±1.14). There was no significant ($p=0.24$) difference but good correlation ($\rho=0.854$, $p<0.01$) between ONSD measured in CT and MRI. Those of US and CT ($\rho=0.662$, $p<0.01$) and US and MRI ($\rho=0.615$, $p<0.01$) showed a modest but significant correlation.

Conclusions:
The comparability of ONSD measurements in patients without known optic nerve disease and assumed normal intracranial pressure appears to be given between CT and MRI while comparability between US and CT or MRI seems to be less reliable.

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Keywords: Optic Nerve Sheath Diameter, Computer Tomography, Magnetic Resonance Imaging, Ultrasound

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Poster 188

Occipital Partial Status Epilepticus With Abnormal MRI Imaging

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INTRODUCTION: A healthy female presented with acute visual phenomenon suspicious for complex migraine. Further work up revealed an occipital simple partial status epilepticus on EEG and changes on MRI brain.

METHODS: Case presentation.

RESULTS: A 30 year old woman presented with a three day history of seeing a large colorful and spinning beach ball intermittently appearing in her right peripheral vision associated with frontal headache, nausea and vomiting. Visual field testing revealed a right homonymous hemianopia. MRI brain showed subtle diffuse abnormal T2 and FLAIR signal involving the left occipital cortex and extending to the left parieto-occipital and temporo-occipital junctions which was more obvious on a follow up scan done about 10 days after symptom onset. Video-EEG monitoring confirmed electrographic seizures arising from the left posterior quadrant. Detailed laboratory tests including CSF studies were unremarkable. She was treated with levetiracitam. She stopped having clinical seizures. The EEG normalized about a month and a half since onset of symptoms. Abnormalities noted on the MRI brain completely resolved.

CONCLUSIONS: Complex migraine versus transient ischemic attack versus seizure is always in the differential of any transient neurologic deficit. An abnormal EEG helped in the diagnosis. MRI findings due to status epilepticus often suggest a combination of cytotoxic and vasogenic edema, however it is unclear why only certain patients show MRI changes.

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Keywords: none

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Poster 189

Neuro-Imaging Characteristics of Common Extraocular Prosthetic Devices

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Introduction:
With more implantable ophthalmic devices available, there is an increased risk that implanted ophthalmic hardware will be misidentified on imaging studies performed for non-ophthalmic indications. The purpose of this study is to describe the neuroimaging characteristics of common extraocular prosthetic devices, including gold weight eyelid implants and common glaucoma drainage devices, and the complications associated with these devices.

Methods:
A retrospective chart review was performed to identify patients who had undergone both an ophthalmic procedure involving an implanted device and a neuro-imaging study performed for a non-ophthalmic condition.

Results:
CT: 1) Axial CT shows prominent beam hardening artifact resulting from the implanted gold eyelid weight. 2) Axial and coronal NECT displays a Molteno implant. 3) Axial NECT in a Ahmed valve implant. Note the plate as a dense curvilinear structure, and the valve as a small focus of low density. 4) Axial NECT of a Baerveldt drainage implant. Note the endplate as a dense curvilinear plate with fenestration.
MRI: 1) Sagittal and coronal MRI shows a gold weight sutured to the anterior tarsal plate of the left eyelid. 2) Coronal and axial MRI with and without contrast in a case of Ahmed valve show hypointense fluid collection around the the plate of the valve within the conjunctival pocket. No abnormal enhancement is seen.
Complications: 1) Infection is a complication of implanted valves. MRI is the best imaging modality for this diagnosis. Axial MRI show abnormal enhancement involving the preseptal and retrobulbar regions. 2) Giant reservoir formation has been reported with Ahmed valve. Large reservoirs may cause mass effect and impaired extraocular muscle movements. Coronal and sagittal NECT images show a relatively large fluid collection surrounding the Ahmed valve.

Conclusions:
These cases demonstrate the different appearances of gold weight eyelid implants and multiple glaucoma drainage devices. Increased communication and cross-specialty educational events between ophthalmologists and radiologists may result in more accurate interpretation of neuro-imaging studies that involve implanted ophthalmic devices.

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Keywords: Neuroimaging

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Poster 190

A Lion In The Bush

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Introduction:
Extrarenal rhabdoid tumors of the thorax and mediastinum are rare, highly aggressive neoplasms with a poor prognosis. We describe a 3 month old child who presented with left arm weakness and left Horner's syndrome from an extrarenal rhabdoid tumor at the left thoracic inlet.

Methods:
Single case report

Results:
A 3 month old girl presented with left arm weakness noticed 4 days earlier and left upper eyelid swelling noted 11 days earlier. CT head and left clavicle Xray elsewhere did not reveal abnormalities. She was born full term via difficult labor and vacuum suction. Developmental milestones were appropriate for age. An inflammatory verrucous epidermal nevus (ILVEN) involving her left gluteal region was noticed two weeks after birth. At presentation the infant had flaccid left arm weakness with reduced deep tendon reflexes. Neuro-ophthalmic exam revealed central, steady and maintained fixation in both eyes, a left Horner's pupil without heterochromia and normal eye exam otherwise. When crying, flushing was noted only on the right half of her face.
A general exam revealed a palpable non-tender firm left supraclavicular neck mass that was missed by the emergency room doctors. Contrast enhanced neck MRI revealed a large solid enhancing mass measuring 5.5 x 4 X 7 cm at the thoracic inlet that encroached the left C7-T1 neural foramen causing mild cord deformity, engulfed the left common carotid artery and large pulmonary metastasis. Carcinoembryonic antigen, alpha fetoprotein, B- HCG, urine homovanillic acid and vanillymandelic acid levels were normal. Biopsy showed extra-renal malignant rhabdoid tumor with lymphovascular invasion. Despite starting chemotherapy she developed progressive respiratory failure from pneumothorax with increasing tumor burden. Care was withdrawn and she passed away after terminal extubation.

Conclusions:
Extrarenal Rhabdoid tumors are highly aggressive tumors which may have metastatic disease at the time of presentation. It remains uncertain if earlier referral could have changed the prognosis.

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Keywords: Extrarenal Rhabdoid Tumor, Horner's Syndrome, Inflammatory Verrucous Epidermal Nevus, Metastasis, Pneumothorax

Financial Disclosures: The authors had no disclosures.

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Poster 191

Why the Delay in Diagnosis? Increased Time From Symptom Onset to Diagnosis in Blepharospasm: A Prospective, Clinic-Based Study

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Introduction:
Blepharospasm is a debilitating dystonia shown to affect quality of life, mood, and sleep quality [1,2,3]. With proper diagnosis, early treatment with botulinum toxin dramatically improved symptoms and quality of life [4,5]. Older studies showed unacceptable lag times from symptom onset to diagnosis prolonging the time to acceptable treatment [6,7]. Despite improved education, we noticed many patients presenting with incorrect diagnoses or on inappropriate treatments. The aim of this study was to explore time from symptom onset to correct diagnosis to evaluate how physician education has changed since initial studies in the United States.

Methods:
A structured questionnaire was administered to consecutive patients with blepharospasm presenting to outpatient tertiary care clinics. Information was gathered from each participant including length of time from symptom onset to diagnosis, types and numbers of providers seen prior to diagnosis, and treatments administered prior to receiving botulinum toxin.

Results:
The study enrolled 72 patients with blepharospasm. Average age was 66.2, (F:M=2.4:1). Mean time from symptom onset to diagnosis was 25.6 months--the delay was over 3 years in 21% of patients. At initial presentation with symptomatology, only 2 patients (3%) were diagnosed correctly, mean number of physicians seen before diagnosis was 3.1. For those diagnosed in the 5 years prior to enrollment, the lag time was 25.5 months with no statistically significant difference before this time (t-value=.193, t>.001).

Conclusions:
Despite classic presenting signs easily identifiable by simple history and examination, a significant lag time to diagnosis exists. It is common for patients with this disease to see multiple providers, receive ineffective treatments, and suffer from symptoms for over a year prior to correct diagnosis. Improved education and awareness with help patients obtain correct diagnosis and treatment more efficiently.

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Keywords: Blepharospasm, Dystonia

Financial Disclosures: Grants as discussed in the abstract.

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Poster 192

Atypical Presentation of Orbital Lymphangioma.

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Introduction:
Orbital lymphangiomas are vascular orbital anomalies, representing less than 4% of all space-occupying orbital lesions, which most frequent forms of presentation are proptosis and hemorrhagic episodes.

Methods:
Review of medical history of a patient with pulsatile progressive enophthalmos associated with compressive optic neuropathy and diplopia. Review of the literature.

Results:
A 29-year-old woman who developed a long-term left orbital enophthalmos, but in the last 4-months became progressive pulsating enophthalmos, positive to Valsalva manoeuvre, associated with restrictive diplopia and compressive optic neuropathy, with best corrected visual acuity (VA) 1.0 in the right eye, and 0.7 in her left eye with a clear RAPD and color vision impairment. Orbital CT and MRI scanning were performed, obtaining lytic signs in orbit, in communication with anterior cranial cavity, with an isodense extra and intraconal contrast-enhanced tissue with tortuous structure and intralesional calcifications. Due to the intensification of the symptoms and signs in the physical examination, RAPD and worsening in VA due to the optic nerve compression, she was remitted to neurosurgery to undergo surgical treatment immediately. Since it was a great diameter lesion, associated with oculomotor impairment and optic neuropathy, transcranial access was performed.The patient rapidly recovered from her compressive optic neuropathy, esthetical improvement of her pulsatile enophthalmos, but diplopia persisted.The hystopathology exam revealed the tumor was a cystic lymphangioma, and CT scanning performed after surgery revealed residual lessional tissue.

Conclusions:
Although orbital lymphangiomas are bening tumors, and the most frequent form of presentation is with proptosis, in this case the onset was atypical. The early diagnosis of this entity should prevent further complications not only in the VA, but in the risk of morbidity that they may lead to if not treated.

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Keywords: Orbit/Ocular Pathology, Tumors, Ocular Motility, Optic Neuropathy, Adult Strabismus With A Focus On Diplopia

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Poster 193

Prospective Assessment of Peri-Oral Weakness Following Peri-Orbital Botulinin Toxin for Blepharospasm.

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Introduction:
In our experience performing peri-orbital injections of botulinin toxin for benign essential blepharospasm (BEB) we have encountered three patients who have experienced persistent ptosis of the upper lip. Notably, these patients have not had injection of any of the apparently weakened peri-oral musculature.. In addition, this appears to be possibly chronic, as the individuals affected have continued to experience lip ptosis even as their blepharospasm symptoms return and they require additional injection, typically at 3-4 month intervals. There are reports of botulinin toxin unmasking previously subclinical myasthenia, although these patients we are describing have never developed any other symptoms of myasthenia. There is a single case series identified in our literature review of three patients who experienced transient lip ptosis following injections done for cosmetic treatment of “crow’s feet.” (Mararasso 2001). To our knowledge, a prospective study to assess for the incidence of this particular side effect has not been undertaken.

Methods:
Patients are enrolled from the eye clinic during routine visits. Patients with conditions other than BEB are included as controls. Patients with myasthenia, history of stroke, history of Bell’s Palsy, and other conditions affecting the facial muscles are excluded from the study. Photographs of the patients at rest and in six different facial expressions are taken, to examine frontalis, orbicularis occuli, risorius, zygomaticus, and orbicularis oris muscles. The SunnyBrook scale (Neely 2010) is used in accompaniment of the photos to assess each patient’s degree of facial weakness qualitatively. Quantitative assessment is graded using the Lip Length and Snout Indices (Janson, 1990). Observers will be blinded to which patients are from the BEB populations and which are from non BEB controls.

Results:
This study is presently ongoing.

Conclusions:
No conclusions are known yet. Our goal is to catalogue the incidence and severity of this as yet largely unreported side effect.

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Keywords: Blepharospasm, Botulinin, Peri-Oral, Weakness

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Grant Support: None.

Poster 194

Vertical Diplopia And Ptosis From Removal Of The Orbital Roof In Pterional Craniotomy

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Introduction:
We describe a newly recognized clinical syndrome consisting of ptosis, diplopia, and limited vertical ductions that occurs following orbital roof removal during orbital-zygomatic-pterional craniotomy.

Methods:
Review of patient records of a single neuro-ophthalmologist from 1998 to 2013 identified 8 patients with persistent vertical diplopia after surgery. In all cases the orbital roof was removed to gain better access to the anterior cranial fossa. The operative report, CT or MRI imaging, intracranial pathology, neurovisual exam, ocular deviation, and degree of ptosis were recorded. Subsequent treatment and patient outcome were documented.

Results:
Eight patients had neuro-ophthalmic findings after pterional craniotomy for meningioma removal or aneurysm clipping. The cardinal features were ptosis, limited elevation and hypotropia. Three patients also had limitation of downgaze and two had limitation of abduction. Imaging showed loss of the fat layers which normally envelop the superior rectus/levator palpebrae superioris. The muscles appeared attached to the defect in the orbital roof. Ptosis and diplopia developed in two patients despite Medpor titanium mesh implants. Deficits in all patients showed spontaneous improvement. Two patients underwent a levator advancement for ptosis repair. In three patients an inferior rectus recession using an adjustable suture was performed to treat vertical diplopia. Follow-up a mean of 6.5 years later revealed that all patients had a slight residual upgaze deficit, but alignment was orthotropic in primary gaze.

Conclusions:
After pterional craniotomy, ptosis, diplopia and vertical gaze limitation can result from tethering of the superior rectus/levator palpebrae superioris complex to the surgical defect in the orbital roof. Lateral rectus function is sometimes compromised by muscle attachment to the lateral orbital osteotomy. This syndrome occurs in about 1% of patients after removal of the orbital roof and can be treated, if necessary, by prism glasses or surgery.

References: None.

Keywords: Ptosis, Diplopia, Pterional Craniotomy, Gaze Restriction

Financial Disclosures: The authors had no disclosures.

Grant Support: National Eye Institute

Poster 195

Treatment of Rivaroxaban Associated Orbital Hemorrhage

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Introduction:
An elderly man awoke with severe pain and bruising of right periocular area. He had taken his usual rivaroxaban the nght before and reported no trauma. CT scanning showed a an orbital hemorrhage. HIs ocular pressure was in the mid thirties and did not respond to glaucoma medications or subsequent canthotomy.Treatment with an antagonist to rivaroxaban was carried out after transfer to my institution. Discussion of the mechanism of rivaroxaban's efficacy and the use of an antagonist drug that is usually used to reverse cardiac -related anticoagulation will be discussed .

References: None.

Keywords: Rivaroxaban And Orbit Hemorrhage

Financial Disclosures: The author had no disclosures.

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Poster 196

Stonewalled: Bilateral Sequential Vision Loss in a Peritoneal Dialysis Patient

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Introduction:
We present a patient with biopsy proven calcific uremic arteriolopathy causing a bilateral anterior ischemic optic neuropathy (AION).

Methods:
A 66-year-old white man who was hospitalized for aortic stenosis leading to congestive heart failure presented with bilateral sequential painless vision loss of the left eye and then the right eye separated by 6 weeks. He had a history of end-stage renal disease on peritoneal dialysis secondary to essential hypertension and type 2 diabetes mellitus as well as left lower extremity deep vein thrombosis, secondary hyperparathyroidism, hyperlipidemia, hypothyroidism and benign prostatic hypertrophy. Outside ophthalmology found erythrocyte sedimentation rate (ESR) of 150 and treated with intravenous and then oral corticosteroids following loss of left eye vision. He had also developed a necrotic penile ulcer 2 weeks prior to admission and firm skin nodules of the lower extremities while admitted with X-rays showing extensive vascular calcifications.

Results:
Neuro-ophthalmological examination was remarkable for acuity 20/70 OD and count fingers OS with a right relative afferent pupillary defect. Visual field testing revealed inferior altitudinal and superior nasal step loss OD with an inferior nasal step OS. Fundus examination was remarkable for right optic nerve edema. ESR was 82 mm/hr with C-reactive protein of 1.42 mg/dL. Prednisone was increased to 80 mg daily empirically. Temporal artery biopsy could not be performed due to other illnesses. MRI of the brain and orbits and lumbar puncture were unremarkable. Review of laboratory results revealed worsened phosphatemia compared to one year prior with a calcium-phosophorus product of 63 mg*mg/dL/dL on admission. The patient died from heart failure while hospitalized. Subsequent autopsy showed extensive vascular calcification. These findings confirmed the presumptive diagnosis of calcific uremic arteriolopathy imitating giant cell arteritis.

Conclusions: Calcific uremic arteriolopathy should be suspected in chronic kidney disease patients presenting with anterior ischemic optic neuropathy.

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Keywords: Calcific Uremic Arteriolopathy, Chronic Kidney Disease, Vascular Calcification, Ischemic Optic Neuropathy, Giant Cell Arteritis.

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Poster 197

Allergic Fungal Sinusitis Mimicking Thyroid Orbitopathy

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Introduction:
22-year-old African-American man presented to our clinic with complaint of tearing and proptosis of both eyes along with occasional blur in the right eye. His medical history is significant for asthma, which is well controlled. His mother has a history of Grave's disease with exophthalmos. Examination was notable for optic neuropathy of the right eye and significant exophthalmos both eyes.

Methods:
Case Report.

Results:
Thyroid labs were normal. Neuro-imaging revealed expansion and opacification of all paranasal sinuses with intracranial and intraorbital extension. Patient underwent oral steroid treatment followed by nasal endoscopy procedure with sinusectomy, sinusotomy and mucous membrane removal. Mucous samples sent to pathology for analysis. GMS stain highlighted abundant branching fungal hyphae.

Conclusions:
The purpose of this submission is to present a case of progressive exophthalmos with associated optic neuropathy caused by advanced allergic fungal sinusitis. This clinical entity, while rare, can cause serious ophthalmic complications that can be reversed if prompt diagnosis and treatment are initiated. The unique radiographic appearance of this process is also highlighted. Allergic fungal rhinosinusitis is a form of fungal sinusitis that is noninvasive and has higher incidence in the southern and southwestern US. While diagnostic criteria have been established, treatment both medical and surgical remains a challenge.

References: None.

Keywords: Orbit Pathology, Allergic Fungal Sinusitis, Optic Neuropathy

Financial Disclosures: The authors had no disclosures.

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Poster 198

Optic Nerve Sheath Meningioma. No Longer Impossible But Still Difficult.

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Introduction:
In 1977 while talking about the difficulty in identifying small meningiomas involving the orbital apex, optic nerve sheath, and canal Susac, Smith, and Walsh wrote an article entitled “The Impossible Meningioma.” The advent of CT scanning (allowing identification of enlarged optic nerve sheath and calcification) substantially improved the situation and the subsequent advent of MRI scanning with gadolinium and fat sat further advanced diagnostic armamentarium. In spite of these advances, optic nerve sheath meningiomas are often discovered after substantial delay. The fact that fractionated radiation therapy may substantially improve the prognosis underlies the importance of timely diagnosis and referral.

Methods:
Retrospective analysis of 7 cases of optic nerve sheath meningiomas with substantial diagnostic delay

Results:
In several cases significant progressive visual loss occurred during the 1-10 year delay in diagnosis. Some of these reversed with radiation therapy. Several conclusions could be drawn regarding the reason for the diagnostic delay.

Conclusions:
1. Lack of ordering imaging studies often due to an alternative diagnosis such as AION or papillitis.2. Lack of appropriately directed imaging (head scans instead of orbital scans, the lack of employment of fat sat and gadolinium).3. Miss-reading requiring reinterpretation.4. Misinterpretation of OCT data because blocked axonal transport masks development of optic atrophy.

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Keywords: Optic Nerve Sheath Meningioma, MRI, OCT, Radiation Therapy, Imaging

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Grant Support: None.

Poster 199

An Advanced Pancoast Tumor Masquerading as Congenital Hereditary Ptosis

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Introduction:
We present a patient with a stage IV Pancoast tumor which masqueraded as worsening congenital hereditary ptosis.

Methods:
A 69-year-old male presented complaining of progressively worsening drooping of his eyelids. He stated that his eyelids had always been droopy and weak, since early childhood. Family history was significant for multiple family members with ptosis and resultant surgical repair. On examination, anisocoria with subtle miosis of the left eye and ptosis of both eyes (left > right), was found, with a measured MRD1 of -1 OD and an MRD1 of -4 OS. Apraclonidine testing confirmed Horner's syndrome. Slit lamp examination showed bilateral nuclear sclerosis with narrow angles by Van Herick's and dilated fundoscopic exam was unremarkable. The patient's past social history was significant for smoking. The past medical history was significant for a recent episode of bronchitis with a negative CXR that was treated successfully with antibiotics, and for a recent palpable nuchal lymph node.

Results:
Chest CT was suspicious for an apical sulcus tumor in the medial aspect of the left apex. PET scan was remarkable for FDG avid left apical soft tissue density, several FDG avid thoracic lymphadenopathies, multiple FDG avid bilateral pleural nodules, multiple FDG avid mesenteric/retroperitoneal lymph nodes in the abdomen and pelvis, FDG avid peritoneal nodules, and intensely FDG avid L3 and L4 vertebral body lesions that were all consistent with metastatic disease. A biopsy of the left scalene axillary node revealed a granulomatous adenocarcinoma that was cytokeratin and thyroid transcription factor-1 positive, further suggesting a Pancoast tumor as the cause of this primary pulmonary adenocarcinoma. The patient was determined to have a stage IV pancoast tumor.

Conclusions:
This stage IV Pancoast tumor likely presented at such a late stage, due to the clinical picture of this patient with long standing ptosis and dark iris pigmentation that masked his diagnosis.

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Keywords: Pancoast, Ptosis, Anisocoria, Adenocarcinoma

Financial Disclosures: The authors had no disclosures.

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Poster 200

It's All Going Dark!

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Introduction:
Restricted diffusion on diffusion-weighted imaging (DWI) has been noted in brain parenchymal lymphomas. It has been reported in ischemic, inflammatory and adult compressive optic neuropathies, but has not previously been reported in pediatric lymphomatous optic neuropathy.

Methods:
Case report and review of literature.

Results:
We present a case of a 6-year-old girl with past medical history of Hemophagocytic lymphohistiocytosis (HLH) and peripheral T-cell lymphoma who reported "blurry vision in her left eye" for 2 weeks. Her corrected VA was 20/20 OD and 20/200 OS with decreased color vision and afferent papillary defect in the left eye. Dilated fundus examination revealed unremarkable fundus appearance in the right eye with florid left optic nerve swelling, diffuse pallor and peri-papillary hemorrhages. MRI of the brain and orbits showed left optic nerve thickening and enhancement extending to the orbital apex. Axial DWI reveals high signal in the left intraorbital optic nerve while ADC map demonstrating a corresponding region of darkness indicating restricted diffusion. Lumbar puncture revealed opening pressure of 38.5 cm H_2O, negative for malignant cells or infectious agents. Diamox 250 mg bid was initiated. Patient received 6 Gy in 3 fractions to the left orbit and 2-3 weeks later received whole brain irradiation getting 18 Gy in12 fractions with an additional 6 Gy in 3 fraction boost to the left orbit with weekly intrathecal triple chemotherapy. On 2 week follow up, her VA improved to 20/20 OD 20/60 OS with the persistence of left APD and left dyschromatopsia.

Conclusions:
Restricted diffusion in the optic nerve has been previously suggested to augur a poor visual outcome, even in inflammatory or neoplastic conditions. Our case suggests that prompt diagnosis and treatment of infiltrative neuropathy may result in visual recovery in a pediatric patient even in the presence of restricted diffusion.

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Keywords: Lymphoma, Ischemia, lymphohistiocytosis, Hemophagocytic

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 201

***Bartonella Henselae*-Associated Neuroretinitis with Orbital Intraconal and Optic Nerve Sheath Involvement**

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Introduction:
We present clinical, radiological and histopathological findings of a patient with neuroretinitis, with positive *Bartonella henselae* IgM and an indeterminate QuantiFERON-TB Gold In-Tube (QFT-GIT) test, who developed orbital intraconal and optic nerve sheath inflammation. This is the first report of intraconal inflammation prompting optic nerve sheath fenestration (ONSF) in association with *B. henselae* infection.

Methods:
Retrospective chart and literature review.

Results:
A 48-year-old male presented with a central scotoma of his left eye (OS). Past medical history included ulcerative colitis, primary sclerosing cholangitis, and recent right eye scleritis and prostatitis. One month prior, an inguinal lymph node biopsy for diffuse lymphadenopathy was negative for malignancy. Visual acuity was count fingers OS, without a frank relative afferent pupillary defect (rAPD). Fundus exam revealed significant disc edema, an inferotemporal perivascular choroidal mass and a serous retinal detachment OS. Subsequent MRI brain demonstrated enhancement of the left intraconal soft tissue and anterior optic nerve sheath. The following day, his left eye exhibited an rAPD, omnidirectional limitation of movement, elevated intraocular pressure, ptosis, proptosis and conjunctival injection with chemosis. Given the patient's severe loss of vision and progression, he underwent ONSF and orbital biopsy. Intraoperatively, there was a paucity of intraconal fat, with dense fibrinous white tissue and cartilaginous-like material in the intraconal orbit. Histopathology revealed dense fibroconnective tissue. Extensive laboratory evaluation revealed elevated *B. henselae* IgM titers (1:40, then 1:80). IgG was negative. Repeated indeterminate QFT-GIT results due to a low response in the mitogen control tube suggested an immunocompromised state. The late funduscopic finding of a macular star was consistent with the presence of a neuroretinitis. Previous reports have described inflammatory masses of the optic nerve head and retrobulbar optic neuritis in bartonellosis, however none have reported intraconal soft tissue involvement.

Conclusions:
Intraconal soft tissue inflammation may be another vision-threatening manifestation of *B. henselae* infection.

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Keywords: Neuro-Ophth And Infectious Disease, Orbit/Ocular Pathology, Optic Neuropathy, Retina, Neuroimaging

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Poster 202

Impact of Injection Site on Dose Escalation in the Treatment of Blepharospasm

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Introduction:
Blepharospasm is a common debilitating condition that can limit a patient's ability to read, drive or work productively. While paralytic toxoid injections have been considered the treatment of choice for this condition, very little data exists to guide practitioners on the most effective ways to administer this therapy. We hypothesize injection site location may impact the dose amount required to achieve symptom resolution.

Methods:
We performed a retrospective review based on billing codes for botulinum toxin injections, cross-referenced with codes for patients with blepharospasm on the neuro-ophthalmology service at an academic institution from January 2009 to September 2014. Patients with <8 treatments were excluded from consideration. Toxoid injection sites were then categorized as either superior to the lid crease (Method 1), or between the superior lash line and lid crease (Method 2). Injection site, dose, and date of treatment were documented for each patient.

Results:
We identified 31 patients who met the selection criteria above. Our results revealed a statistically significant difference ($p = 0.019$) between patients treated by Method 1 (30 dose escalations) compared to Method 2 (6 dose escalations). Furthermore, there was a trend of dose reduction in patients switched from Method 1 to Method 2, though the number of patients switched was too small to be significant.

Conclusions:
Preliminary data indicates that injection site selection impacts dosages for successful treatment of blepharospasm patients. Patients who were treated with Method 2 were able to maintain or decrease the amount of toxoid needed to achieve symptomatic improvement, whereas patients treated with Method 1 experienced more frequent escalations in injection amount. This study suggests a preferred method for botulinum toxoid injections for the effective treatment of blepharospasm.

References: None.

Keywords: Blepharospasm, Injections

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 203

A Case of Nasopharyngeal Carcinoma Masquerading as Primary Orbital Tumour

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Introduction:
Nasopharyngeal Carcinoma (NPC), although rare in North America, is a common malignancy in Southeast Asia and Southern China. Ophthalmic manifestations of NPC include isolated or multiple cranial nerve palsies, orbital apex or cavernous sinus syndromes, papilloedema or unilateral optic disc swelling.

Methods:
We report a rare case of NPC masquerading as a primary orbital tumour.

Results:
The patient is a 34 year old Chinese gentleman who first presented at a foreign hospital with right sided facial numbness. He was seen by a Neurologist and the MRI (Brain) performed was reported as normal. He gradually developed symptoms of dry eye, diplopia and right proptosis over the next couple of months and an MRI (Orbits) was later performed. MRI (Orbits) showed a lesion in the right orbital apex, extending into the infratemporal fossa, pterygoid muscle and lateral sphenoid wall. A right lateral orbitotomy and biopsy was performed, with histology reported as squamous cell carcinoma. A right orbital exenteration was subsequently planned, following which the patient came to our centre to seek a second opinion. A multidisciplinary team was involved in the management of this patient at our centre. The otolaryngologist in the team performed a nasoendoscope and noted that the posterior nasal space was normal looking. A blind biopsy was nontheless taken and subsequently returned positive for non-keratinizing undifferentiated NPC. The patient was subsequently treated with chemotherapy and radiotheapy.

Conclusions:
We report a rare case of NPC masquerading as a primary orbital tumour. A high level of suspicion should always be maintained for atypical presentations of primary orbital tumours.

References: None.

Keywords: Nasopharyngeal Carcinoma, Orbital Mass

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 204

Visual Field and Graves Ophthalmopathy

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Introduction:
Whether primary or secondary to thyroid disease, Graves' ophthalmopathy is surprising by its evolution despite correct treatment. Transformation to acute mode may occur very quickly. Focal signs (edema, proptosis) and oculomotor signs (diplopia) are likely to alert physician. Visual field, as the indicator of optic nerve function appears to be an excellent element to monitoring disease progression.

Methods:
With analysis of several clinical cases we try to assess the risk of transformation of the evolutionary mode to enable a finer monitoring of this disease

Results:
Visual fields analysis shows that its alterations are often a sign of fat or muscular intra orbital change . Sometimes alterations are linked with superficial corneal involvement (drought, superficial punctate keratitis,corneal abcess). Association with another disease of optic nerve (glaucoma), is possible, thought quite rare, while many patients with ocular hypertension are frequent . After initiation of corticosteroid therapy bolus, it is surprising to see a high recovery rate.

Conclusions:
Graves ophthalmopathy neuropathy remains a dreaded complication. Corticosteroid therapy in bolus is, according to us, the treatment of choice and allows us to get frequent ameliorations. Central visual field is a method for reliable monitoring

References: None.

Keywords: Graves (Systemic Disease), Optic Neuropathy, Perimetry, Visual Fields

Financial Disclosures: The authors had no disclosures.

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Poster 205

Veps To Lateralized Stimuli To Measure The Interhemispheric Transfer Time (IHTT)

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Introduction:
To evaluate in a population of normal subjects the VEPs to lateralized stimuli to measure the interhemispheric transfer time (IHTT), and methodological variability factors.

Methods:
We recorded in 36 young right-handed women evoked responses of visual occipital regions right (O2) and left (O1) in response to visual stimulation achieved through a screen with checkerboards alternants either in open fields, or half-fields when the line of sight coincides with a central focus. The test is performed in monocular eye test is chosen by lot with balancing choices, not to have any effect of precession. The atmosphere is scotopic total. The reversal of checkerboard is carried out at a frequency of 1.7Hz. Depending on the distance, the size of the checkerboard is 1 °.Were recorded average of 100 traces for each lead, during two successive series.

Results:
The results are presented according to three factors analyzed: the eye, the conditions (reproducibility and effect number), the observer. For stimulation in the full field, there is no effect or observer eye for the latencies of waves N75 and P100, and no effects eye or averaging effect for the latency of the N135 wave. For the half-full stimulation, there is no eye effect, or observer reproducibility, but there is a half-full field effect in the left eye. For TTIH, there is no significant difference between half-full fields, or effect or observer reproducibility, but there is an effect eye. Linear regression was highly significant between the P100 and TTIH.

Conclusions:
The VEPs to lateralized stimuli seem a good method to calculate the IHTT, with good reproducibility and a minimal observer-effect. Further work on patient disease would be interesting to screen for a prolonged IHTT in inflammatory demyelinating CNS.

References: None.

Keywords: Visual-Evoked Potentials (Veps), Half-Full Stimulation (To Lateralized Stimuli), Interhemispheric Transfer Time (IHTT), P100, Posterior Afferent Visual Pathway

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Poster 206

The Heidenhain Variant of Creutzfeldt-Jakob Disease

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Introduction:
Creutzfeldt-Jakob disease (CJD) presents with ataxia, dementia, and myoclonus prior to ophthalmologic symptoms. The Heidenhain variant is different. Below are two cases presenting with initial visual symptoms emphasizing the critical role of ophthalmology.

Methods:
A 66-year-old male presented to an optometrist with photophobia. Examination only revealed a right homonymous hemianopsia. Initial work up was for a cerebrovascular accident based on an intial MRI read as a “left parieto-occipital infarct.” With progressive cognitive decline, he was referred for further work up. Ophthalmology consultation revealed only a right homonymous hemianopia as before. Ophthalmology’s clinical suspicion for CJD, coincided with neurology’s findings of rapidly progressive dementia. Repeat MRI revealed faint cortical changes on diffusion weighted imaging in the left frontal temporal and occipital cortex. EEG changes and cerebrospinal fluid (CSF) positive for tau and 14-3-3 protein confirmed the clinical suspicion of the Heidenhain variant of CJD. 53-year-old male presented with “difficulty focusing” prompting referral for cataract surgery. Exam revealed mild central vision loss, color desaturation and perimetry showing a right homonymous field defect. Initial MRI was read as normal. Repeat MRI brain and discussion with the neuroradiologists revealed cortically-based diffusion abnormalities in the left hippocampus, caudate heads, occipital and temporal lobes. Ophthalmic and imaging suspicion for CJD prompted admission, although overt neurologic findings were lacking. EEG changes and CSF positive for tau, 14-3-3 protein, and RT-QuIC confirmed clinical suspicion. Within a month, he passed with rapid decline in neurologic and cognitive status.

Results:
Heidenhain variant CJD

Conclusions:
Heidenhain variant of CJD is a diagnostic challenge due to the variable visual symptoms, normal structural eye exam, subtle MRI findings and the lack of initial, overt, neurologic abnormalities. Due to the rapidly progressive fatal course, early clinical suspicion by ophthalmology is critical in diagnosis, especially when future treatment is present.

References: None.

Keywords: Prion Disease, Creutzfeldt-Jakob Disease, Visual Field Defect

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Poster 207

Six-Year Follow-Up Of The Progression Of Cortical Vision Loss In A Patient With HIV-Related Progressive Multifocal Leukoencephalopathy

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Introduction:
A 43- year- old right-handed African American man with 20-year history of HIV presented to with blurred vision in both eyes. He also had right hemiparesis and right arm flailing. Neuro-exam revealed right hemiparesis, hemiataxia and hemibalismus, alexia without agraphia and dysnomia. Ophthalmic exam showed BCVA 20/25 OD, 20/40 OS. EOM was intact. Slit lamp and fundoscopic exam was normal. Humphrey visual field 30-2 demonstrated a left homonymous para-central scotoma.

Methods:
His symptoms started 6 years ago as diplopia and progressive right-sided weakness. About 4 months later, he developed headache and blurred vision. MRI/MRA head revealed “hypointense T1 and hyperintense T2 lesions within both occipital lobes of the brain with mild peripheral enhancement. There was a non-enhancing T2 signal in both middle cerebellar peduncles extending into the left medial cerebellum and no diffusion restriction”. Blood test showed CD3/CD8 36, HIV1 RNA by PCR 244580 copies/ml, and it was negative for coagulopathy panel. Lumbar puncture was negative for DNA direct probe for JC and BK viruses. Highly active antiretroviral therapy medications were optimized and he was discharged home on antiplatelet.

Results:
One year later, he developed kaleidoscopes of colors in front of his eyes. It followed by an episode of grandmal seizure. EEG was normal. Repeat MRI head w/ wo/ gadolinium showed worsening of the confluent lesions. He refused lumbar puncture but agreed with a brain biopsy. After right occipital craniotomy, a 3.5*3*1cm tissue was resected. The pathology demonstrated a white matter- centric, focally demyelinating process consistent with PML and immune reconstitution inflammatory syndrome (IRIS) concomitant with an opportunistic infection by JC virus. Immunostaining for John Cunningham (JC) virus (SV40) highlighted several infected oligodendroglial cells at the edge of the lesions.

Conclusions:
The diagnosis of PML should be considered in immunocompromised patients with neuro-ophthalmic findings, particularly those with cortical blindness.

References: None.

Keywords: Cortical Blindness, Progressive Mulifocal Leukoencephalopathy, Hemibalismus, Alexia

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Poster 208

Retrograde Degeneration of Retinal Ganglion Cells in Homonymous Hemianopia

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Introduction:
To demonstrate the relationship between topographic reduction in macular ganglion cell complex (GCC) thickness as detected with spectral-domain optical coherence tomography (SD-OCT) to visual field defects caused by ischemic occipital cortical injury.

Methods:
Retrospective review of all patients who presented to our eye institute between January 2012 and July 2014 with visual field defects secondary to ischemic cortical injury. The visual field defect pattern and mean deviation were analyzed. Retinal nerve fiber layer (RNFL) and macular GCC were both assessed with SD-OCT. Patients with any ocular pathology that could affect these measurements were excluded. The topographic relationship of visual field defect to reduction in GCC was specifically analyzed.

Results:
Nine patients met the inclusion criteria. The average age was 54 (range 16-72 years), 88% were men, and 67% had right hemianopsias. The laterality of the visual field defect was used to assign an affected and unaffected side of analysis for RNFL and GCC layer thickness. A right hemianopsia meant that the nasal fibers of the right eye and temporal fibers of the left eye were assigned as “affected side,” and the temporal fibers of the right eye and nasal fibers of the left eye were assigned “unaffected.” There was no statistically significant difference between affected and unaffected segments of RNFL. However, there was significant difference between the GCC layer reduction in affected and unaffected sides ($p = 0.03$)

Conclusions:
There may be retrograde trans-synaptic retinal ganglion cell loss in patients with homonymous hemianopsias from cortical visual impairment. This relationship is reflected in the general reduction in RNFL and more specifically in the GCC as the pattern of reduction maintains the topographic relationship of the visual field defect.

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Keywords: Homonymous Hemianopsia, Ganglion Cell Complex, Retrograde Transsynaptic Degeneration

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Poster 209

Lesions of the Optic Tract: A Review of 35 Cases

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Introduction:
Previous case series reports, (1,2,3,) the largest involving 21 cases, have documented that optic tract lesions are usually tumors. The imaging detail has been sparse. We have encountered 35 cases that demonstrate a much broader range of causes with diverse imaging features.

Methods:
Retrospective review of case records from a single institution between 2000 and 2014. Inclusion criteria were 1) homonymous hemianopia; 2) lesion demonstrated on MRI in the region of the optic tract; 3) if the imaged lesion extended into the retrogeniculate region, a relative afferent pupil defect had to be present in the eye with temporal field loss.

Results:
Causes included brain hemorrhage--6, anterior choroidal infarction–5, head trauma—3, aneurysmal coiling–3, temporal lobectomy–2, sarcoidosis--2, craniopharyngioma--2, glioblastoma--2, herpes zoster, lymphoma, aneurysm, demyelination, astrocytoma, deep venous thrombosis, radiotherapy, arteriovenous malformation, cavernoma, congenital infarction—1 each. In some cases, the imaging abnormalities were subtle and the localization of the lesion was therefore challenging.

Conclusions:
Our series enlarges the number of known causes for optic tract lesions and demonstrates a broad spectrum of imaging abnormalities, some quite subtle.

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Keywords: Neuroimaging

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Poster 210

Hydrocephalus and More!

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Introduction:
The differential diagnosis of multifocal central nervous system lesions is quite broad. We present a case of progressive neurological deficits, visual loss and multiple intracranial lesions due to an unexpected etiology.

Methods:
Case report and review of the literature.

Results:
A 67-year-old female presented with headaches, altered mental status, leg weakness and dysarthria. Exam revealed patient confusion and mild bilateral leg weakness. Brain MRI showed a confluent abnormal flair signal involving the left periventricular and corpus callosum with hydrocephalus. CSF protein was 130, with 4 WBCs, 1 neutrophil, and 78% lymphocytes. Viral PCRs and cytology were negative. Right frontal ventriculostomy was placed with improvement in mental status followed 5 days later by ventriculoperitoneal shunt and left parietal brain biopsy. Biopsy revealed demyelination with relative preservation of axons. Intravenous dexamethasone treatment caused improvement over 3 weeks. One year later, she presented with forgetfulness, headache, and ataxia. Brain MRI showed abnormal flair and enhancement around the left occipital horn. CSF protein was 156, with normal IgG index and no oligoclonal bands. Repeat biopsy revealed no atypical B cells with active demyelination and axonal sparing. ANA, SSA-B, Lyme, Vitamin B_{12}, RPR, and toxoplasma were normal. A C-spine and T-spine MRI looking for evidence of similar lesions was normal. Five months later, she presented with acute onset of painless bilateral vision loss. She initially had a dense bitemporal hemianopsia. Two days later, she had complete loss of vision in both eyes except for small right nasal island. Brain MRI showed enhancement of the optic chiasm, subependymal frontal horns, and floor of third ventricle. Chest CT was normal. Aquaporin-4 antibodies were positive in serum and CSF.

Conclusions:
Neuromyelitis Optica has a wide spectrum of neurological presentations. It should be considered early on the differential of multifocal CNS lesions especially with chiasmal involvement.

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Keywords: Optic Neuritis, Neuromyelitis Optica, Hydrocephalus, Demyelination

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Poster 211

Ipratropium-Induced Mydriasis: A Possible Exception to the Current Anisocoria Diagnostic Pathway

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Introduction:
Pupillary abnormalities often evoke significant clinical concern, especially in ICU settings. We have observed cases of transient anisocoria among critically-ill patients who received nebulized bronchodilators via face mask. Though it is suspected that nebulized ipratropium could induce mydriasis if accidentally administered topically to the eye (23 case reports between 1986 and 2012 have described dilated pupils among patients using ipratropium inhalers and nebulizers) [1-23], only 3 studies have attempted to reproduce this anecdotal association. [6, 24, 25]The use of topical pilocarpine 1% is considered a definitive diagnostic test to distinguish between pharmacological mydriasis and a third nerve palsy. We have, however, observed cases of presumed ipratropium-induced mydriasis at our institution in which the dilated pupil constricted when challenged with pilocarpine 1%. We suspect that ipratropium-induced mydriasis may be reversed by topical pilocarpine 1%, contradicting the widely-accepted anisocoria diagnostic algorithm.

Methods:
An interventional case study was performed on a willing volunteer. After an ophthalmological examination revealed no pupillary abnormalities, nebulized ipratropium bromide 0.02% and nebulized ipratropium/albuterol (0.5 mg / 3 mg per 3 mL) solutions were instilled in mist and drop form OD. Serial ophthalmological examinations were performed at 30 minutes, 60 minutes, 6 hours, 12 hours, and 18 hours. Pilocarpine 1% was administered OU at varying times from initial recognition of mydriasis.

Results:
After instillation of ipratropium, mydriasis gradually developed OD over several hours, lasting greater than 18 hours. After administration of pilocarpine 1% OU, pupillary constriction OU was noted within one hour.

Conclusions:
Ipratropium bromide can produce mydriasis when administered topically to the eye. This effect appears to be dose-dependent and relatively long-lasting (approximately 18-24 hours). Furthermore, ipratropium-induced mydriasis may be reversed by pilocarpine 1%, challenging the currently accepted anisocoria diagnostic pathway. Pharmacological testing should be interpreted with caution in this clinical context.

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Keywords: Pupils

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Poster 212

Automated Pupillograph as a Screening Tool in Ophthalmology Clinic

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Introduction:
To evaluate the efficacy of an automated pupillograph as a screening tool in ophthalmology clinic.

Methods:
110 subjects in the study were enrolled in the study, 80 normals (72.7%) and 30 (27.3%) patients with Glaucoma. Pupillary reactions were measured using RAPDx Expanded Pupil Diagnostics (Konan Medical USA, Inc., Irvine, CA) and were compared with Neutral Density Filter (NDF) (Gulden Ophthalmics). In addition, 30 Glaucoma patients also underwent analysis of Macular Ganglion cell (mGCC) thickness using a Spectral domain -Optical Coherence Tomography(Optovue RTVue XR AVANTI).

Results:
The pupillary reactions in normal 80 patients (57% males, 43 % females) assessed by NDF was found to be less than 0.3 log units. On RAPDx the same was found to be 0.28 log units. Statistically significant correlation ($p<0.001$) was seen between the two.Mean amplitude of pupillary reactions on RAPDx (0.14 log units) in 30 glaucoma subjects, correlated significantly with the mGCC thickness ($P<0.05\%$). However mean latency of the pupillary reactions (0.12 msec) showed a weak correlation with mGCC.

Conclusions:
This pilot study concludes that RAPDx is comparable to NDF in measuring RAPD and can be used interchangeably. In glaucomatous patients the log-scaled RAPD amplitudes correlated moderately with the mGCC thickness, but the log-scaled RAPD latencies showed a weaker correlation.RAPDx may be used as a screening tool in Ophthalmology clinic.

References: None.

Keywords: Pupillograph, Macular Ganglion Cell Complex, Pupillary Reactions, Rapdx, Neutral Density Filter

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Poster 213

The Yield of Diagnostic Imaging in Patients with Isolated Horner's Syndrome

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Introduction:
We conducted a retrospective chart review to determine the yield of diagnostic neuroimaging for patients with isolated Horner's syndrome.

Methods:
We conducted a retrospective chart review of 123 patients seen by our service between 2000 and 2014, who were coded as having Horner's syndrome with clinical and/or pharmacologic confirmation of the diagnosis. We excluded infants and patients with congenital Horner's syndrome.

Results:
Patient age ranged from 6 to 87 years old, with an average age of 50 years old. There were 123 cases of clinically- or pharmacologically-confirmed Horner's syndrome, with 63 male and 60 female patients. On initial presentation, 19 patients had a known cause or constellation of findings that indicated the etiology of their Horner's syndrome. Imaging of the oculosympathetic pathway was pursued in 94 patients (76.4%). Prior to imaging, 5 of the 94 patients (5%) had a known etiology for their Horner's syndrome. There were 89 patients with an isolated Horner's syndrome who underwent neuroimaging in search of a causative lesion. Of these, 17 (19%) were found to have a lesion on neuroimaging that was causative for the Horner's syndrome. The most common finding was carotid artery dissection in 7 patients (8%), with all but one having an acute-onset painful Horner's syndrome. None of the imaged patients were found to have a primary malignancy, but one patient with known metastatic disease was found to have a new metastatic lung lesion. Seven of the patients (7%) had incidental findings on imaging that were unrelated to the oculosympathetic defect.

Conclusions:
To our knowledge, this is the largest series evaluating the diagnostic yield of neuroimaging for isolated Horner's syndrome. Imaging identified a causative lesion in 19% of patients with an isolated Horner's syndrome. About 7% of patients had an incidental finding on neuroimaging that was unrelated to the oculosympathetic defect.

References: None.

Keywords: Pupils, Neuroimaging

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Poster 214

Evaluation of Pupil Response as Ocular Marker for Pre-Clinical Alzheimer's Disease

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Introduction:
Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive deficits and visual dysfunction. There is increasing interest in the use of ocular markers as a surrogate for disease activity and progression in AD[1]. Several studies have shown that the pupillary light response (PLR) can differentiate AD patients from healthy controls[2,3] . However, the majority of these studies have assessed the PLR in subjects with established Alzheimer's disease, and it remains unclear whether the PLR is affected in subjects with pre-clinical AD.

Methods:
We recruited participants from our institution's Alzheimer's Disease Research Center. All participants completed positive emission tomography-Pittsburgh compound B imaging, cerebrospinal fluid analysis and at least 1 neuropsychiatric assessment after their baseline assessment. All participants were assigned a clinical dementia rating (CDR) and underwent a complete neuro-ophthalmic examination. Participants were divided into a dementia biomarker + and – group based on preclinical risk for or presence of dementia. Pupillometry measurements were performed by using the NeurOptics PLR-200 Pupillometer.

Results:
A total of 39 participants were recruited with 12 dementia biomarker + and 27 dementia biomarker- individuals. A variety of PLR parameters were assessed. Comparisons between groups were analyzed using Generalized Estimating Equations. The Minimum Pupil Size was significantly smaller in the dementia biomarker + group ($p= 0.012$). The Maximum Pupil Size was also smaller in the biomarker dementia + group, and approached significance ($p= 0.06$). None of the other pupillary parameters showed a significant difference between groups.

Conclusions:
We found a significant difference in the PLR between dementia biomarker +, pre-clinical AD subjects versus controls. We are continuing to recruit subjects to determine whether our preliminary results are validated. The PLR is a potential candidate for non-invasive screening of pre-clinical AD, and might also be used as a surrogate marker for disease progression in future clinical trials.

References: None.

Keywords: Pupils, Neuro-Ophth & Systemic Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 215

A Case Of Horner's Syndrome After Clipping Of The Internal Carotid-Posterior Cerebral Artery Aneurysm Associated With Subarachnoid Hemorrhage

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Introduction:
Internal carotid-posterior cerebral artery (IC-PC) aneurysm is a cause of parasympathetic nerve paresis of the pupil. We have experienced a case of sympathetic nerve paresis of the pupil after clipping of IC-PC aneurysm associated with subarachnoid hemorrhage. We will report the case and discuss the mechanism.

Methods:
A Case report and review of the literature.

Results:
A 59-year-old woman had a subarachnoid hemorrhage caused by a rupture of left IC-PC aneurysm in September 2007. She was treated by a clipping procedure with the complication of the rupture of the aneurysm. After the intervention, she noted to have left blepharoptosis. She was referred to us for the treatment of left blepharoptosis in April 2014. Her visual acuity was 20/20 in both eyes. Pupils measured 5mm OD and 3.5mm OS in dark, 3mm OD and 2.5mm OS in light, constrict briskly to light OU. There was no afferent pupillary defect. Her ocular motility was 100% in all directions without nystagmus. She was orthotropic in all directions. Confrontational visual field was normal. Her palpebral fissure width was 9mm OD and 7mm OS. Corneal sensation was normal. Systemic neurological examination revealed a motor aphasia, right hemiplegia, and sensory deficit on the whole right side body including face. After the instillation of 10% cocaine, pupils measured 7mm OD and 4mm OS. After the instillation of 1% hydroxyamphetamine, pupils measured 7mm OD and 5mm OS. After the instillation of 0.1% epinephrine, pupils measured 5mm OD and 7mm OS. Following these results, we diagnosed her to have a postganglionic Horner's syndrome on the left. A CT angiography revealed a left internal carotid artery obstruction.

Conclusions:
Similar case has not been found as far as we investigated. Sympathetic nerve paresis of the pupil could occur after clipping of the IC-PC aneurysm associated with subarachnoid hemorrhage.

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Keywords: Horner Syndrome, IC-PC Aneurysm, Subarachnoid Hemorrhage, Anisocoria, Internal Carotid Obstruction

Financial Disclosures: The authors had no disclosures.

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Poster 216

Test–Retest Reliability of Hemifield, Central-Field and Full-Field Chromatic Pupillometry for Assessing the Function of Melanopsin-Containing Retinal Ganglion Cells

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Introduction:
A sustained pupil constriction can be observed after the offset of a bright blue light stimulus. This post-illumination pupil response (PIPR) is produced by the intrinsically photosensitive melanopsin-containing retinal ganglion cells (ipRGCs), and can be measured by chromatic pupillometry. We previously described a clinically friendly chromatic pupillometry protocol that can induce PIPR with a brief blue light stimulus. The present study is to evaluate the test-retest reliability of current methods of inducing PIPR under hemifield, central-field and full-field stimulation conditions.

Methods:
Pupil response was recorded with an eye tracker in 10 visually normal participants. Light stimuli were presented using a Ganzfeld screen with a custom-built device that allows specific regions of the retina to be stimulated. Blue light stimulation at 400 cd/m2 intensity was presented for 400 ms to the lower and upper halves of the central 30° fields (hemifields), both halves of the central 30° field (central-field) and full-field to induce PIPR. Red light full-field stimulation was also presented with the same intensity and duration as a control condition. Test-retest reliability of the PIPR measures were assessed by calculating the intra-class correlation coefficient (ICC) of 6 repetitions for lower and upper hemifield stimulation, and 3 repetitions for central-field and full-field stimulation.

Results:
Hemifield, central-field, and full-field blue light stimulation induced increasingly greater PIPR in ascending order, while full-field red light stimulation induced no PIPR. Mean lower and upper hemifield PIPR were highly symmetric. Mean ICC of blue light PIPR was 0.87 for lower hemifield, 0.88 for upper hemifield, 0.95 for central-field, and 0.94 for full-field stimulation.

Conclusions:
We validated a new and repeatable method to measure PIPR induced by hemifield, central-field and full-field light stimulation. Good PIPR measurement reliability was obtained under all conditions. This practical and reliable protocol will facilitate the clinical application of PIPR testing in different disease populations.

References: None.

Keywords: Pupil Light Reflex, Pupillometry, Test-Retest Repeatability, Melanopsin, Retinal Ganglion Cells

Financial Disclosures: The authors had no disclosures.

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Poster 217

Unique Presentation of Anti-GQ1b Antibody Syndrome

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Introduction:
Anti-GQ1b antibody syndrome can present along a spectrum: from acute ophthalmoparesis to Miller Fisher Syndrome to Bickerstaff's brainstem encephalitis to Guillain Barre Syndrome. Here, we report a patient who presented with an interesting combination of neuro-ophthalmological findings.

Methods:
Case report.

Results:
The patient was an 18 year-old, previously healthy, Caucasian man, who presented with one day of acute onset binocular diplopia. He was in his usual state of health until one week prior to presentation, when he developed upper respiratory tract infection symptoms.On exam, his bilateral pupils were dilated (8mm), didn't constrict to direct light stimulation or accommodation, but constricted readily with 1% pilocarpine drops, thus ruling out direct muscarinic blockade. Right eye was esotropic with a 20% limitation in abduction, consistent with a partial right cranial nerve VI palsy. Left upper eyelid had a 2mm ptosis, with a negative ice test. Left eye was hypotropic with a 10% limitation in upgaze, potentially consistent with a partial left cranial nerve III palsy. Extraocular movements were otherwise full with normal saccadic velocities. His ophthalmic exam was otherwise normal. His neurological exam was otherwise normal, with normal reflexes and no ataxia or dysdiadochokinesia.MRI of the brain and orbits was unremarkable. Acetylcholine receptor binding antibodies and striated muscle antibodies were negative. Single fiber electromyography of the frontalis muscle showed no evidence of myasthenia gravis. Lumbar puncture showed normal basic studies with no albuminocytologic dissociation. CSF infectious work up was negative. His serum GQ1b antibody titer was significantly elevated at 1:3200.

Conclusions:
To our knowledge, this is the first reported case in which the patient has the unique combination of bilateral mydriasis with complete internal ophthalmoplegia to both light and near stimuli, in the absence of ataxia and areflexia. It should serve to extend the clinical spectrum of disease associated with anti-GQ1b antibodies.

References: None.

Keywords: Pupils, Neuro-Ophth & Systemic Disease

Financial Disclosures: The authors had no disclosures.

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Poster 218

Novel Retinal Observations in Genetically Confirmed Kearns Sayre Syndrome

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Introduction:
Kearns Sayre Syndrome (KSS) is a complex mitochondrial syndrome typically caused by a single, large-scale mitochondrial DNA (mtDNA) deletion that presents before the age of 20 years with progressive external ophthalmoplegia, pigmentary retinopathy, and other neurologic and medical problems. We emphasize the retinal changes, including several novel observations, in three clinically and genetically characterized patients with KSS.

Methods:
Evaluation of three unrelated patients with retinal and neuro-ophthalmologic examinations, medical chart review, and mitochondrial genetic evaluation.

Results:
All three patients were recognized during early childhood to have progressive external ophthalmoplegia and pigmentary retinopathy bilaterally. All had small stature and other cardiac, endocrinologic, or neurologic signs. Two patients underwent muscle biopsies revealing histopathological changes consistent with mitochondrial myopathy. All had abnormal neuroimaging with hypodense cerebral white matter on CT or bright signal on T2-weighted magnetic resonance images in hemispheric white matter, thalami, and midbrain. All three had modestly reduced visual acuity OU with a pigmentary retinopathy involving predominantly the posterior pole and low amplitude electroretinographic waveforms. One patient had bilateral subretinal fibrosis worse on the left with a full thickness macular hole on the right, neither of which have been reported previously in KSS. All three patients had single, large-scale mtDNA deletions between 5.0-7.6 kb with blood heteroplasmy levels varying between 20% and 58%.

Conclusions:
Subretinal fibrosis and macular hole are novel clinical observations in KSS. In these three patients, severity of pigmentary retinopathy correlated grossly with retinal electrophysiologic changes but not obviously with ptosis, ocular motility, other clinical and radiologic features, or the severity of the mtDNA rearrangement.

References: None.

Keywords: Kearns Sayre Syndrome, Mitochondria, Pigmentary Retinopathy, Epiretinal Fibrosis, Progressive External Ophthalmoplegia

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Poster 219

Autoimmune Retinopathy And Optic Neuropathy In A patient With Anti-GAD And Other Retinal Antibodies

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Introduction:
Autoimmune retinopathy (AIR) is a spectrum of rare acquired retinal diseases, including cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), and presumed non-paraneoplastic autoimmune retinopathy (npAIR). Autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome is characterized by the presence of antibodies against retinal or optic nerve antigens in the absence of cancer. We report a case of acquired autoimmune cone dystrophy and optic neuropathy in a patient without cancer involving an abnormal immunologic reactivity against a 20-kDa optic nerve antigen and 40-kDa and 62-kDa retinal antigens and anti- glutamic acid decarboxylase (GAD) antibodies.

Methods:
Single case report

Results:
Multifocal electroretinography (MERG) revealed centrally depressed responses, and visually evoked potential (VEP) testing revealed left eye extinguished waveforms at 20/100. Fundus autofluorescence showed central macula hypofluorescence OU and fundus fluoroscein angiography showed unusual diffuse patchy hyperfluorescence OU. MRI of the brain and orbits, whole body PET scan, cerebrospinal fluid analysis and testing for Leber hereditary optic neuropathy were unremarkable. Hemoglobin A1C was 8.6%, and serum glucose was 283 mg/dl. Commercial paraneoplastic antibody testing revealed an elevated anti-GAD antibody titer. Experimental auto-antibody testing showed reactivity in the 40-kDa region, consistent with either rhodopsin or the 40-kDa CAR antigen, anti-retinal antibodies in the 62-kDa region and anti-optic nerve antibodies in the region of 20-kDa region.

Conclusions:
This case expands the spectrum of autoimmune antibody related disease of the retina and optic nerve. To our knowledge, the presence of anti-GAD antibody as well as anti-retinal and anti-optic nerve antibodies in our patient is unique.

References: None.

Keywords: Autoimmne Retinopathy, Autoimmune Neuropathy, Anti-GAD Antibody, Anti-Retinal Antibody, Anti-Optic Nerve Antibody

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Poster 220

GM2-gangliosidosis, AB variant: An Elusive Cause of Neurodegenerative Cherry Red Spots

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Introduction:
Introduction: GM2-gangliosidosis, AB variant is a rare form of GM2-gangliosidosis due to a deficiency of GM2 activator protein. This autosomal recessive disorder is caused by mutations in GM2A that can only be confirmed by molecular analysis.

Methods:
Methods: Retrospective case analysis with cherry red spots confirmed by molecular analysis to be due to GM2 gangliosidosis.

Results:
Results: A one-year-old Hmong girl was evaluated for global developmental delay, hypotonia and cherry red spots. The parents were not known to be consanguineous. Her examination was notable for hypotonia with hyperreflexia and excessive startling. The head circumference was normal. An extensive neurometabolic evaluation including hexosaminidase A enzyme assay in white blood cells was negative. Retinal examination at 16 months of age disclosed bilateral cherry red spots with heaped up whitish infiltrate surrounding both foveae but no evidence of optic atrophy or peripheral retinal abnormalities. MR imaging revealed delayed myelination associated with abnormal signal intensity of the bilateral thalami, presenting as T2-hyperintensity of the posterior thalami in the region of the pulvinar nuclei and T2- hypointensity in the anterior thalami. Sequencing of the GM2A gene revealed a homozygous c.160 G>T mutation, predicted to result in a premature protein termination p. Glu54*.

Conclusions:
Conclusions: Deficiency of GM2-activation protein is a rare but important cause of infantile cherry red spots that is not detected by routine neurometabolic screening.

References: None.

Keywords: Gangliosidosis, Cherry, Red, Spot, Activator

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Poster 221

Malignant Optic Nerve Glioma Manifesting as Central Retinal Vein Occlusion and Papilledema

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Introduction:
Malignant optic nerve glioma is a disease of older adults that often progresses to bilateral blindness and death[1]. This is in contrast to optic nerve gliomas of childhood, which are typically benign[2]. It may present under the veil of other diagnoses, including optic neuritis, non-arteritic ischemic optic neuropathy, or retinal vascular occlusion.

Methods:
A case report.

Results:
A 67-year-old woman presented with decreased Snellen acuity and color vision in the left eye (OS) and pain with eye movement. Fundus exam showed optic disc edema in both eyes and signs of a central retinal vein occlusion OS. Magnetic resonance imaging demonstrated a right thalamic mass extending to the left optic nerve. Intracranial biopsy of this lesion was initially felt to be too dangerous. Vision declined to no light perception (NLP) OS. A left optic nerve biopsy was performed in order to obtain tissue and reach a definitive diagnosis. Unfortunately the biopsy only revealed fibrosis and chronic inflammation. Progression of the radiologic findings, decline in mental status, and development of NLP vision in the right eye prompted a stereotactic thalamic biopsy that revealed glioblastoma multiforme. The patient died three months after her initial presentation.

Conclusions:
Malignant optic nerve glioma is a rare condition that suggests a poor visual and overall prognosis, often leading to death within months of the initial presentation. It should be considered as a possible diagnosis in the setting of a central retinal vein occlusion with other intracranial signs.

References:
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Keywords: Retina, Neuroimaging, Tumors, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

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Poster 222

Comprehensive Postmarketing Review of Visual Defects Reported With Topiramate

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Introduction:
Treatment-emergent adverse events (TEAEs) including visual field defects (VFDs) reported with topiramate use, are usually reported as reversible. The objective was to determine possible mechanisms of action (MOA) for VFDs and patterns for development of VFDs with topiramate treatment.

Methods:
A comprehensive topiramate database review included: preclinical data – to evaluate topiramate's MOA compared with other antiepileptic drugs (AEDs) associated with VFDs, sponsor's clinical trials database, postmarketing spontaneous reports, and medical literature. All TEAEs suggestive of retinal dysfunction or damage were summarized by system and organ class (SOC) and preferred term (MedDRA version 14.0). A relative risk (RR) analysis was conducted using data from topiramate double-blind, placebo-controlled trials (DBPCTs).

Results:
Topiramate-treated patients (N=5679) showed greater frequency of TEAEs suggestive of retinal dysfunction or damage versus placebo-treated (N=1834) (0.3%-0.7% vs. ≤0.1%) patients in DBPCTs for approved indications; similar incidence was noted in open-labels (OLs) and in DBPCTs for investigational indications. In OLs (each investigational indications), incidence was <0.1% (except diabetic peripheral neuropathy [1.4%]). 88% of TEAEs were mild-moderate. Serious events were rare, and most were not treatment limiting and resolved. Most common visual TEAEs were VFD, scotoma and optic atrophy (approved indication trials), and VFD, tunnel vision, retinopathy, retinal hemorrhage and retinal detachment (investigational indication trials). Incidence of TEAEs in DBPCTs (approved and investigational indications) was higher in topiramate-treated (N=9169) versus placebo-treated patients (N=5023) (0.36% vs. 0.24%), RR to placebo-treated patients was 1.51 (95% CI, 0.78-2.91); not statistically significant.

Conclusions:
As VFD is not a common TEAE with other AEDs that have a gamma-aminobutyric acid-ergic MOA similar to topiramate; therefore, retinal function is not a class effect. A comprehensive review of topiramate data revealed an increased incidence of visual TEAEs in topiramate-treated versus placebo-treated patients, however, RR was not statistically significant. Topiramate prescribing information includes warnings related to visual TEAEs.

References: None.

Keywords: Topiramate, Visual Field Defects, Retinal Damage, Retinal Dysfunction, Clinical Trials

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Poster 223

Sequential Fundus Findings After Platelet Rich Plasma For Facial Rejuvenation

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Introduction:
Injections of dermal filler as autologous fat, collagen, hyaluronic acid, polylactic acid, calcium hydroxylapatite, and polymethylmethacrylate are used for facial rejuvenation. Complications for these procedures are cerebral ischemia and infarction, central retinal artery occlusion, ischemic optic neuropathy, ocular ischemia, palsy nerve ischemia, skin necrosis and even death. The mechanism of these event presumably via high pressure retrograde flow from the supratrochlear, supraorbital, and dorsal nasal artery to central retinal artery and long posterior ciliary artery oclussion. Platelet rich plasma have been used in plastic surgery by scars and skin rejuvenation.

Methods:
A 61 year old woman developed painful severe visual loss immediately after platelet rich plasma injection into the supraorbital area. Skin redness was observed in the injection site. Her visual acuity was no light perception in the affected eye. The fundus of the eye showed diffused whitening of the retinal, retinal edema, cherry red spot in the fovea, and retinal arterioles attenuation. Fluorescein angiography demonstrated patchy choroidal non perfution and incomplete filling of the retinal arterioles in the later frames. Optical coherence tomography demonstrate retinal edema.

Results:
Over time the followings fundus findings were observed: retinal edema decreased, diffuse whitening of the retinal persisted until patchy of pigment appeared over peripheral and macular area; lipid filled arterioles with perivascular sheathing until become in a phantom vessel, the optic disc become pale and pigmented in the superior pole. The fluorescein angiography demonstrated incompleted filling of the choroidal and arterial vessels. The optical coherence tomography demonstrate retinal thinning, hiperreflectivity areas, epiretinal membrane, loss of ganglions cells and nerve fiber layer. In the skin, necrosis in the injection area was observed.

Conclusions:
Dermal injection of cosmetic filler injected in the forehead can cause irreversible blindness. The sequential fundus findings after cosmetic filler injections demonstrated the difficulty to reestablished vision.

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Keywords: Central Retinas Artera Oclusión, Cosmetic Filler

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Poster 224

Contrast Sensitivity Visual Acuity is Degraded in REM Sleep Behavior Disorder

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Introduction:
REM Sleep Behavior Disorder (RBD) is a sleep disorder that produces motor enactment during REM sleep. Although pathophysiology is uncertain, studies demonstrate nigrostriatal dopamine deficiencies in RBD patients,[1] a condition frequently linked to alpha-synuclein-associated disorders i.e. Parkinson's disease (PD), characterized by cellular alpha-synuclein aggregation and death in dopamine producing cells. We previously reported contrast sensitivity visual acuity (CSVA) deficits in early-stage Parkinsonism.[2] A recent study identified that misfolded alpha-synuclein, a regulator of dopamine synthesis, is present in the inner retina of PD patients.[3] We therefore speculated that CSVA might be impaired in individuals with RBD.

Methods:
To analyze CSVA in patients with RBD versus controls. 18 RBD patients and 29 control subjects. Participants completed a visual function questionnaire. Tests included: SLOAN CSVA wall charts at 100%, 2.5%, and 1.25%, and general ophthalmologic and neurologic examinations and Spectral Optical Coherence Tomography (OCT). Exclusion criteria: Visual acuity <20/40, co-morbid ophthalmologic pathologies, and dementia. Results were submitted to independent-samples t-test for statistical analysis.

Results:
There was a statistically significant difference in mean contrast sensitivity between RBD and controls, with the RBD group scoring lower than the aged matched control group 6.379 ± 3.06 [mean ± standard error], $t(45) = 2.08$, $p = 0.043$.

Conclusions:
CSVA is diminished in patients with RBD. It seems plausible that visual deterioration is a consequence of misfolded alpha-synuclein in the inner retinal layers. Loss of CSVA in this population increases risk for falls.

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Keywords: REM Sleep Behavior Disorder, Contrast Sensitivity Visual Acuity, Alpha-Synuclein

Financial Disclosures: The authors had no disclosures.

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Poster 225

Ophthalmoscopy Vs. MRI – Sometimes Less Is More.

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Introduction:
The purpose is to describe a case of retinal disorder mimicking intracranial pathology.

Methods:
Case report.

Results:
56-year-old female presented to her local ophthalmologist with painless, progressive worsening vision and glare. Vision was 20/50 OD, 20/40 OS. Slit lamp examination showed cataracts and undilated fundus examination revealed macular pigmentary changes bilaterally that were attributed to early macular degeneration. Optical coherence tomography (OCT) showed thin ganglion cell complex and macula bilaterally. Subsequently, she underwent bilateral cataract extraction with intraocular lens placement. Postoperatively, vision improved to 20/25 OD, 20/30 OS. Four months later, she returned with decreased visual acuity of 20/40. Humphrey perimetry revealed dense temporal field loss nearly respecting the vertical midline OS and subtle dampening of superior nasal field OD, resembling an incongruous homonymous defect. Given these findings, MRI brain/orbits was obtained and showed mild microvascular disease but no structural abnormality. The patient was referred to Neuro-Ophthalmology where examination revealed an APD, dyschromatopsia, and left disc pallor, which further suggested optic neuropathy. However, dilated funduscopy revealed a large peripapillary area of retinal atrophy with yellowish peri-foveal deposits and vertical zone of pigmentary demarcation temporal to fovea. OCT macula revealed loss of ellipsoid layer corresponding to the region of abnormality visualized on fundoscopy. Serologic evaluation excluded inflammatory disorders, syphilis, tuberculosis, and TORCH infections. Cone-driven responses were undetectable on full-field ERG with inter-ocular difference in rod amplitude. Retina consultation was obtained and genetic counseling evaluation revealed consanguinity and presumptive diagnosis of autosomal recessive retinal dystrophy (genetic panel pending). Widefield color fundus, fluorescein angiography, and OCT all support a retinal etiology for her symptoms, with differential diagnoses including AZOOR, chronic chorioretinitis, and autoimmune retinopathy.

Conclusions:
Retinal pathology should be considered in the differential diagnosis of cases presenting with unilateral visual loss mimicking optic neuropathy, and evaluated appropriately prior to obtaining neuroimaging.

References: None.

Keywords: Retina, Visual Field, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 226

Retinal Vessel Oximetry and Vessel Diameter Measurements: A Novel Metabolic Marker of Multiple Sclerosis

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Introduction:
Optic neuritis (ON), a common manifestation of multiple sclerosis (MS), often results in optic atrophy, a clinical finding characterized by optic disc pallor and retinal vessel attenuation. To date, there is no objective *in vivo* method for measuring the magnitude of pallor or vascular attenuation. We sought to characterize retinal vascular oximetry (oxygen saturation [SO2] and partial oxygen pressure [PO2]) and retinal vessel diameter in a cohort of MS patients using a novel technology – the Oxymap® T1 Retinal Oximeter.

Methods:
A cohort of healthy controls, and MS patients with a prior history of unilateral ON underwent assessments using spectral-domain optical coherence tomography and fundus photography. Further, using the Oxymap®, we measured the mean retinal vessel SO2, PO2, and corresponding diameter.

Results:
Compared to healthy controls, we found that the mean retinal vascular SO2 and PO2 were higher in MS patients, particularly in eyes with prior ON. Alternately, the mean retinal vessel diameter was reduced in the eyes of MS patients, when compared to those of healthy controls. The higher SO2 and PO2, and reduced retinal vessel diameter corresponded to decreased retinal nerve fiber layer thickness (RNFLT).

Conclusions:
To our knowledge, we report the first application of objective, *in vivo*, ascertainment of retinal oxygenation and vessel diameter in MS patients, and confirm differentiation (especially ON affected eyes) from measures derived from controls. Further, we demonstrate an inverse relationship between increased SO2 and PO2, and corresponding measures of RNFLT. Alternately, a direct relationship was identified between decreased retinal vessel diameter and RNFLT. We hypothesize that the pathobiological mechanisms in MS, culminate in retrograde degeneration of retinal ganglion cells, thereby reducing metabolic demand, oxygen extraction, and retinal vessel caliber. The application of retinal oximetry in MS, may facilitate the development of visual system biomarkers, germane to the identification of novel neurotherapeutic strategies in MS treatment trials.

References: None.

Keywords: Retina, Oximetry, Multiple Sclerosis, Optic Neuritis, Biomarker

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Poster 227

Acute Zonal Occult Outer Retinopathy Presenting As Retrobulbar Optic Neuritis

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Introduction:
Acute zonal occult outer retinopathy (AZOOR) is an inflammatory retinopathy in the category of white dot syndromes characterized by acute loss of one or more zones of outer retinal function associated with photopsia, minimal funduscopic changes and abnormal electroretinography findings. The authors report a case of AZOOR in a patient presenting as retrobulbar optic neuritis.

Methods:
A 33 year-old male without underlying disease was referred with retrobulbar optic neuritis in the right eye. He presented with blurring in the right eye of 2 weeks duration. His visual acuity was 20/20 in left eye and 20/100 in the right eye with no ophthalmoscopic and fluorescein angiographic abnormalities. The cecocentral scotoma was found in the right eye. The amplitudes of pattern visual evoked potential (PVEP) was reduced in the right eye.

Results:
The amplitudes of the multifocal electroretinographics (ERGs) were reduced in the area of the cecocnetral scotoma. Irregularities in the inner segment/outer segment (IS/OS) line of the photoreceptors were observed over the superior fovea by optical coherence tomography (OCT). The diagnosis of the AZOOR was made. The patient was followed with steroid treatment. The cecocentral scotoma disappeared in 3 months after the onset. At 6 months, the multifocal ERGs in the area corresponding to the cecocental scotoma and irregularities in the IS/OS line on OCT were improved. His visual acuity was 20/20 in both eyes.

Conclusions:
The clinical distinction between a retinal versus an optic nerve problem may be difficult in case of subtle retinopathies. The multifocal ERGs and OCT images are helpful in this regards. The abnormalities of the inner/outer segment (IS/OS) junction and reduced amplitude corresponding to the scotoma area can be detected in patient with suspected AZOOR.

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Keywords: Retina, Optic Neuropathy, Diagnostic Tests

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 228

Long-term Follow-up of Laser Pointer Induced Macularopathy

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Introduction:
To evaluate the clinical characteristics and natural course of laser pointer induced macularopathy by long-term follow-up .

Methods:
14 cases (18 eyes) with laser pointer macularopathy were followed up for at least 6 months. Fundus photography, BCVA, visual field and OCT were examined at each follow-up, fundus fluorescein angiography (FFA) was tested in 10 patients at presentation.

Results:
At presentation, all patients with laser pointer macularopathy complained of sharp decline in BCVA accompanied by central scotoma immedially after laser exposure; fundus examination revealed yellow-white foveal lesions in 12 cases (16 eyes) and slightly elevated subfoveal hemorrhage in other 2 cases (2 eyes), which corresponded to a hyperreflection between outer neuroretina and RPE layer or hyporeflection within neuroterina respectively by OCT, as well as late fluorescein staining or persistently blocked fluorescence respectively by FFA; Visual field test revealed central scotoma in all eyes. During follow-up, significant visual improvement was achieved within 2 weeks in most eyes except the eye with subfoveal hemorrhage, no matter oral steroid was used or not. At one month follow-up, most injured eyes showed BCVA of 0.8 or above, fundus examination showed foveal retinal depigmentation or mostly absorbed subfoveal hemorrhage, visual field test revealed relative or dense scotoma in all injured eyes. OCT shows the foveal pigment epithelium and cones IS/OS discontinuity. At 3 month and later follow-up, all patients showed normal BCVA and mild foveal depigmentation, although 2 cases (3 eyes) still complained of mild scotoma, which was proved by visual field test. OCT shows normal IS/ OS junction and mild RPE atropthy in most cases, while discontinued IS/ OS junction and RPE layer accompanied by cystic hyporeflection in outer neuroretina in eyes with scotoma complaint.

Conclusions:
High powered laser pointer can cause macular damage with different severity. Although visual prognosis is good in most patients, persistant scotoma might occur in some cases.

References: None.

Keywords: Macular Injury, Laser Pointer, Optical Coherence Tomography, Visual Field

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 229

Use Of Wide-Field Retinography For Periphlebitis Detection In Patients With Multiple Sclerosis.

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Introduction:
Retinal periphlebitis (RP) is characterized by perivascular exudation, hemorrhage, and retinal venous sheathing. The relationship between RP and multiple sclerosis (MS) is known and has a variable incidence among series (5-39%). RP has been related to a more active disease (1). Retinal inflammation parallels the inflamatory processes in the central nervous system and his presence of RP might favor the election of a more effective drug, even assuming a greater risk of side effects. The objetive of this study was evaluate the role of wide-field retinography to detect periphlebitis in patients without ocular symptoms.

Methods:
A prospective cohort including 118 patients with remittent-recurrent multiple sclerosis (aged 18–55 years), underwent a ophthalmic examination, between May/2013 to May/2014. We collected demographic and MS-related variables, measured high- and low-contrast monocular visual acuity using ETDRS (Early Treatment Diabetic Retinopathy Study), Color vision was tested using Hardy-Rand-Ritter pseudoisochromatic plates, and ophthalmic fundus was registered using ultra-widefield scanning laser ophthalmoscopy (Optomap). Images were evaluated by and trained ophthalmologist.

Results:
Six patients (5,08%) without ocular symptoms showed retinal venous sheathing, perivascular exudation and or hemorrhage compatible with periphlebitis.

Conclusions:
The incidence asymptomatic periphlebitis detected with wide field retinography in our serie was similar to previous experience with slit lamp fundus ophthalmoscopy and pupil dilatation with tropicamide 1%. Ultra-widefield scanning laser ophthalmoscopy appears to be a useful tool for assessing easily the presence of phlebitis in patients with multiple sclerosis.

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Keywords: Demeylinating Disease, Diagnostic Tests, Retinography, Periphlebitis, Multiple Sclerosis

Financial Disclosures: P. Villoslada has received consultancy fees from Roche, Novartis, MedImmune, TFS, Heidelberg Engineering, Digna, Biotech,Neurotech Pharma. And shareholder of Bionure.

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Poster 230

An Atypical Presentation of Giant Cell Arteritis

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Introduction:
We observed an atypical presentation of giant cell arteritis that initially made the diagnosis difficult.

Methods:
A 71-year-old man began experiencing recurrent transient vision loss in the right eye in April 2014. Each episode lasted for 10-15 minutes and could sometimes be triggered by Valsalva maneuver. The episodes occurred 5-8 times daily, but gradually decreased in frequency and transitioned to episodes of "silver blurriness." He also experienced two episodes of "overall weakness" that lasted 10-15 minutes. At the end of May, he began to experience similar transient vision loss in the left eye. Fundus fluorescein angiography showed significant delayed retinal arterial, venous, and choroidal filling along with poor peripheral perfusion and microaneurysms bilaterally. ESR was 47mm/hr, brain MRI and head and neck MRA were unremarkable, and there was 25% blockage of the right carotid artery seen on carotid ultrasound. During our neuro-ophthalmologic evaluation in June, best corrected visual acuities were 20/40-1 OD and 20/25-2 OS, intraocular pressures were normal bilaterally, and there was no iris neovascularization. His funduscopic examination was unchanged. Automated visual field testing showed scattered non-specific changes OD and a paracentral scotoma OS. Five days later, he awoke with a persistent central scotoma in the left eye associated with headache, jaw pain, and bilateral temple tenderness.

Results:
Color Doppler of the orbits revealed no flow through the left posterior ciliary arteries with normal flow through the left central retinal artery. A temporal artery biopsy was consistent with giant cell arteritis. He was treated with three days of intravenous Solumederol, followed by an oral Prednisone taper with no improvement in vision.

Conclusions:
Giant cell arteritis can have atypical presentations and should still be highly considered in elderly patients with recurrent transient vision loss. Immediate treatment with steroids is important to prevent vision loss in the fellow eye.

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Keywords: Vascular Disorders, Retina, Orbit/Ocular Pathology

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Poster 231

Discordance Rates in Healing/Healed Arteritis in Temporal Artery Biopsies: The Role for Bilateral Biopsies

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Introduction:
Temporal artery biopsy (TAB) is the gold standard diagnostic modality for giant cell arteritis (GCA). Since bilateral positivity for active GCA is 90+%, unilateral TAB is considered standard of care for diagnosing GCA. (1,2) However, GCA can present with active, healing/healed and no injury in a segmental uneven distribution along the extracranial carotid artery tree. Healing/healed arterial injuries are important to identify since they are usually treated as active GCA. We studied the discordance rate for healing/healed arterial injury in bilateral TAB to verify whether unilateral biopsies would render as high diagnostic yield as they do in active GCA.

Methods:
We retrospectively studied TAB performed by two neuro-ophthalmologists at our institution during the last 4 years. We classified them into 3 categories: negative, healing/healed arterial injury, and active GCA. We defined healing/healed arterial injury as fibromyxoid intimal change, fragmentation and/or loss of the internal elastic lamina and medial scarring, with or without neovascularization. Focal areas of persistent chronic inflammation may remain. Statistical analysis was used to compare diagnostic sensitivity between both groups.

Results:
Of the 257 TAB studied, 166 were negative, 56 were positive for active GCA and 35 showed healing/healed arterial injury. Fifty-two of the active GCA cases (52/56) and 34 of the healing/healed arterial injury cases (34/35) had bilateral TAB performed. Bilateral positivity was observed in 46/52 (88%) of active GCA cases, while 6/52 (12%) cases showed unilateral positivity. Healing/healed arterial injury was identified bilaterally in 11/34 (32%) cases, while unilateral lesions were observed in 23/34 (68%) cases. Thirty-four of the 35 cases (97%) with healing/healed arterial injury had high clinical suspicion and were treated as active GCA. Diagnostic sensitivity of unilateral TAB is significantly ($p<0.01$) lower for healing/healed arterial injury compared to active GCA.

Conclusions:
Bilateral TAB should be standard of care to detect the characteristic histopathological features of healing/healed arterial injury.

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Keywords: Giant Cell Arteritis, Temporal Artery Biopsy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 232

Bilateral Intracranial Optic Nerve and Chiasmal Involvement in IgG-4 Related Disease

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Introduction:
IgG-4 related disease (IgG4-RD) is a disease that can affect many organs and is characterised by lymphoplasmocytic infiltration of IgG4-positive cells, obliterative phlebitis and storiform fibrosis. Orbital and ocular adnexal involvement in IgG4-RD has been reported with reports of optic nerve involvement. Systemic steroids are the primary treatment used in IgG4-RD. However, the visual outcome is not frequently reported. We present a case of severe loss of vision due to biopsy-proven IgG4-RD bilateral intracranial optic nerve and chiasmal involvement with pachymeningitis.

Methods:
Case report and literature reviw

Results:
The patient was treated with IV Rituximab which led to moderate improvement of visual function.

Conclusions:
IgG4-RD can present as recurrent pachymeningitis and involvement the intracranial optic nerves and optic chisam. Treatment with Rituximab may have role in the the treatment of lesions of the visual pathway in IgG4-RD.

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Keywords: Igg4-Related Disease, Pachymeningitis, Rituximab, Optic Neuropathy, Chiasmal Syndrome

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 233

Neuromyelitis Optica Preceded Be Seizure Disorder

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Introduction:
We present a case of a girl with Sturge Weber and NMO in which the seizure activity and the NMO attacks concur.

Methods:
Case report and review of literature

Results:
An 11-year-old female with past medical history significant for IUGR at birth, cleft palate as part of Pierre Robin sequence, and Sturge Weber syndrome diagnosed at the age of three due to seizures. She was otherwise neurologically intact until the age of 11 when she had her first seizure in 8 years. Following the seizure she started complaining of tingling in left arm and hand that quickly progressed to weakness, and was diagnosed with transverse myelitis. Weakness gradually improved after three days of IV methylprednisolone treatment. NMO –IgG were positive and she was started on azathioprine. A month after initiation of treatment she experienced a couple of focal seizures and one episode of generalized seizure with urinary incontinence, after which she complained of vision loss in the left eye and was diagnosed with optic neuritis. She was treated with rituximab followed by IVIG, but 3 month later she came in with another episode of optic neuritis in the same eye that was preceded by a generalized seizure. Given the rituximab failure she was treated with IV steroids again, PLEX for 5 consecutive days, mycophenolate mofetil and levetiracetam.

Conclusions:
This case report demonstrates a temporal relationship between the seizure activity and NMO attacks. There is no known pathogenic link among these two condition and we believe that the disruption of the blood-brain barrier (BBB) could explain this concurrent appearance. It is unclear if BBB disruption by the seizure promotes the NMO attack or vice versa.

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Keywords: Neuromyelitis Optica, Seizures, Blood-Brain Barrier

Financial Disclosures: The authors had no disclosures.

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Poster 234

Optic Nerve Meningioma Masquerading as Neurosarcoidosis

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Introduction:
Meningiomas are typically benign tumors often affecting middle-aged women. The orbit is a common location for meningiomas, with many of these involving the optic nerve[1]. These optic nerve sheath meningiomas may have a variety of presentations, including optic atrophy, papilledema, or shunt vessels[2]. Rarely, neurosarcoidosis can mimic an optic nerve sheath meningioma due to their similar appearance on radioimaging[3].

Methods:
A case report.

Results:
A 25-year-old healthy woman with a two-year history of facial lesions, previously diagnosed as cystic acne, presented with normal visual acuity and color vision. She had been diagnosed with right optic nerve edema on a routine eye exam. Magnetic resonance imaging (MRI) revealed a right intraconal enhancing mass. The patient had two skin biopsies that revealed non-caseating granulomatous inflammation felt to represent sarcoidosis. Given this finding, the optic nerve lesion was attributed to neurosarcoidosis and the patient was treated with intravenous and oral prednisone. Six months later, she presented with a substantial decline in visual acuity to hand motions vision in the right eye. She was also unable to identify any color plates with the right eye and had worsened optic nerve swelling. A repeat MRI showed a slightly larger enhancing lesion. Due to a decline in vision and lack of response to systemic therapy, an optic nerve biopsy and partial tumor excision was performed. Pathologic examination revealed an optic nerve meningioma. The patient was referred to radiation oncology for further therapy.

Conclusions:
In this case, biopsy-proven cutaneous sarcoidosis with an optic nerve lesion prompted a diagnosis of neurosarcoidosis. The true diagnosis was not confirmed until months later when the patient's vision significantly declined, prompting an optic nerve biopsy that provided the correct diagnosis of optic nerve meningioma.

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Keywords: Neuroimaging, Tumors, Orbit, Orbit/Ocular pathology

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Poster 235

Comparison of the Clinical Characteristics of Patients with Active Arteritis and Healed Arteritis, the Two Histopathological Patterns Considered Positive in Giant Cell Arteritis

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Introduction:
Histopathologically, there are two patterns considered diagnostic of giant cell arteritis (GCA): those with inflammation of the vessel wall (active arteritis) and those with post-inflammatory alterations (healed arteritis). The aim of our study was to determine the clinical characteristics and outcomes for patients with these two types of positive temporal artery biopsy.

Methods:
An IRB-approved retrospective review was conducted of all patients with a positive temporal artery biopsy between 2004 and 2013. Twenty-two patients with biopsy-proven GCA were found. All biopsy specimens had been examined and interpreted by a single ocular pathologist. Eleven patients had active arteritis and eleven patients had healed arteritis. We compared presenting symptoms, ischemic ocular events, inflammatory markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], and platelet count), relapses, and dosage requirements of steroids between the two groups.

Results:
Seven of the 11 patients with active arteritis had an initial ocular ischemic event compared to 3 of the 11 patients with healed arteritis. There was no statistical difference in initial ESR between the two groups, but CRP and platelet counts on initial presentation were statistically higher in the active group ($p = 0.0002$ and $p < 0.0001$ respectively). Patients with active arteritis on biopsy required higher doses of steroids over a 2-year follow-up compared to the healed group: on average, 11 mg/day to 1 mg/day at 1 year ($p = 0.0008$), and 7 mg/day to 0.5 mg/day at 2 years ($p = 0.0208$), respectively. During the follow-up period, 2 of the 11 patients in the active group demonstrated a recurrent ischemic ocular event either to the same or fellow eye while in the healed group there were no recurrent ischemic ocular events.

Conclusions:
Patients with a healed arteritis pattern on histopathological examination of temporal artery biopsy appear to have a better prognosis and may require less aggressive treatment than those with active inflammation.

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Keywords: Optic Neuropathy, Neuro-Ophth And Systemic Disease

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Poster 236

Autologous Hematopoietic Stem Cell Transplantation in Neuromyelitis Optica - An Update

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Introduction:
Neuromyelitis Optica (NMO) is an immune-mediated astrocytopathy characterized by frequent demyelinating/necrotizing attacks of optic nerves and spinal cord. Treatments are highly toxic and incompletely effective. Fifty percent of patients are blind in one eye or require a mobility aide within 5 years. The immunological features of NMO, coupled with its severity make it an ideal candidate for a trial of autologous non-ablative hematopoietic stem cell transplantation (AHSCT) with the goal of disease remission and freedom from immunosuppressive medications. The objective of this study is to determine if NMO patients, despite maintenance therapy, experience a reduction in relapses and disability without ongoing immunosuppressants after AHSCT. We hypothesize a greater than or equal to 50% reduction in the proportion of patients relapsing 3 years post-transplant.

Methods:
Patients 18-65 with greater than or equal to 1 relapse in 12 months, or 2 (or more) relapses in 24 months, despite immunotherapy and EDSS less than 6.5 are eligible. Patients undergo non-ablative stem cell mobilization and infusion using cyclophosphamide, rituximab and ATG. Outcomes include EDSS, NMO-IgG titers, OCT and MRI q6-12 months for 5 years. Ten subjects provide 80% power for our primary outcome.

Results:
Three NMO patients have undergone transplantation thus far. A 28F was transplanted in May 2011 with pre-transplant annualized relapse rate (ARR) of 5 and EDSS 4.5, now 0 and 2.0 at month 41 respectively. A 36F was transplanted in April 2012 with pre-transplant ARR of 5, now 1 and 3.5 at month 30 respectively, who started on mycophenolate mofetil at her request. A 39M was transplanted in January 2014 with pre-transplant ARR of 1.3 and EDSS 3.5 who remains stable at 10 months. Despite clinical improvement in all patients, the latter two patients remain NMO-IgG seropositive.

Conclusions:
Thus far, this AHSCT regimen is well tolerated with marked clinical improvement. Additional patients and longer follow-up will determine if these benefits persist.

References: None.

Keywords: Neuromyelitis Optica, Optic Neuritis, Autologous Hematopoietic Stem Cell Transplantation, Clinical Recovery

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 237

Social Media and Susac Syndrome

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Introduction:
The advent of social media has revolutionized societal communication. Patients also use this medium to better educate themselves. Facebook is one of the leading social media forums and is utilized by sufferers of Susac Syndrome (SS) and caregivers. The impact of social media on impressions of disease states is unknown. The current study attempts to answer several questions regarding patient usage of Facebook.

Methods:
Users of the Susac Syndrome Facebook Group (SSFG) were submitted to a 44 item questionnaire. Several questions were directed at perceptions of disease state and interactions with fellow users via a linear 5-point scale.

Results:
On 10/30/2014, the SSFG contained 479 members and 37 subjects (7.7%) returned questionnaires. Twenty seven (73%) were female and mean age of symptom onset was 32.3 years (16-54). The first symptom was visual in 13 (35%) and auditory in 8 (22%). Fourteen (38%) were initially diagnosed with multiple sclerosis and 30 (81%) were seen by two or more physicians prior to their allegedly correct diagnosis. Regarding feeling listened to by other users of the SSFG, 30 (81%) listed a 5 on the linear scale indicating strong agreement. Support by other users scored a 5 in 25 (68%) and 23 (62%) listed a 5 in relation to presentation of useful information by other SSFG users. However only nine (24%) felt that their treatment was fully effective.

Conclusions:
Most users of the SSFG had very favorable experiences. Very few agreed that the disease was effectively treated however. A limitation of this study is the definitive diagnosis of SS sufferers could not be confirmed. Future study should be directed at the impact of the SSFG on parameters such as vision, cognition, or hearing or if subsequent users received an earlier correct diagnosis reducing disease morbidity.

References: None.

Keywords: Susac Syndrome, Social Media, Vascular Disorders, Neuro-Ophth & Systemic Disease

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Poster 238

Horner's Syndrome as Initial Manifestation of a Malignant Peripheral Nerve Sheath Tumor

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Introduction:
Horner's Syndrome may be the rare presenting manifestation of an occult malignancy. In a previous study, 13% of 450 patients presenting with Horner's Syndrome had tumors, but only 3% had undetected malignancies. This case illustrates a patient who presented with Horner's Syndrome several months prior to his neuroimaging studies and diagnosis.

Methods:
Case Report.

Results:
We report a 56-year-old male who has a history of Neurofibromatosis Type I diagnosed at age 15. Within the past year, the patient began to notice a droopy lid OD of several months duration. Subsequently he began to have difficulty swallowing both liquids and solids, associated with 100-pound weight loss over a period of 6 months. His physical examination showed bilateral Lisch Nodules, bilateral optic nerve hypoplasia, multiple cutaneous neurofibromas, palpable neck mass and café au-lait spots. The cocaine test was strongly positive confirming the diagnosis of Horner's Syndrome. The degree of anisocoria following the administration of cocaine was greater than 2.2 mm. Neuroimaging studies demonstrated a large right parapharyngeal space soft tissue tumor, measuring up to 6 cm, stretching and displacing the carotid sheath. The patient underwent surgical resection of the tumor and pathology was consistent with a malignant peripheral nerve sheath tumor. It is noteworthy that these peripheral nerve sheath tumors often arise from pre-existing neurofibromas, and up to 50% of these tumors occur in patients with Neurofibromatosis Type I.

Conclusions:
A sarcoma is specifically defined as a malignant peripheral nerve sheath tumor when it arises from a preexisting benign nerve sheath tumor (neurofibroma). The patient underwent subtotal resection of the tumor, however he developed pulmonary metastasis, which portends a poor prognosis. This case illustrates that patients suspected of having Horner's Syndrome require prompt attention, specific pharmacologic testing with regards to neuroanatomical localization and appropriate neuroimaging studies and investigations.

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Keywords: Horner's Syndrome, Neurofibromatosis, Malignant Peripheral Nerve Sheath Tumor, Neuroimaging

Financial Disclosures: The authors had no disclosures.

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Poster 239

Birefringence of Retinal Nerve Fiber Layer and Retinal Blood Flow Velocity in Multiple Sclerosis

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Introduction:
Cerebral hypoperfusion in the normal-appearing white matter of MS patients are reported, indicating the role of vascular dysfunction in MS pathophysiology. The retina has been used to study the pathophysiology of MS. Retinal nerve fiber layer (RNFL) thinning is established as an ocular biomarker of neurodegeneration. The goal of this project is to determine the relationship between the birefringence of RNFL (microtubule integrity), retinal blood flow velocity and clinical MS manifestation.

Methods:
Custom built polarization sensitive optical coherence tomography (PS-OCT) was used to measure the averaged birefringence and thickness of the peripapillary RNFL. A retinal function imager (RFI, Optical Imaging Ltd, Rehovot, Israel) was used to study the velocity of blood flow of retinal arterioles and venules. A clinical OCT (Zeiss Cirrus) was used to measure the peripapillary RNFL thickness and macular ganglion cell layer (GCL) thickness. Seven MS patients were clinically assessed and recruited (averaged age 48.4 ± 14.0 yrs old, 6 females and 1 male).

Results:
PS-OCT derived birefringence of the peripapillary RNFL is related to RNFL thickness measured by Cirrus OCT ($r = 0.65$, $P < 0.05$) and PS-OCT ($r = 0.43$, $P < 0.05$). The birefringence is also related to blood flow velocities in arterioles ($r = 0.40$, $P<0.05$) and venules ($r =0.68$, $P<0.05$). The birefringence is not related to EDSS scores, but related with disease duration ($r = - 0.86$, $P<0.05$). In addition, the birefringence is related to GCL thickness ($r = 0.66$, $P<0.05$).

Conclusions:
This is the first study using PS-OCT to study the RNFL birefringence and its relationship with retinal microvascular function. The strong correlation between these two measurements indicates the coexistence of RNFL microtubule dysfunction and retinal microvascular dysfunction. Further studies with a large sample of MS patients are needed to further elucidate the findings.

References: None.

Keywords: Demyelinating Disease, Neuro-Ophth & Systemic Disease (MS), Retina, Polarization Senstive OCT & Bireferingence, Retinal Microvascular Function

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Poster 240

Botox For Chronic Intractable Headache Among Veterans At VA Medical Center, Long Beach, California

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Introduction:
Veterans with chronic migraine often associate with comorbidity including traumatic brain injury (TBI), PTSD, control medication addition (RxA) and occipital headache with cervical spondylosis(C-DJD). Botox (Onabotulinumtoxin A) has not been well reported the efficacy for veterans with chronic migraine and multiple comorbidity. We review the effect of Botox in this group of veterans at the Neurological Clinic, VA Long Beach CA to determine the impact of these comorbidities on the efficacy of Botox.

Methods:
The veterans with chronic migraine (more than 4 hours daily and 15 days monthly) who failed 3 out of 4 prophylactic medications (TCA, beta-blocker,topiramate, divalproex) without contraindication to Botox were recruited. The comorbidities were reviewed. Botox injection was performed according to 2010 Allergan Inc. protocal. The efficacy was graded by percentage of reduce in intensity and days of headache along the use frequency of acute medications at end of 3 months.

Results:
16 patients (9 F, 7 M; age 29-67, average 43 y) with chronic migraine for average of 16.1 years (2- 41 years) received treatments (1 to 8 times) from 9/2012 to 10/2014 with follow-up of 3 to 25 months. Totally 70 treatments were performed. Nine (56 %), 8 (50%), 5 (31%) and 7 (44%) patients had PTSD, RxA, TBI and C-DJD respectively. Four (25%), 7 (43.7%), 1 (6.2%), and 2 (12.5 %) patients had 1, 2, 3 and 4 comorbidities respectively. Twelve patients (75%) reported satisfactory response with severe headache (> 7 on scale) reduced to less than 8 days monthly; 6 of them had severe headache less than 3 days monthly. Among the 70 treatments, 53 (75.7%) reduced severe headache to less than 8 days, and 38 (54%) after the 3rd treatment reduced to less than 3 days monthly.

Conclusions:
The comorbidities do not impact the Botox effect on treating the chronic migraine among the veterans. The small sample size cannot determine the individual comorbidity against Botox treatment. The favorable response among PTSD or control-medicine addicted veterans will be better determined by long term and larger sample-sized study.

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Keywords: Migraine, Headache, Botox

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 241

Thin-Film Optical Notch Filter Spectacle Coatings for the Treatment of Migraine and Photophobia

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Introduction:
Previous evidence suggests that optical treatments hold some promise for treating migraine and photophobia. We designed an optical notch filter, centered at 480 nm to reduce the direct stimulation of intrinsically photosensitive retinal ganglion cells. We used thin film technology to integrate the filter into spectacle lenses that could be worn by migraine patients.

Methods:
We designed a prospective, randomized, double-masked crossover study. Our primary endpoint was the 6-item Headache Impact Test (HIT-6). We developed two thin-film optical notch filters: the therapeutic filter blocked visible light at 480 nm, while a 620 nm filter was designed to act as a sham filter. Each participant was asked to wear a set of lenses with one of the filters for two weeks; after a 2-week washout period during which no study lenses were worn, the participant wore lenses with the other filter for two weeks

Results:
We enrolled 48 subjects with chronic migraine and 37 completed all study procedures. Wearing either the 480 nm or the 620 nm spectacle lenses resulted in clinically and statistically significant reductions in HIT-6 score. However, there was no significant difference when comparing the overall effect of the 480 nm lenses and the 620 nm lenses.

Conclusions:
Although the 620 nm filter was designed as a sham intervention, basic science research published since the institution of the trial has indicated that melanopsin, the photopigment found in intrinsically photosensitive retinal ganglion cells, is bistable. This property of the melanopsin molecule may explain the unexpected efficacy of the 620 nm filter. The effect of the two filters does not appear to be a placebo effect and we conclude that spectacle lenses outfitted with a thin-film optical notch filter may be a useful adjunct in the treatment of chronic migraine.

References: None.

Keywords: Neuro-Ophth & Systyemic Disease, Migraine, Photophobia, Light Sensitivity, Intrinsically Photosensitive Retinal Ganglion Cells

Financial Disclosures: Drs. Katz and Blair have equity interests in and hold management positions in Axon Optics, a limited liability corporation that markets eyewear for the treatment of migraine and photophobia. Drs. Katz, Blair, Digre and Warner are inventors on a patent pending for the thin-film coatings described in this research and stand to receive royalties on any commercial sales of products based on these coatings.

Grant Support: This investigation was supported in part by: Axon Optics, LLC, Salt Lake City, UT NIH T35HL007744 (RNH, AS) The University of Utah Study Design and Biostatistics Center, with funding in part from the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant 8UL1TR000105 (formerly UL1RR025764) and an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York, USA, to the Department of Ophthalmology and Visual Sciences, University of Utah, Salt Lake City, Utah. JG was supported by the University of Utah, Office of Undergraduate Research, Undergraduate Research Opportunities Program (UROP). RNH and AS were supported by the Medical Student Research Program at the University of Utah School of Medicine, funded by NIH/NHLBI Training Grant # T35 HL007744 (PI: Jerry Kaplan, PhD) and University of Utah institutional support.

Poster 242

Monitoring Alzheimer's Disease with Retina Examination

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Introduction:
We aimed to monitor patients with Alzheimer's Disease (AD) with retina examination using optical coherent tomography (OCT) and fundus autofluorescein (FAF) .

Methods:
30 patients with mild cognitive impairment (MCI) were examined for 6 months. At the 3rd and 6th months, OCT and FAF tests were repeated. Curcumin (Turmeric Phytosome with Meriva) was also given 80 mg bid for 3 days. We tried to detect new changes on OCT and FAF. Any change in curcumin stained lesions (increase in number and size) and apperance of lesions on FAF were taken into account. No other tests like PET- CT were ordered.We also followed up 10 healthy age- matched controls at the same intervals.

Results:
In 8 patients progression in neurodegeneration was detected in the follow up. In 5 patients, appearence of the lesions on FAF changed. Hyperfluorescent images became hypofluorescent which demonstrated atrophy of RPE . In 3 patients new curcumin stained beta amyloid plaques were detected which was consistent with increased amyloid burden.In 22 patients images showed stable lesions.No defects were found in the control group.The patients in whom progression were found were sent for neurologic examination. Either drug dosages were changed or new drugs were started.

Conclusions:
We believe that OCT and FAF examinations with curcumin are very useful and trustable in the follow up of AD patients.

References: None.

Keywords: Monitoring, Alzheimer's Dısease, OCT, FAF, Retina

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 243

Why is He Losing His Sight? He is Losing His Photoreceptor!

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Introduction:
Retinitis pigmentosa has a wide spectrum of clinical and retinal presentation and can lead to progressive visual field loss. Papilledema can also lead to visual field defects and decreased vision. We describe here an unusual case of combined optic neuropathy and retinal degeneration leading to vision loss.

Methods:
Case report presentation.

Results:
26 years old male with history of nonspecific myopathy (biopsy proven) and chronic mild renal failure (biopsy showed focal segmental glomerulonephritis), was referred to the ophthalmology clinic due to difficulties in his vision especially at night. On exam visual acuity was 20/25 in both eyes, with mildly constricted visual fields. Fundus showed normal optic disc color and arteriolar narrowing. Eelectroretinography was compatible with combined rod and cone diffuse dystrophy.2 years later he reported progressive decrease vision, headache and tinnitus. He had a vision of 20/30 and tunnel vision of central 10 degrees. The retina had only few pigmented spicules and he had chronic optic disc edema. Investigation revealed increased intracranial hypertension with elevated protein. Treatment with topiramate was initiated. High Resolution Optical coherence tomography (HRT-OCT) showed diffuse loss of photoreceptors with only less than 1 μm^2 of subfoveal photoreceptors area. We presume that the main reason for the vision loss in this patient was the progressive retinal degeneration and not optic neuropathy. He is currently treated by oral topiramate with good compliance.

Conclusions:
We describe a rare case of combined syndrome of myopathy, nephropathy, Retinitis pigmentosa and elevated intracranial pressure, who experienced progressive visual field loss.

References: None.

Keywords: Increased Intracranial Hypertension, Papilledema, Retinal Degenration, HRT-OCT

Financial Disclosures: The authors had no disclosures.

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Poster 244

Extensive Macular Serous Retinal Detachment As The Initial Presentation Of *Bartonella Henselae* Induced Neuroretinitis

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Introduction:
The clinical appearance of *Bartonella henselae* associated neuroretinitis is thought to develop primarily from prelaminar optic nerve head inflammation leading to disk edema and serous retinal detachment can occur. A macular star classically develops, however many cases without star formation have been reported. We report a case of extensive serous macular detachment without clinically apparent optic disk changes or macular star appearance.

Results:
A 28 year old female presented with a two day history of decreased vision, mild pain in the left eye. She had been scratched by a cat, although not recently. Visual acuity measured 6/9 OD and 6/120 OS with a small left RAPD. On dilated fundoscopic examination the optic nerves did not appear elevated and their margins were sharply defined. A serous macular retinal detachment (~6 500 µm in diameter) was noted in the left eye (right eye within normal limits). Fluorescein angiography showed progressive fluorescence at the optic nerve head consistent with leakage and mild pooling within the macula. There was no evidence of RPE damage, focal leakage, or choroidal neovsacularization. Optical coherence tomography confirmed a neurosensory retinal detachment. CT and MRI scans were found to be normal. CRP, syphilis serology, ANA, ACE level and a chest x-ray were all negative or within normal levels. Bartonella serology revealed an IgG titre of 1:64 indicating prior exposure, although a time course could not be established. Her clinical findings spontaneously resolved over one month. Stellate macular exudates did not develop. Subsequent fluorescein angiography and indocyanine green angiography did not reveal any abnormalities.

Conclusions:
Our case is an atypical presentation of Bartonella neuroretinitis. There are only two other case reports of serous neurosenory retinal detachment without clinically apparent optic nerve swelling. Our case highlights the importance of performing fluorescein angiography in this setting and screening for Bartonella in patients with neurosensory detachment accompanied by angiographic leakage at the optic nerve head.

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Keywords: Neuro-Ophth & Infectious Disease, Optic Neuropathy, Retina

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 245

Visual Outcomes in Giant Cell Arteritis in Patients with Polymyalgia Rheumatica on Prior Corticosteroids

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Introduction:
Blindness caused by giant cell arteritis (GCA) is usually severe. Some patients with GCA have an earlier diagnosis of polymyalgia rheumatica (PMR), in which case they receive relatively low dose corticosteroids to alleviate discomfort.[1] We hypothesized that GCA patients who were receiving corticosteroids prior to visual loss would have less severe visual loss than patients who had not received corticosteroids in advance.

Methods:
A retrospective chart review was performed of all patients with GCA who presented to the Massachusetts Eye and Ear Infirmary between the years of 2005-2013 and who underwent detailed Neuro-Ophthalmic examination. Visual fields were performed by automated (i.e. Humphrey) technique, unless there was severe visual loss, in which case patients underwent Goldmann perimetry or confrontation testing. Visual fields were graded as being normal or showing partial or "diffuse" (i.e. defects in all four quadrants) visual loss. Presently, 34 charts of patients with visual loss and adequate clinical information have been reviewed. Eleven of the 34 patients had PMR and visual loss secondary to GCA. Five of these patients had been on oral steroids prior to developing visual loss.

Results:
Three of the five PMR patients who were on corticosteroids before developing visual loss had a visual acuity of 20/25 or better; whereas, 3 out of 29 patients not on prior corticosteroids had a visual acuity ≥ 20/25 ($p = 0.006$). For visual field testing, two of the five PMR patients on corticosteroids before visual loss had diffuse field loss versus 16 of 29 patients not on corticosteroids ($p<0.001$).

Conclusions:
Patients with PMR who were on steroids prior to loss of vision from GCA had better visual acuity and visual field results in comparison to patients not on prior steroids. Our preliminary results demonstrate that even low dose corticosteroids may lessen the severity of blindness caused by GCA.

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Keywords: Vascular Disorders, Optic Neuropathy, Giant Cell Arteritis, Arteritic Ischemic Optic Neuropathy, Polymyalgia Rheumatica

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Poster 246

Progressive Supranuclear Palsy (PSP) After Ascending Aorta Dissection Surgery

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Introduction:
Progressive supranuclear palsy (PSP) is a rare brain disorder that causes serious and progressive problems with control of gait and balance, along with complex eye movement and thinking problems. We present a case in which developed a neurologic syndrome including PSP after ascending aorta dissection surgery.

Methods:
Observational case report of PSP after aortic surgery and brain ischemia.

Results:
A 41-year-old man complained of blurred vision and difficulty in moving both eyes. Three months ago, under the diagnosis of type A aortic dissection, he received emergency ascending and total arch replacement surgery. During surgery, cardiac arrest occurred for 5 minutes and hypothermia treatment was applied following surgery. Neuro-ophthalmic examination revealed vision 20/80 in both eyes. He also showed horizontal and vertical supranuclear gaze palsy. Neurologic examination showed a wide based ataxic gait and dysphagia. Neuro-imaging revealed multiple old infarct in both basal ganglia and corpus callosum and old microhemorrhage in both cerebellum, parietal, right occipital and left frontoparietal white matter. Nerve conduction study showed no specific findings. CBC, CSF analysis, vasculitis panel, myositis antibody profile, ESR, CRP, HIV, B12, and thyroid studies were normal. Nine months later the patient still complained of gait difficulty, blurred vision, and supraduction limitation. Genetic tests and muscle biopsy results were normal.

Conclusions:
This is an unusual case in which the neurologic syndrome cannot be explained as a postoperative cerebral syndrome. Neuronal damage may produce a syndrome of supranuclear gaze palsy, dysarthria, dysphagia and gait ataxia. Given to these findings we were able to recognize the possibility of PSP as a complication after aortic surgery. Wider recognition of this complication of cardiac surgery should lead to better understanding of its pathogenesis and appropriate management.

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Keywords: Progressive Supranuclear Palsy (PSP), Ascending Aorta Dissection Surgery, Supranuclear Gaze Palsy, Ataxia, Dysphagia

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Grant Support: None.

Poster 247

Delineation Of Natural History For Spinocerebellar Ataxia Type 7 (SCA-7) In Anticipation Of Rnai Therapy

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Introduction:
Among hereditary spinocerebellar ataxias, type 7 (SCA-7) is notable for a prominent retinal degeneration that adds blindness to the severe neurologic disabilities suffered by those affected with this disorder. Preclinical testing of RNAi therapy for SCA-7 has encouraged movement of this therapy to clinical trials in the near future. Critical to accurate evaluation of the safety and efficacy of such treatments are clear delineation of the disease natural history and of reliable quantitative outcome measures. We report the development of a single-center longitudinal natural history study emphasizing detailed evaluation of the retinal and optic nerve phenotype, and results from initial evaluation of two siblings with SCA-7.

Methods:
25 patients with genetically confirmed SCA-7 are being recruited and will undergo detailed ophthalmologic and neurologic examination, Cambridge Color Testing (CCT), spectral domain optical coherence tomography (OCT), static &/or kinetic perimetry, microperimetry (MP-1), full-field electroretinography (ERG), evaluation of ataxia with both subjective and quantitative measures, video quantification of eye movement abnormalities, and brain MRI.

Results:
In a pilot evaluation, two siblings with moderately advanced SCA-7 demonstrated differences in severity of gait and limb ataxia, dysmetria, dysarthria, eye movement abnormalities, and pigmentary retinal degeneration. Striking were a distinctive retinotopic pattern of the retinal dystrophy and mildly anomalous optic nerve appearance, as well as distinctive features of CCT and ERG.

Conclusions:
Successful evaluation of potential treatments for SCA-7 will benefit from further refining our understanding of its natural history, as well as identifying those measures of retinal and optic nerve structure and function, and of eye movement control, that progress most rapidly and may be most amenable to being slowed or reversed. A particular advantage is the ability to directly observe the treated neural tissue and correlate any changes with functional ones, increasing the likelihood that lessons learned will also apply to other neurodegenerative and nucleotide repeat disorders.

References: None.

Keywords: Neuro-Ophth & Systyemic Disease, Genetic Disease, Retina, Optic Neuropathy, Diagnostic Tests

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Poster 248

Study Of The Dynamics Of Axonal Degeneration In Chemotherapy-Induced Neuropathy By In Vivo Corneal Confocal Microscopy.

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Introduction:
Peripheral neuropathy secondary to drugs is a cause of severe disability. Usually Invasive techniques as cutaneous nerve biopsy are employed for diagnosis. Corneal confocal microscopy (CCM) is a noninvasive and rapid technique to assess in vivo all structures of the cornea, including the sub-basal nerve plexus. We designed a prospective study to evaluate the usefulness of CCM for determinate peripheral neuropathy.

Methods:
Ten patients with a high probability of developing peripheral neuropathy secondary to drug treatment were evaluated. Specifically, patients who started treatment with taxanes, cisplatin and / or oxaliplatin.No patients with prior use of chemotherapy, previous corneal surgery or infection and /or contact lenses were included in the study.The patients were visited before treatment and two, four months, at the end of chemotherapy and 3 months after treatment. These images were subsequently analyzed by CCmetrics Software (Manchester University) analyzing the Nerve Fibre Density (CNFD), Nerve Branch Density (CNBD), Nerve Fibre Length (CNFL), Nerve Fibre Total Branch Density (CTBD), Nerve Fibre Area (CNFA) and Nerve Fibre Width (CNFW). Results were analizad by means Generalized Estimated Equations (GEE) models with SPSS ver.20.

Results:
All patients showed statistically significant decrease in all measurements except in CNFW. After ending the treatment all patients showed improve in the last evaluation of the corneal sub-basal nerve plexus. This data correlates with the evolution of the clinical periphery neuropathy.

Conclusions:
Confocal microscopy appears to be a reliable method for assessing acute neuropathy in chemotherapy peripheral neuropathy safely and noninvasively. It is necessary to extend the number of patients to to confirm these findings.

References:
1. Argyriou, A. a, Koltzenburg, M., Polychronopoulos, P., Papapetropoulos, S., & Kalofonos, H. P. (2008). Peripheral nerve damage associated with administration of taxanes in patients with cancer. Critical Reviews in Oncology/Hematology, 66(3), 218–28.
2. Cruzat, A., Pavan-Langston, D., & Hamrah, P. (2010). In vivo confocal microscopy of corneal nerves: analysis and clinical correlation. Seminars in Ophthalmology, 25(5-6), 171–7.
3. Dabbah, M. a, Graham, J., Petropoulos, I. N., Tavakoli, M., & Malik, R. a. (2011). Automatic analysis of diabetic peripheral neuropathy using multi-scale quantitative morphology of nerve fibres in corneal confocal microscopy imaging. Medical Image Analysis, 15(5), 738–747.
4. Ferrari, G., Gemignani, F., & Macaluso, C. (2010). Chemotherapy-associated peripheral sensory neuropathy assessed using in vivo corneal confocal microscopy. Archives of Neurology, 67(3), 364–5.

Keywords: Corneal Nerves, Axonal Degeneratio, Chemotherapy-Induced Neuropathy, Confocal Microscopy, Diagnostic Tests

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North American Neuro-Ophthalmology Society

41st Annual Meeting

February 21-26, 2015
Hotel del Coronado • San Diego, California

Program Schedule

WEDNESDAY, FEBRUARY 25, 2015

6:30 a.m. – 12:30 p.m.	**Registration**	**Ballroom Foyer**
6:30 a.m. – 7:30 a.m.	**Breakfast**	**Crown Room**
7:00 a.m. – 7:30 a.m.	**Annual NANOS Business Meeting (all encouraged to attend)**	**Ballroom**
7:30 a.m. – 9:30 a.m.	**Sizzling Hot Topic: The IIHTT: What Have We Learned? [2 CME]** *Moderators: Michael Wall, MD & Kathleen B. Digre, MD*	**Ballroom**

This symposium is designed to give NANOS members detailed results and discussion of the IIHTT. The primary and secondary study outcomes including adverse events and treatment failures will be discussed. The 6 month outcome of changes in the OCT and quality of life measures will be presented along with the effects of weight loss in the context of all of the findings.

Upon completion of this course, participants should be able to: 1) Discuss the four main outcomes of the IIHTT (visual field MD, papilledema grade, QoL and CSF pressure; 2) Describe when acetazolamide-plus-diet should be considered as a treatment; 3) Describe 3 side effects to be aware of in recommending acetazolamide therapy; 4) Describe key OCT findings in IIH; 5) Recommend weight loss to patients with IIH and understand its importance in treatment of IIH; and 6) List 3 aspects of quality of life that will need to be addressed in patients with IIH.

		PAGE
7:30 a.m. – 8:00 a.m.	**What Have We Learned from the Idiopathic Intracranial Hypertension Treatment Trial** *Michael Wall, MD*	**421**
8:00 a.m. – 8:10 a.m.	**Q&A**	
8:10 a.m. – 8:20 a.m.	**Quality of Life in IIHTT Subjects 6 Months after Diagnosis and Treatment** *Kathleen B. Digre, MD*	**427**
8:20 a.m. – 8:25 a.m.	**Q&A**	
8:25 a.m. – 8:35 a.m.	**Treatment of Failures in the Idiopathic Intracranial Hypertension Treatment Trial** *Julie Falardeau, MD*	**435**
8:35 a.m. – 8:40 a.m.	**Q&A**	
8:40 a.m. – 8:50 a.m.	**Safety and Tolerability of Acetazolamide: The IIHTT Experience** *Martin ten Hove, MD, M.Eng, FRCSC*	**439**
8:50 a.m. – 8:55 a.m.	**Q&A**	
8:55 a.m. - 9:05 a.m.	**Change in Body Weight after a 6-Month Telephone Weight Loss Intervention in Normal Weight, Overweight, and Obese Subjects with the Idiopathic Intracranial Hypertension** *Betty Kovacs, MS, RD*	**449**

9:05 a.m. – 9:10 a.m.	**Q&A**	
9:10 a.m. – 9:30 a.m.	**Panel Discussion**	
9:30 a.m. – 9:45 a.m.	**Coffee Break**	**Crown Room**
9:45 a.m. – 11:00 a.m.	**Mechanical Causes of Strabismus [1.25 CME]** *Moderators: Stacy Pineles, MD & Nicholas J. Volpe, MD*	**Ballroom**

This symposium will present a case initiated discussion of a variety of topics covering the entire spectrum of mechanical, non-neurogenic strabismus in adults and children. Speakers will discuss various broad etiologic categories of mechanical strabismus, focusing on recent literature, state-of-the-art diagnostic techniques, favorite methods of distinguishing mechanical and neurogenic strabismus, anecdotal experience, and treatment options. Topics will be introduced by a short clinical case illustrating the overlap of mechanical and neurogenic strabismus with careful emphasis on differential diagnosis.

Upon completion of this course, participants will have an increased understanding of mechanical causes of strabismus and describe how to differentiate mechanical from neurological causes of strabismus. Specifically, they will describe: 1) Emerging concepts in the pathogenesis of "divergence insufficiency" esotropia as a form of mechanical strabismus; 2) How various ocular surgeries can be complicated by post-operative restrictive strabismus; 3) Pathological processes of the eye muscles that can cause vertical and horizontal restrictive strabismus; 4) The presentation of various congenital processes that cause mechanical strabismus in children and adults; and 5) How strabismus from orbital and peri-orbital disease presents and differs from neurologic causes of strabismus.

		PAGE
9:45 a.m. – 10:15 a.m.	**Sagging Eye Syndrome and Distance Esotropia in the Elderly** *Joseph L. Demer MD, PhD* Case: Vertical Strabismus after Glaucoma Valve – Is it a Skew Deviation?	**453**
10:15 a.m. – 10:24 a.m.	**Pathological Processes of Eye Muscles** *Stacy Pineles, MD* Case: Bilateral Upgaze Restriction from CFEOM – is it Supranuclear Upgaze Palsy?	**459**
10:24 a.m. – 10:33 a.m.	**Mechanical Strabismus Following Ocular Surgery** *R. Michael Siatkowski, MD* Case: Acquired Esotropia with Abduction Deficit in an adult from Thyroid Disease – Is it a Sixth Nerve Palsy?	**465**
10:33 a.m. – 10:42 a.m.	**Congenital Processes that Cause Incomitant Strabismus** *Gena Heidary MD, PhD* Case: Hypertropia Worse in Contralateral Gaze from a Mucocele – Is it a Fourth Nerve Palsy?	**469**
10:42 a.m. – 10:51 a.m.	**Orbital and Periorbital Disease Causing Mechanical Strabismus** *Nicholas J. Volpe, MD*	**477**
10:51 a.m. – 11:00 a.m.	**Panel Discussion**	
11:00 a.m. – 11:10 a.m.	**NOVEL Update**	**Ballroom**
11:10 a.m. – 12:00 p.m.	**Jacobson Lecture: Neuroendocrine Tumors In Neuro-Ophthalmology [1 CME]** *Presenter: Thomas Slamovits, MD*	**Ballroom**
12:15 p.m. – 1:30 p.m.	**Research Committee Meeting Luncheon**	**Garden Room**

1:30 p.m. – 3:30 p.m. **Optional Symposium: IIHTT- Weight Loss and Management [2 CME]** **Ballroom**
Moderator: Kathleen B. Digre, MD
Speakers: Betty Kovacs, MS, RD & Shana McCormack, MD

The recently published idiopathic intracranial hypertension treatment trial (IIHTT) recommends weight loss along with acetazolamide to treat idiopathic intracranial hypertension. While most Neuro-Ophthlamologists advise weight loss to patients who are overweight or obese, most are unsure of what to recommend for achieving this. Successful weight loss and maintenance requires diet, physical activity, and behavior modification, along with a strong support system. Most diets fail to provide this and doctors are not trained to address all of these, so patients are unsuccessful with long-term maintenance. In this session we will review the basic principles of weight loss including the physiology, the roles of diet, exercise, and behavior modification. We will differentiate between the facts vs fiction of weight loss and maintenance. We will also review evidence-based weight loss strategies and programs with the goal that each Neuro-Ophthalmologist has a practical action plan that fits their type of clinic population.

Upon completion of this course, participants should be able to: 1) Describe basic principles of weight loss—the myths and realities behind them; 2) Address what the IIHTT taught us about weight loss and what works for women and men with IIH; 3) Be able to list reputable weight loss strategies and programs and find these resources; and 4) Have a practical action plan on how to approach weight loss in their practice setting (private practice, academic, multi-specialty); and 5) Discuss weight loss strategies in children.

2:30 p.m. – 5:30 p.m. **Optional Symposium: Eye Movement and Vestibular Skills Transfer Session [3 CME]** **Carousel Room**
Moderators: Janet Rucker, MD and David Newman-Toker, MD, PhD

Dizziness and visual symptoms resulting from abnormal eye movements are common chief complaints in a Neuro-Ophthalmology practice and etiologies range from benign to ominous. The examination skill set required for optimal localization and accurate diagnosis demands familiarity with pattern recognition, special techniques for elicitation of exam signs, and identification of subtle abnormalities. Further, the ideal exam skill set for such symptoms encompasses overlapping areas of neuro-ophthalmologic and neuro-otologic expertise. This skills transfer session will provide a hands-on learning opportunity, supplemented with video examples of pathology, during participant rotation through stations for each of the following skills: vestibular ocular reflex assessment, positional testing of posterior and horizontal semicircular canals, provocative testing techniques for nystagmus elicitation, gaze testing of dynamic eye movements such as saccades and smooth pursuit, and interpretation of nystagmus patterns.

Upon completion of this course, participants should be able to: 1) Competently perform core neuro-vestibular examination skills; 2) Distinguish peripheral vestibular disorders from brainstem and cerebellar disease based on examination findings; and 3) Correctly identify nystagmus patterns.

2:30 p.m. – 2:55 p.m. **Introduction to the Vestibular Exam (with ARS)**
David Newman-Toker, MD

2:55 p.m. – 4:50 p.m. **Hands-on Training Sessions (6 station rotations, 15 minutes each / 2 minutes to rotate with additional time to revisit stations after formal rotations) VOR Testing**
David Newman-Toker, MD, PhD and John Pula, MD

Positional Testing of Posterior Semicircular Canals
Eric R. Eggenberger, DO and Preston C. Calvert, MD

Positional Testing of Horizontal Semicircular Canals
Luis Mejico, MD and Kevin Kerber, MD

Provocative Testing (nystagmus elicitation)
Jorge C. Kattah, MD and Catherine Cho, MD

	Gaze Testing (ocular alignment, saccades, smooth ocular pursuit, and smooth eye-head tracking) *Janet Rucker, MD and Matthew Thurtell, MD*	
	Nystagmus Interpretation *Marc Dinkin, MD* and *Mark J. Morrow, MD*	
4:50 p.m. – 5:30 p.m.	**Unknown Case Presentation and Summary** *Jorge C. Kattah, MD*	
4:30 p.m. – 5:30 p.m.	**Abstract Committee Meeting**	**Garden Room**
4:30 p.m. – 5:30 p.m.	**International Relations Committee Meeting**	**Tudor Room**
4:30 p.m. – 5:30 p.m.	**Productivity/Compensation Committee Meeting**	**Hanover Room**
5:30 p.m. – 6:30 p.m.	**Bylaws Committee Meeting**	**Garden Room**
5:30 p.m. – 6:30 p.m.	**Patient Information Committee Meeting**	**Tudor Room**
5:30 p.m. – 6:30 p.m.	**Publications Committee Meeting**	**Hanover Room**
6:45 p.m. – 10:00 p.m.	**Annual NANOS Reception and Banquet** Event is casual.	**Windsor Lawn**

WHAT HAVE WE LEARNED FROM THE IDIOPATHIC INTRACRANIAL HYPERTENSION TREATMENT TRIAL

Michael Wall, MD

University of Iowa, Carver College of Medicine
Iowa City, IA

LEARNING OBJECTIVES

1. Understand the effect of acetazolamide on vision, papilledema and CSF pressure
2. Be aware of the OCT advances made by the study
3. Appreciate the limitations of the IIHTT

CME QUESTIONS

1. The IIHTT showed statistically significant improvement due to acetazolamide for which of the following (choose all correct answers):
   a. CSF pressure
   b. Perimetric mean deviation
   c. A low sodium weight reduction diet
   d. Quality of life measures
   e. Papilledema grade
2. Which of the following are true about acetazolamide use in the IIHTT (choose all correct answers):
   a. High dosages are poorly tolerated.
   b. Most of its effect on papilledema and vision occurs in the first month of use.
   c. Potassium levels need to be monitored due to frequent hypokalemia from acetazolamide.
   d. Acetazolamide-related permanent morbidity occurred.
   e. Acetazolamide-related weight loss was its mechanism of action to reduce papilledema and improve vision.
3. True/False: The IIHTT verified that weight loss was an effective treatment for IIH.

KEYWORDS

1. Idiopathic Intracranial Hypertension
2. Pseudotumour cerebri
3. Acetazolamide
4. Clinical trials

INTRODUCTION

Importance: Acetazolamide is commonly used to treat idiopathic intracranial hypertension (IIH) but there is insufficient information to establish an evidence base for its use.

Objective: To determine whether acetazolamide is beneficial in improving vision when added to a low sodium, weight reduction diet in IIH patients with mild visual loss.

Design: Multicenter randomized, double-masked, placebo-controlled study of acetazolamide in IIH participants with mild visual loss who are receiving a low sodium, weight reduction diet.

Setting: Participants were enrolled at 38 academic and private practice sites in North America.

Participants: Participants (n = 165) were enrolled from March 2010 to November 2012 and followed for 6 months. All participants met the modified Dandy criteria for IIH and had a perimetric mean deviation (PMD) between -2 dB and -7 dB. The mean age was 29 years and all but four participants were women.

Interventions: Low sodium, weight reduction diet plus the maximally tolerated dosage of acetazolamide (up to 4 g/day) or matching placebo for six months.

Main Outcome: The preplanned primary outcome variable was the change in PMD from baseline to Month 6 in the most affected eye, as measured by Humphrey Field Analyzer. PMD is a measure of global visual field loss (mean deviation from age-corrected normal values) with a range of +2 to -32 dB; larger negative values indicate greater vision loss. Secondary outcome variables included changes in papilledema grade, quality of life (VFQ-25 and SF-36), headache disability, and weight at Month 6.

Results: The mean improvement in PMD was greater with acetazolamide (1.43 dB, from -3.53 dB at baseline to -2.10 dB at Month 6, n = 86) than with placebo (0.71 dB, from -3.53 dB to -2.82 dB, n = 79); the difference was 0.71 dB (95% CI, 0.00 to 1.43 dB; p = 0.050). Mean improvements in papilledema grade (acetazolamide: -1.31, from 2.76 to 1.45; placebo: -0.61, from 2.76 to 2.15; treatment effect -0.70; 95% CI, -0.99 to -0.41; p < 0.001) and vision-related quality of life as measured by the NEI VFQ-25 (acetazolamide: 8.33, from 82.97 to 91.30; placebo: 1.98, from 82.97 to 84.95; treatment effect 6.35, 95% CI, 2.22 to 10.47; p = 0.003) and

its 10-item neuro-ophthalmic supplement (acetazolamide: 9.82, from 75.45 to 85.27; placebo: 1.59, from 75.45 to 77.04; treatment effect 8.23, 95% CI, 3.89 to 12.56, p < 0.001) were also seen with acetazolamide. Those assigned to acetazolamide also experienced a reduction in weight (acetazolamide: -7.50 kg, from 107.72 kg to 100.22 kg; placebo: -3.45 kg, from 107.72 kg to 104.27 kg; treatment effect -4.05 kg, 95% CI, -6.27 to -1.83 kg; p < 0.001).

Conclusions and Relevance: We found a statistically significant improvements in visual field function, quality of life measures, papilledema grade and CSF pressure in the acetazolamide group. We recommend using the maximally tolerated dosage of acetazolamide along with a low sodium weight reduction diet in IIH patients with mild visual loss.

BODY

Idiopathic intracranial hypertension (IIH) is a disorder of overweight women in the childbearing age characterized by increased intracranial pressure with its associated signs and symptoms in an alert and oriented patient. Neuroimaging and CSF analysis is normal except for raised intracranial pressure and its associated findings including debilitating headaches and vision loss. Also, no secondary cause of intracranial hypertension is apparent.

Treatments have evolved from subtemporal decompression,[1] CSF shunting procedures[2] and optic nerve sheath fenestration[3] to pharmacologic therapies. Paterson[4] in 1961 reported the use of corticosteroids for treating IIH with beneficial results in in five of six consecutive patients. Long-term side effects and rebound intracranial hypertension limit its use. Jefferson and Clark[5] treated 30 patients with various diuretics and reported improvement in symptoms and signs.

Lubow and Kuhr[6] reported a series of IIH patients, many of whom were treated successfully with acetazolamide and weight reduction – the latter, another mainstay of medical therapy.[7] Gücer and Viernstein[8] used intracranial pressure monitoring and showed gradual CSF pressure reduction in patients receiving acetazolamide once they reached a dosage of four grams per day. These studies were uncontrolled and there are no properly designed clinical trials to guide therapy in IIH.[9] With this in mind, the IIH Study Group developed the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), a multicenter, double-blind, randomized, placebo-controlled study of acetazolamide in subjects with mild visual loss.[10] All subjects received a lifestyle modification program that included weight-reduction with a low sodium diet. The purpose of the trial was to determine the effect of acetazolamide in reducing or reversing visual loss after 6 months of treatment.

METHODS

The methods are covered in detail in a publication.[11] In summary, subjects needed to meet the modified Dandy criteria for IIH ad be aged 18-60. They needed to have reproducible mild visual loss (−2 to −7 dB perimetric mean deviation [PMD]). Participants needed to have bilateral papilledema, have an elevated CSF opening pressure, be untreated with regard to IIH, and have no secondary cause of increased intracranial pressure present.

Participants were enrolled at 38 sites in North America from March 2010 to November 2012,with follow-up ending in June 2013. They were randomly assigned to receive a supervised diet either with acetazolamide or with matching placebo. Randomization was stratified by site and included blocking to ensure balance among the treatment groups within a site after every 4 participants had been enrolled at that site.

A specific dietary plan and lifestyle modification program was offered to all study participants through the New York Obesity Nutrition Research Center. The study drug was acetazolamide (250mg) or matching placebo tablets. The initial dosage of study drug was 4 tablets daily in 2 divided doses, followed by dosage increases of 1 tablet every week up to a maximum dosage of 4 g/d for participants receiving acetazolamide. The dosage escalation was stopped if the participant's papilledema grade became less than 1 in both eyes and the PMD improved to equal to or better than −1 dB in each eye, unless the presence of other symptoms such as headache or pulse synchronous tinnitus suggested that the dosage escalation continue.

Possible treatment failure at a follow-up examination was operationally defined as when 1.the baseline average MD was -2 to -3.5 dB and visual function worsens more than 2 dB PMD from baseline average or 2.the bBaseline average MD is >-3.5 dB and <= -7 dB and visual function worsens more than 3 dB MD from baseline average. The worsening *had to be* confirmed with a repeat visual field examination at least one-half hour from the original visual field and within four days. An adjudication committee decided whether the possible treatment failure was most likely due to increased intracranial pressure (treatment failure) or another cause (such as poor perimetry performance – performance failure).

RESULTS

We enrolled 161 women and four men. Their average age was 29.0 years (range 18-52). Figure 1 (see next page) shows the frequency of symptoms at baseline. The baseline characteristics were comparable in the two treatment groups; additional baseline information is published elsewhere.[12] Participant disposition is summarized in Figure 1.[10] There were 7 participants who reached the endpoint of treatment failure in the trial, 6 in the placebo group and 1 in the acetazolamide group (p = 0.06).

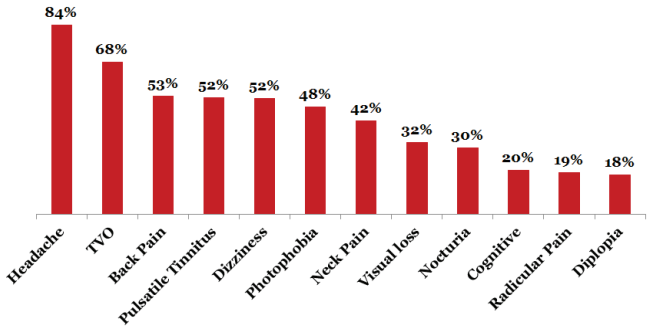

Figure 1. Baseline symptoms in the IIHTT.

Both treatment groups experienced improvement in PMD over time in the study eye (Figure 2) with the mean improvement in the acetazolamide group being significantly larger than that in the placebo group at Month 6 (acetazolamide: 1.43 dB, from -3.53 dB at baseline to -2.10 dB at Month 6; placebo: 0.71 dB, from -3.53 dB at baseline to -2.82 dB at Month 6; treatment effect 0.71 dB, 95% CI 0.00 to 1.43 dB, p = 0.05). Secondary analyses of the primary outcome variable using different strategies for accommodating missing data yielded similar results. PMD in the fellow eye also improved with acetazolamide treatment at Month 6 (acetazolamide: 0.87 dB, from -2.28 dB to -1.41 dB; placebo: 0.42 dB, from -2.28 dB to -1.86 dB; treatment effect 0.44 dB, 95% CI 0.01 to 0.87 dB, p = 0.045; Table 3). An analysis that included all eyes that had a PMD between -2 dB and -7 dB at baseline (165 study eyes and 96 fellow eyes) also yielded a significant effect of acetazolamide at Month 6 (acetazolamide: 1.47 dB, from -3.33 dB to -1.86 dB; placebo: 0.81 dB, from -3.33 dB to -2.52 dB; treatment effect 0.66 dB, 95% CI 0.16 to 1.17 dB, p = 0.01).[10]

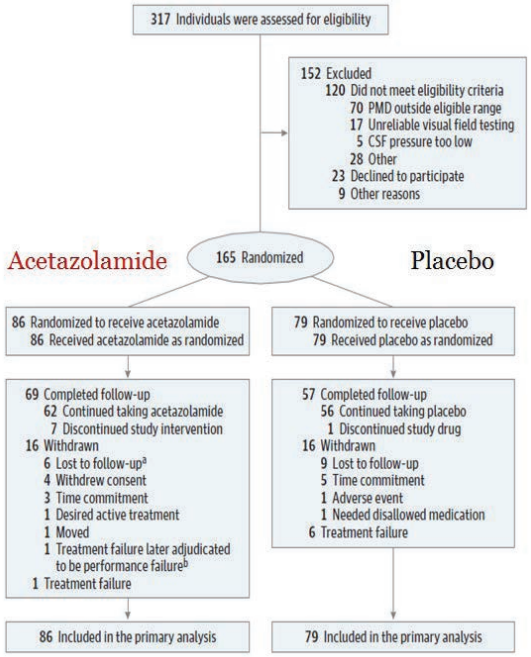

Figure 2. IIHTT CONSORT Diagram

The treatment effect on the primary outcome variable was substantially greater in those with a baseline papilledema grade of 3-5 (2.27 dB) than in those with a baseline papilledema grade of 1-2 (-0.67 dB).[10]

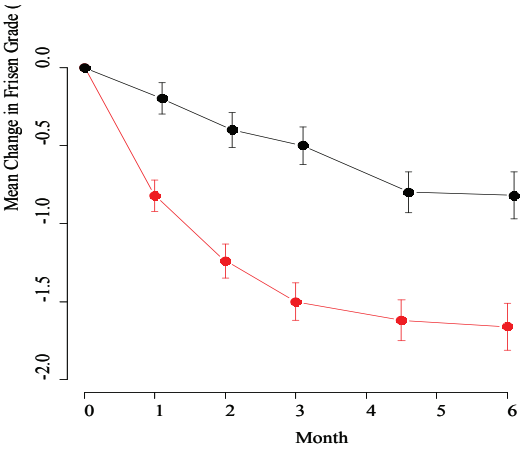

Figure 3. Papilledema grade change in the IIHTT.

There was significant improvement in Frisén papilledema grade associated with acetazolamide treatment in the study eye and in the fellow eye for both the fundus photography and site investigator ratings (Figure 3). Acetazolamide-treated participants also experienced significant improvement in quality of life measures, including the VFQ-25 total score (acetazolamide: 8.33, from 82.97 to 91.30; placebo: 1.98, from 82.97 to 84.95; treatment effect 6.35, 95% CI 2.22 to 10.47, p = 0.003) and its 10-item neuro-ophthalmic supplement (acetazolamide: 9.82, from 75.45 to 85.27; placebo: 1.59, from 75.45 to 77.04; treatment effect 8.23, 95% CI 3.89 to 12.56, p < 0.001) as well as the SF-36 Physical Component Summary and Mental Component Summary scores. No significant treatment effects were noted with respect to headache disability (HIT-6 total score) or visual acuity. At Month 6, headaches were reported by 69% of participants in the acetazolamide group and 68% of participants in the placebo group (adjusted odds ratio 1.10, 95% CI 0.53 to 2.28, p = 0.80).

85 participants (47 (55%) in the acetazolamide group and 38 (48%) in the placebo group) agreed to a lumbar puncture at Month 6. The adjusted mean change in CSF pressure was -112.3 mmH2O (from 357.2 mmH2O at baseline to 244.9 mmH2O at Month 6) in the acetazolamide group and -52.4 mmH2O (from 357.2 mmH2O at baseline to 304.8 mmH2O at Month 6) in the placebo group (treatment effect -59.9 mmH2O, 95% CI -96.4 to -23.4 mmH2O, p = 0.002). Participants on acetazolamide lost more weight over 6 months (mean -7.50 kg, from 107.72 kg to 100.22 kg) than those on placebo (mean -3.45 kg, from 107.72 kg to 104.27 kg) (treatment effect -4.05 kg, 95% CI -6.27 to -1.83 kg, p < 0.001. Acetazolamide also led to reductions in waist circumference and systolic and diastolic blood pressure.[10] In the mediation analysis, the total effect of acetazolamide on PMD in the study eye was estimated to be 0.75 dB (95% CI 0.06 to 1.44 dB, p = 0.03), with the direct effect being 0.72 dB (95% CI 0.02 to 1.42 dB, p = 0.04) and the indirect effect (that mediated through the effect on weight) being only 0.03 dB (95% CI -0.10 to 0.16 dB, p = 0.64).

Classification	Study Eye Total	%	Nonstudy Eye Total	%	Both Eyes Total	%
Localized nerve fiber bundle (NFB) defects, with and without an enlarged blind spot (EBS)	472	71.5	318	48.2	790	59.9
EBS, no localized NFB defects	78	11.8	123	18.6	201	15.2
Diffuse	36	5.5	40	6.1	76	5.8
Neurologic-like	9	1.3	7	1.1	16	1.2
Other	36	5.5	45	6.8	81	6.1
Normal	29	4.4	127	19.2	156	11.8
Total	660	100.0	660	100.0	1320	100.0

Table 1. Visual field defects in the IIHTT at baseline.

The visual field defects found a baseline are listed in Table 1.[13] The prototype defect was an enlarged blind spot coupled with an inferior nasal nerve fiber bundle defect. However, there was usually loss across the visual field although often towards the more central portions of the visual field, the loss did not reach the 95 percentile confidence bound.

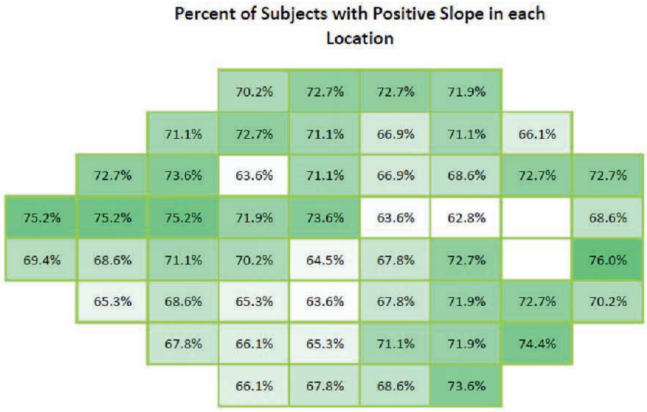

Figure 4. Results of pointwise linear regression show generalized improvement across the visual field.

Visual field change was studied by using pointwise linear regression across all visits from baseline to six months. We found visual field change to occur across the visual field (Figure 4). In eyes that worsened, the loss was again found across the visual field.

48 eyes from 35 patients met visual field criteria for possible treatment failure (see methods above). Seven subjects were found by the adjudication committee to have treatment failure. Upon retest, these other subject had there PMD return to acceptable limits. Four of the the variable performance subjects had large changes on retest and were reviewed by the adjudication committee and determined to be "performance failures."

Adverse events that occurred in > 5% of study participants are summarized and are covered in another syllabus article. A mild decrease in mean potassium level was also seen with acetazolamide, but this did not require potassium supplementation in any participants. No significant changes in sodium levels or in liver function tests were apparent with acetazolamide except for the case noted above.

Average compliance (as measured by counts of dispensed and returned pills) was 89% (19%) in the acetazolamide group and 93% (14%) in the placebo group. The mean (SD) dosage of study medication that participants were taking at the conclusion of their participation was 2.5 g (1.5 g) in the acetazolamide group and 3.5 g (1.1 g) in the placebo group.

DISCUSSION

This is the first multicenter, double-blind, randomized controlled clinical trial to show that acetazolamide has an important effect on improving visual outcome in IIH. Our results apply to subjects with mild visual loss defined as having a perimetric mean deviation from -2 to -7 dB. They also apply in the setting of a concurrent low sodium, weight reduction diet. In addition, six of the seven subjects that met criteria for treatment failure were on placebo, suggesting that acetazolamide may protect against substantial worsening of visual outcome.

The treatment effect on PMD was 1.6 dB greater in subjects with a papilledema grade ≥ 3 at baseline (2.27 dB) than in those with lower grades (-0.67 dB). Treatment effects also tended to be greater in those with a worse PMD in the study eye at baseline. This may be due to more affected eyes having more room for improvement with acetazolamide treatment, but the differential treatment effect was more apparent for subgroups defined by papilledema grade than for those defined by PMD in the study eye. It might also relate to improved visual function because of less axoplasmic flow stasis.

Acetazolamide treatment was also associated with a significant reduction in papilledema grade. Papilledema can improve by a reduction in CSF pressure or by loss of optic nerve axons. It is not likely that the latter occurred in many cases since few subjects had worsening of their visual field status.

We found acetazolamide-associated improvements in quality of life measures. The VFQ-25 total score and its 10-item neuro-ophthalmic supplement and the SF-36 Physical Component Summary and Mental Component Summary scores all significantly improved. Suner et al.[14] have shown that a 4- to 6-point change in NEI VFQ-25 score represents a clinically meaningful change corresponding to a 15-letter change in best corrected visual acuity. Thus, the mean

6.4-point improvement with acetazolamide appears to represent clinically meaningful improvement.

Clinical improvement in IIH has been reported to be associated with about 6% weight loss.[15] IIHTT subjects in both the placebo group (3.45 kg) and the acetazolamide group (7.50 kg) lost weight, with the group difference being 4.05 kg (8.9 pounds). Our mediation analysis demonstrated that the benefit of acetazolamide on PMD was not via its impact on weight.

Acetazolamide is thought to work by inhibition of carbonic anhydrase that causes a reduction in transport of sodium ions across the choroid plexus epithelium. It has been shown to reduce CSF production in humans by 6-50%.[16] This inhibition appears to require a higher dosage than is routinely used.[8]

There were few unexpected adverse events associated with acetazolamide use. No subject, to our knowledge, suffered permanent morbidity from using acetazolamide. A larger number of subjects discontinued acetazolamide use during the trial (9) than discontinued placebo (1), most due to adverse events. While serum sodium remained unchanged in both groups, a mild decrease in serum potassium was found (0.23 units, 95% CI 0.12 to 0.34, $p < 0.001$) but subjects did not require potassium supplementation as a result, similar to another report. [17] There were 2 cases of renal stones (both in the acetazolamide group). There was one case of transaminitis and one case of pancreatitis in the acetazolamide group; each resolved with discontinuation of acetazolamide.

A limitation of our study is the 19% withdrawal rate, although the frequency of and reasons for withdrawal were similar in the two treatment groups. This rate may be due, in part, to the intensity of the visit schedule. More subjects on acetazolamide than on placebo discontinued treatment, most of whom completed follow-up, which may have attenuated the estimated treatment effect.

MISCONCEPTIONS ABOUT WEIGHT LOSS AND THE IIHTT

There have been some misconceptions about what the IIHTT found with regard to weight loss. *The trial did not compare acetazolamide with weight loss.* It compared acetazolamide with placebo in the setting where all were receiving a weight loss intervention. The IIHTT cannot estimate an effect of weight loss as we did not design our study to determine the effect of weight loss. We did *not* find that both acetazolamide and weight loss improved visual field function; acetazolamide improved visual field function. Weight loss might have as well, but we cannot determine this without studying people who did not have a weight loss intervention.

We also did not show what percent weight loss is required to have resolution of IIH. We don't know if these people would have had resolution even without a weight loss intervention -- we did not have this control group. Also, we don't know if acetazolamide would work the same way if given in a setting without a concurrent weight loss intervention.

The results of the IIHTT, a multicenter randomized, double-masked, placebo-controlled study of acetazolamide in subjects with mild visual loss, demonstrate improvements in visual field function, papilledema grade, and quality of life measures. We recommend using the maximally tolerated dosage, up to 4 grams daily, of acetazolamide with a low sodium, weight reduction diet in IIH patients with mild visual loss. The results of this study may not apply to patients with more severe visual loss; randomized controlled trials are needed to address that issue.

WHAT HAVE WE LEARNED FROM THE IIHTT:

1. Acetazolamide when used in IIH patients with mild visual loss produces a modest improvement in PMD over six months. The improvement is much greater in subjects with moderate to high grade papilledema.
2. Acetazolamide has its greatest effect on visual field function and papilledema in the first month of escalating dosage.
3. Acetazolamide-plus-diet patients lost twice as much weight as placebo-plus-diet patients but the acetazolamide effect on PMD was independent of the weight loss.
4. Treatment failure was much less common in the acetazolamide-plus-diet group compared to the placebo-plus-diet group and risk factors for treatment failure were presence of high grade papilledema and lower ETDRS visual acuity measures at baseline.
5. Many IIHTT subjects tolerated maximal dosages of acetazolamide. While there were many expected side effects, quality of life measures were significantly better in the acetazolamide-plus-diet group. There was no permanent morbidity from acetazolamide use.
6. IIH patients on acetazolamide as the only diuretic do not need potassium supplementation.
7. Perimetry performance failures were common and were characterized by major worsening of the PMD with no change or improvement in other clinical measures.
8. Study of pointwise change across the visual field shows evidence of generalized improvement and worsening suggesting perimetric mean deviation is an excellent measure for follow-up.

CME ANSWERS

1. a, b, d, e
2. b
3. False

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QUALITY OF LIFE IN IIHTT SUBJECTS 6 MONTHS AFTER DIAGNOSIS AND TREATMENT

Kathleen B. Digre, MD and Beau Bruce, MD, PhD on behalf of the IIHTT study group

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LEARNING OBJECTIVES

1. List the factors that affect quality of life (QOL) before the treatment in IIH
2. List symptoms that improved and resulted in improved QOL at 6 months with acetazolamide treatment
3. Discuss the effect of IIH symptoms on the QOL

CME QUESTIONS

1. True/False: The visual quality of life in IIH at baseline is similar to individuals with optic neuritis and multiple sclerosis
2. True/False: The SF 36 improved remarkably after 6 months of treatment with acetazolamide
3. True/False: Treatment in the acetazolamide arm of the IIHTT showed improvement in the visual QOL

KEYWORDS

1. Idiopathic Intracranial Hypertension
2. Quality of Life (QOL)
3. Headache
4. NEI VFQ 25, 10 Item supplement, SF36

ABSTRACT

Quality of Life (QOL) in idiopathic intracranial hypertension (IIH) has been shown to be reduced at diagnosis (baseline visit of the IIHTT). Factors that most affected QOL at baseline were visual symptoms and signs (reduced perimetric mean deviation [PMD], reduced visual acuity, transient visual obscurations, diplopia) and pain symptoms (headache, neck pain). Other influential factors included: dizziness, a positive sleep apnea screening (Berlin Questionnaire) and self-reported cognitive dysfunction. BMI was not associated with the reduced QOL. The baseline IIHTT study showed QOL is reduced in patients with IIH at the time of diagnosis and at a level worse than even that reported by patients with optic neuritis and/or multiple sclerosis. The purpose of this study was to determine what effect six month of treatment had on QOL and what changes in signs and symptoms mediated any changes in QOL.

Methods: Source of all patients and data was the Idiopathic Intracranial Treatment Trial (JAMA. 2014 Apr 23-30;311(16):1641-51). Patients were randomized to receive acetazolamide or placebo, data was collected at regular intervals, and the primary outcome was change in PMD at 6 months. Overall QOL was assessed using the SF36's physical and mental component summaries (Physical Composite Score (PCS) & Mental Composite Score). Visual QOL was assessed by VFQ 25 and its 10 item neuro-ophthalmic supplement at baseline and again at 6 months. We used analysis of covariance (ANCOVA)to determine which changes in QOL scales and subscales were associated with treatment at 6 months and mediation analysis was performed with structural equation modelling.

Results: The IIHTT found that treatment with acetazolamide resulted in a significant improvement in PMD. Although those treated with acetazolamide also lost more weight than those on placebo, the effect of acetazolamide on PMD was not found to be mediated by this weight loss. Overall and vision-related QOL improved on acetazolamide compared to controls: NEI VFQ 25 6.35 points (p=0.003); 10 item Neuro-ophthalmic supplement 8.23 points (p=0.001); SF36 PCS 3.02 points (p=0.03); and SF36 MCS 3.45 points (p=0.03). QOL subscales significantly associated with acetazolamide treatment were the NEI VFQ 25's near vision, social functioning, and mental health subscales and the 10 item Neuro-ophthalmic supplements' questions about performing tasks in bright sunlight and vision being not clear or fuzzy. The most important factor that mediated the effect of acetazolamide on quality of life was PMD although pain symptoms (headache and neck pain) were specifically important for improvements in the SF36 MCS. Overall signs and symptoms associated with baseline QOL mediated 31.6-51.6% of the effects of acetazolamide on improved QOL. While there was no difference in the HIT 6 between treatment groups in the IIHTT, headaches in both groups improved. Those whose headaches improved, had improved quality of life scores. Improvement in transient visual obscurations, cognitive dysfunction, and dizziness/vertigo were also consistently associated with QOL improvements.

Discussion: Acetazolamide treatment resulted in significant improvements in QOL. However, these improvements were modest and individuals still showed reduced QOL compared to published normative data. Improvements in signs and symptoms of IIH from acetazolamide, primarily driven by improvements in PMD, accounted for only about one third to one half of the improvement. Other important factors related to QOL included headache, reduced transient visual obscurations, cognitive dysfunction, and dizziness/vertigo.

Conclusion: In IIHTT patients with mild visual loss, acetazolamide and a weight reduction diet resulted in improvement in visual QOL compared to diet plus placebo.

INTRODUCTION

The etiology of idiopathic intracranial hypertension (IIH) is unknown. The symptoms of headache, transient visual loss, visual field changes, pulse synchronous tinnitus, cognitive changes, pain in the neck and back as well as photophobia all affect the individuals at varying degrees, making this condition far from benign. Previous studies have shown QOL to be affected in this condition (Kleinschmidt et al; Daniels et al). Recently the first prospective randomized trial of individuals with IIH had QOL measured. Our goal in this summary is to review the baseline QOL, and the related 6 month outcomes.

METHODS

Patients were prospectively enrolled into the IIHTT in a randomized, double-masked placebo controlled trial of acetazolamide. Study method details may be found in JAMA. 2014 Apr 23-30;311(16):1641-51. The study was conducted in accordance with the Declaration of Helsinki. All patients satisfied the Modified Dandy Criteria for IIH (Smith JL) and all individuals had baseline computerized automated perimetric mean deviation between -2 and -7 dB in the worst affected eye on 24-2 SITA standard test (Humphrey, Carl Zeiss Meditec). Patients underwent screening, and were followed at regular intervals. Patients completed a medical history, baseline examination (that included visual acuity, visual field, weight, height, and direct and indirect ophthalmoscopy). All measures were repeated at 6 months.

QOL questionnaires were administered on line at baseline and at 6 months. These included the SF36 to assess the overall QOL. For vision specific QOL, the 25-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ 25) (Mangione 1998;Mangione website; Raphael et al), and its 10 item Neuro-ophthalmic supplement (Raphael 2006) were used. Other questionnaires included: the Headache Impact Test (HIT 6) which assesses headache disability, and the Berlin sleep apnea questionnaire which assesses symptoms at risk for sleep apnea. At baseline, one subject's NEI VFQ 25, 10-item Neuro-Ophthalmology Supplement, and SF36 were unavailable/incomplete, along with two other subjects' 10-item Neuro-Ophthalmology Supplement. Thirty subjects' follow-up ended before the six-month visit (12 at 4 weeks, 6 at 8 weeks, 6 at 13 weeks, 6 at 19 weeks) and five subjects only had baseline data.

For the baseline QOL, statistical analyses were performed using R 3.1.1 (The R Foundation for Statistical Computing, http://www.r-project.org). For baseline analyses, univariable linear regression models, were used to examine the association between baseline QOL scores and each subject characteristic. Robust (sandwich) variance estimates were used with linear regression for confidence intervals and p-value calculations due to heteroskedasticity. All variables considered in the univariate analyses were considered for inclusion in a multiple linear regression model, and an all subsets approach was used to select models for consideration based on the Mallows' Cp and Bayesian information criterion (BIC).

For the six month analyses, the principle of intention to treat was followed. If data was available after the baseline visit on a subject, these observations were carried forward to the 6 month time point. Missing data were accommodated in the analyses by multiple imputation using fully conditional specification (FCS) implemented by the multivariate imputation by chained equations (MICE) algorithm (Van Buuren & Groothuis-Oudshoorn. Multivariate Imputation by Chained Equations in R; J Stat Software 2011). Mediation analysis was performed using structural equation models. Analysis of symptom/sign changes associated with changes in quality of life were performed with linear regression models using imputed data and subjects with completed data. For these models, baseline QOL, treatment status, and baseline value of the relevant symptom/sign were controlled.

RESULTS

There were 161 women and 4 men analyzed. There were 84 women (97.7%) and 2 men in the acetazolamide group and 77 women (97.5%) and 2 men in the placebo group.

QUALITY OF LIFE AT BASELINE

Baseline attributes were comparable in both groups and showed that all of the patients were overweight (88% were obese), had symptoms of transient visual obscurations, diplopia, photophobia, headache, pulsatile tinnitus and similar headache disability scores. In addition, baseline QOL questionnaires had similar scores. See table 1 (see next page) which describes the baseline characteristics of the patients in the IIHTT at baseline.

Table 1: Baseline Data For The Iihtt

Variable	Acetazolamide (N=86)	Placebo (N=79)
Race: White	54 (63%)	54 (68%)
Black	25 (29%)	16 (20%)
Other	7 (8%)	9 (11%)
Weight mean kg	108.1	107
BMI	40	40
TVO	55 (64%)	57 (72%)
Diplopia	20 (23%)	16 (20%)
Photophobia	42 (49%)	28 (35%)
Headache	70 (81%)	69 (87%)
Pulsatile tinnitus	45 (52%)	41 (52%)
Perimetric mean deviation: study eye	-3.5	-3.5
Fellow eye	-2.3	-2.3
HIT 6	60.3	59
CSF pressure	349	342
BASELINE QOL DATA		
VFQ 25 mean	84	82
10 item neuro-ophthalmic supplement	76	75
SF 36 component—Physical	45	46
Mental	45	44

The baseline IIHTT QOL study was the first to examine the QOL in individuals with IIH at the time of diagnosis among subjects with mild visual loss, and from the baseline analysis we learned many interesting things. We compared our findings with previously reported studies including Daniels et al. which examined individuals within the first year from the diagnosis and the Kleinschmidt study which examined patients who had the condition chronically (see table 2 below and continued on next page). Compared with the previous studies, patients at baseline with IIH were already showing similarly reduced QOL scores. In fact, the vision specific QOL scores (NEI VFQ 25) and the 10 item Neuro-ophthalmic supplement were actually comparable to published scores in individuals with multiple sclerosis and a history of optic neuritis (Raphael et al; Mowry et al).

Table 2. Baseline characteristics for IIHTT participants (n=165), with comparison to cohorts from other published studies of IIH

	IIHTT Cohort, 2014 (JAMA Neurology 2014)	Daniels et al., 2007	Kleinschmidt et al., 2000
Study Design	Randomized, double-masked, placebo-controlled clinical trial	Case-control study with prospective ascertainment	Case-control study with retrospective ascertainment

Table 2 continued on next page

Table 2. Baseline characteristics for IIHTT participants (n=165), with comparison to cohorts from other published s tudies of IIH

Controls in Study	Not Applicable	Patients with other neuro-ophthalmologic disorders at tertiary care centers, category-matched for age and sex	Healthy age-and weight-matched
	IIHTT Cohort, 2014 (JAMA Neurology 2014)	Daniels et al., 2007	Kleinschmidt et al., 2000
Sample Size	n=165	n=34	n=28
Age (years), mean ± SD	29.2 ± 7.5	32 ± 10	33 ± 7
Sex	Women, n=161 (98%) Men, n=4 (2%)	Women, n=34 (100%)	Women, n=28 (100%)
Time from IIH Diagnosis to Study Entry (months), median (range)	All were entered within 2 months of diagnostic MR and not treated with drug for more than 2 weeks	5.1 months (0.5-57)	55 months (0-204)
BMI (kg/m2), mean ± SD, or median (range)	39.9 ± 8.3 (24.9-71.2)	31.8 (20-70)	37.4 ± 7.0
Weight Gain Prior to Study Entry	45% reported weight gain within 6 months prior to enrollment	Median weight gain in year prior to symptom onset 7.4% (0-43%)	Not Captured
Education (years), mean ± SD (range)	14.0 ± 3.1 (1-24)	Not Captured	13.8 ± 2.4
Visual Acuity for Study Eye (# letters on ETDRS chart, max 70), mean ± SD (range)	56.3 ± 5.5 (36-70)	Not Captured	Not Captured
Humphrey Visual Field Mean Deviation for Study Eye (dB), mean ± SD (range)	-3.5 ±1.1 (-2.0- -6.4)	Not Captured	Not Captured
CSF Opening Pressure (mm water), mean ± SD (range)	345.6 ± 83.5 (210-670)	Not Captured	Not Captured
Headache (% reporting symptom)	84%	Not Captured	78%
HIT-6 Headache Disability Score, mean ± SD (range)	59.7 ± 9.0 (36-78)	Not Captured	Not Captured
% of patients reporting a premorbid history of migraine.	41%	Not Captured	Not Captured
Fatigue (% reporting symptom)	Not Captured	Not Captured	85%
Depression (% reporting symptom)	Not Captured	33% (by self-report)	68% (by Beck Depression Inventory scores)
Anxiety (% reporting symptom)	Not Captured	Not Captured	0% (by Spielberger State-Trait Anxiety Inventory, STAI)
Sleep Difficulties	64% at risk for sleep apnea (by Berlin Sleep Questionnaire)	Not Captured	82% (by self-report)

Six factors were found to be independently associated with NEI VFQ 25 at baseline: PMD, best eye, VA worst eye, HIT 6, neck pain, TVO, and diplopia. See table 3

Table 3. Multiple linear regression model for the NEI-VFQ-25 composite score

Factor	Change in NEI-VFQ-25	95% CI	P-value
PMD, best eye (per dB)	1.87	(0.16, 3.58)	0.03
VA, worst eye (per letter)	0.43	(0.11, 0.75)	0.01
HIT-6 (per 10 points)	-5.61	(-7.81, -3.41)	<0.0001
Neck pain (present – absent)	-5.46	(-9.35, -1.57)	0.006
Transient visual obscurations (present – absent)	-7.62	(-11.91, -3.32)	0.001
Binocular diplopia (present – absent)	-5.20	(-10.23, -0.17)	0.04

CI = confidence interval; PMD = perimetric mean deviation; VA = visual acuity

The Supplement items that were most affected (lowest mean scores) included difficulty seeing when eyes are tired, feeling that the two eyes see differently, and vision being blurry or fuzzy, not clear. The SF36 physical component score was associated with self-reported changes in cognitive function, dizziness, nocturia, radicular pain, HIT 6 score, high risk Berlin Sleep apnea test, tinnitus, and self-reported change in vision in either eye as well as transient visual obscurations. The SF36 mental component summary correlated most with dizziness, neck pain, photophobia, recent weight gain, Berlin score, and self-reported change in vision.

Degree of obesity was NOT associated with worsened QOL testing.

QUALITY OF LIFE AT 6 MONTHS IN THE IIHTT

See table 4 (see below) for the main effects of treatment with acetazolamide and weight loss vs placebo and weight loss

Main treatment effects at 6 months included improvements in PMD, weight loss, improvement in VFQ25, NOS10, and SF 36 both PCS and MCS.

Table 4: Main treatment effects at 6 months

Variable	Acetazolamide	Placebo	Treatment effect	pvalue
PMD	-2.28 to -1.41	-2.28 to -1.86	.44	0.045
Weight	107.72 to 100.22 kg	107.72 to 104.27	-4.05	0.001
HIT 6	59.7 to 50.14	59.70 to 50.59	-0.45	0.77
VFQ 25	82.97 to 91.30	82.9 to 84.95	6.35	0.003
10 item N-O sup	75.45 to 85.27	75.45 to 77.04	8.23	0.001
SF 36				
PCS	45.82 to 51.66	45.82 to 48.64	3.02	0.03
MCS	44.61 to 50.23	44.61 to 46.78	3.45	0.03

Effect of treatment on QOL subscales

In the VFQ 25, we found that three subscales were significantly improved: Near vision: 5.4 (95%CI: 0.14-10.6; p=0.04), Social functioning: 3.7 (95%CI: 0.02-7.3; p=0.049), and Mental health: 9.8 (95%CI: 3.4-16.2; p=0.003).

In the Neuro-ophthalmic supplement: visual tasks in bright sunlight: 8.7 (95%CI: 0.41-17.1; p=0.04) and vision not clear/fuzzy: 14.7 (95%CI: 4.7-24.7; p=0.005) seemed to improve the most.

None of the SF36 subscales differed significantly based on treatment.

Mediation of QOL improvements from acetazolamide treatment

When we examined the 6 factors independently associated with baseline QOL (PMD, best eye; VA, worst eye; HIT-6; neck pain, TVO, binocular diplopia) with respect to change in QOL over 6 months we found:

For VFQ 25, 51.6% of the improvement in QOL from acetazolamide was mediated by improvement in PMD (25.9%) followed by improved neck pain (9.2%), TVO (8.7%), and headache (5.7%); diplopia (1.3%) and VA (0.8%) did not mediate much of the VFQ 25 improvement.

For the Neuro-ophthalmic supplement, 40.0% of the improvement from acetazolamide was mediated by the six symptoms: PMD (23.1%) TVO,(6.2%), neck pain, (3.6%), headache (3.6%), diplopia (2.5%), and visual acuity (1%).

For SF36 PCS, 31.6% of the improvement from acetazolamide was mediated by the six symptoms: PMD (13.2%), TVO (6.4%), headache (5.3%), neck pain (4.4%), visual acuity (1.9%), and diplopia (0.4%).

For SF36 MCS, 47.0% of the improvement from acetazolamide was mediated by the six symptoms: PMD (21.6%), headache (14.4%), neck pain (7.5%), TVO (1.4%), diplopia (1.2%), acuity (0.8%).

Symptom/sign changes associated with 6 month quality of life changes

When using multiple imputation to minimize potential bias from loss to follow-up related to changes in QOL and the other symptoms and signs of IIH, we found that improvements in PMD were associated with improved VFQ 25, NOS10, and SF36 PCS.

Improving transient visual obscurations likewise improved the NEI VFQ 25, NOS10 and SF36 PCS. Improving cognitive dysfunction and dizziness improved the VFQ 25.

When restricting analyses to only those subjects who completed two QOL questionnaires, improvements in the HIT-6 headache disability scale, cognitive dysfunction, dizziness/vertigo, and transient visual obscurations were associated with improvements in all four quality of life scales.

Because the Berlin Sleep Apnea score was not repeated at 6 months, we are unable to comment on effects of changes in the symptoms of sleep apnea on quality of life.

DISCUSSION

These studies (baseline and 6 month follow-up) show that IIH patients have reduced visual QOL at baseline even when visual loss is mild. At baseline, the visual QOL is comparable to patients with multiple sclerosis. Even with treatment of weight loss and acetazolamide, visual QOL improves but is not normal.

Treatment with acetazolamide improves QOL in IIH. The effects of acetazolamide are primarily mediated by improvements in PMD for QOL in patients with IIH and mild visual loss. Reducing TVOs seems to be the second most important symptom improved by acetazolamide that results in improved QOL. Improvement of acuity and diplopia were NOT primary drivers of improved QOL.

For the SF36 mental composite score pain symptoms (headache and neck pain) in the acetazolamide treated group were as important as improvements in PMD.

Improvements in signs and symptoms of IIH from acetazolamide, primarily driven by improvements in PMD, accounted for only about one third to one half of the improvement. Other important factors related to QOL included reduced transient visual obscurations, cognitive dysfunction, dizziness/vertigo, and headache. Symptom management appears important for improving the QOL of patients with IIH.

Treatment of other symptoms of IIH including TVO, cognitive dysfunction, headache and dizziness other than by acetazolamide, if necessary, will also likely improve the quality of life of patients with IIH.

This study indicates that treatment with acetazolamide is not only important for improving perimetric mean deviation but for also improving QOL. Acetazolamide should be considered valuable to the treatment of IIH patients even when vision is mildly affected due to the marked effect it has on patients quality of life.

CME ANSWERS

1. True
2. False
3. True

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TREATMENT FAILURES IN THE IDIOPATHIC INTRACRANIAL HYPERTENSION TREATMENT TRIAL

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LEARNING OBJECTIVES

1. Review our experience with treatment failure during the first 6 months of the IIHTT
2. Discuss risk factors associated with treatment failure in patients with idiopathic intracranial hypertension and mild visual loss at presentation

CME QUESTIONS

1. Which of the following was found to be a risk factor for treatment failure in our cohort of IIHTT participants with mild visual loss?
   a. BMI greater than 40
   b. High grade papilledema
   c. Baseline CSF pressure
   d. Baseline perimetric mean deviation
2. All of the following have been reported in the literature as risk factors for poor visual outcome in IIH EXCEPT?
   a. Hyperopic eyes
   b. Black patients
   c. Male patients
   d. Morbid obesity
3. True/False: IIHTT subjects with worse ETDRS acuity in the study eye were more likely to have treatment failure.

KEYWORDS

1. Intracranial hypertension
2. Vision loss
3. Treatment failure
4. Transient visual obscuration
5. Papilledema

INTRODUCTION

The purpose of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) was to determine whether acetazolamide is beneficial in improving vision when added to a low sodium, weight reduction diet in idiopathic intracranial hypertension (IIH) patients with mild visual loss. During the first six months of the intervention phase, six subjects on placebo and one subject on acetazolamide met criteria for treatment failure. Male patients, those with high grade papilledema and those with decreased visual acuity at baseline were more likely to experience treatment failure.

Idiopathic intracranial hypertension (IIH) is a disorder affecting primarily young overweight women and typically presenting with signs and symptoms of increased intracranial pressure. Its main morbidity is vision loss, however data on the incidence of blindness in IIH is very sparse. Studies from academic centers give estimates that are in the 5-10% range. [1-3] Now that we have completed the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), we are able to report our treatment failure cases and investigate the risk factors for treatment failure.

STUDY CRITERIA FOR TREATMENT FAILURE

Possible treatment failure was defined when a participant with baseline perimetric mean deviation (PMD) up to -3.5 dB had visual function worsen by more than 2 dB PMD from baseline in either eye, or when a participant with baseline PMD between -3.5 dB and -7 dB had visual function worsen by more than 3 dB PMD from baseline in either eye. The decrease in PMD needed confirmation by a second perimetric examination. All participants had automated perimetry using Humphrey Field Analyzer SITA Standard program 24-2, and the testing was performed by a technician certified by the Visual Field Reading Center (VFRC). To be classified as a treatment failure, an adjudication committee, using all available clinical information, decided whether the worsening of PMD was most likely due to uncontrolled intracranial pressure and worsening of IIH or was due to another cause (such as poor perimetric performance).[4] Participants who experienced treatment failure were withdrawn from further participation in the trial and referred to their physicians for further treatment.

During the six month period of the IIHTT intervention phase, seven subjects (4.2%) had substantial worsening of their IIH and met study criteria for treatment failure; six were in the placebo group.

Here are 3 examples of treatment failure from our cohort of IIHTT participants.

CASE #1

A 31-year-old otherwise healthy obese Caucasian man presented with bilateral transient visual obscurations (TVO) for two weeks. He reported a migraine history since age 14. Best corrected visual acuity was 20/20 OU with no relative afferent pupillary defect. Visual field testing showed a mean deviation (MD) of -3.14 dB OD and -1.96 dB OS with enlarged blind spot right eye and mild nasal steps bilaterally. Grade V and grade IV papilledema were present in the right eye and left eye, respectively. Brain MRI showed a partially empty sella tursica and narrowing of the transverse venous sinuses.

The patient was enrolled into the IIHTT three days later. Lumbar puncture showed an opening pressure of 510 mm water with normal CSF constituents. The patient was randomized to placebo. The visual acuity remained well preserved at 20/16 OU, and the visual field deficits (-2.88 dB OD, -2.21 dB OS) and grade V papilledema OD and grade IV papilledema OS persisted.

Two months later he returned with worsening headaches and a TVO frequency of 126 per month. Nortriptyline 10 mg daily was initiated. The patient had lost 16 lbs.

Five months after randomization, the patient reported worsening of vision and increased frequency of TVO to 400 per month. Visual acuity remained 20/16 OU. He had now lost a total of 47 pounds. The visual fields worsened (-5.57 dB OD, -5.05 dB OS) by nearly 3 dB bilaterally with nasal step defects. The papilledema remained at grade V OD and grade IV OS. The patient was judged to be a treatment failure 20 weeks after randomization. He was placed on acetazolamide ER 500 mg four times daily. Follow-up evaluation three weeks later showed much improved frequency of TVO to 9 per month with improved perimetry results but the severity of the papilledema remained unchanged.

Two months later, he developed a rash while on acetazolamide. The acetazolamide was discontinued and methazolamide 50 mg three times daily was initiated.

One month later he reported increased TVO of the right eye. Visual acuity remained at 20/16 OU, and the visual fields showed mild changes (-4.40 dB OD, -4.25 dB OS). The papilledema remained at grade V OD and grade IV OS. Furosemide 20 mg twice daily was started, and the patient's TVO resolved.

By sixteen months after randomization, he had regained 29 pounds, his visual function remained stable and the papilledema was in the grade IV to V range. The patient was last seen 21 months after randomization and his status remained stable. Methazolamide, furosemide and nortriptyline were continued.

CASE #2

A 38-year-old Caucasian woman presented with headaches for 6 months, TVO for 2 months, and pulse synchronous tinnitus. Neuroimaging study including a magnetic resonance venogram was normal and lumbar puncture showed an opening pressure of 480 mm water. She had a history of hypertension, depression, polycystic kidney disease, liver cysts, spondylolisthesis and renal insufficiency. Medications included amitriptyline, escitalopram, amlodipine, lisinopril, bupropion, and acetaminophen #3.

Examination showed a best corrected visual acuity of 20/40 in the right eye, the study eye, and 20/25. Pupil examination showed a trace right afferent pupillary defect. Extra-ocular motility was full and fundus exam showed grade IV papilledema OD and grade III OS. Perimetry showed an MD of -4.88 dB OD and -4.18 dB OS and she was randomized to the acetazolamide-plus-diet arm of the study. One month later perimetry showed a MD of -9.73 OD and -8.52 OS and at 10 weeks she was deemed a treatment failure.

Following discontinuation of study drug the patient was placed on oral acetazolamide 1 gram twice daily. Her headache symptoms persisted and her examination remained stable. She was diagnosed with obstructive sleep apnea and was fit with a continuous positive airway pressure (CPAP) mask. Compliance with CPAP was poor. She lost 36 pounds overall. Acetazolamide dose was decreased 3 months post treatment failure and discontinued completely one year post treatment failure. Her papilledema resolved leaving mild pallor of the right optic disc. Examination and visual function have remained stable throughout follow-up. Her last perimetry examination, seven months post treatment failure, showed bilateral nasal visual field loss and a MD of -7.52 OD and -4.06 OS.

CASE #3

A 19-year-old woman presented with a one-month history TVO, which had increased in frequency to four times a day. She had occasional pulse synchronous tinnitus. There was no headache but low back pain had begun recently. Her weight had increased by 65 pounds over the previous four years.

Her examination showed best corrected visual acuity of 20/20 bilaterally and grade IV papilledema with peripapillary hemorrhages OU. Perimetry demonstrated enlarged blind spots and mild depression, with MD of -3.9 dB OD and -5.0 dB OS. Neuroimaging study showed no acute process and her lumbar puncture showed an opening pressure of 440 mm water. Nine days after presentation,

she entered the IIHTT and was randomized to the placebo-plus-diet arm. Her acuity was 20/25 OD and 20/20 OS.

Three weeks after presentation, she developed horizontal diplopia followed over the next 2 weeks by distortion of vision in both eyes, photophobia, nausea and constant pulse synchronous tinnitus. Funduscopy showed bilateral grade V papilledema, peripapillary hemorrhages, macular exudates and choroidal folds. Best corrected visual acuity was 20/30 OD and 20/25 OS. Perimetry results worsened, with MD of -13 dB OD and -18 dB OS. There was a comitant esotropia measuring 20-25 prism-diopters, with full ocular ductions. She was declared a treatment failure and underwent a temporary lumbar drain followed by bilateral optic nerve sheath fenestrations. She was given acetazolamide 1 gram four times daily and prednisone 60 mg per day. MRI and MRV showed no abnormalities other than tapered narrowing of both transverse sinuses.

Her symptoms and papilledema improved over the next 3 weeks. Prednisone therapy was discontinued. Six months after optic nerve sheath fenestration, she was asymptomatic and had no papilledema. Visual acuity was 20/25 OD and 20/30 OS. Perimetry showed MD of -7.4 dB OD and -15 dB OS. Acetazolamide was discontinued. Seventeen months after optic nerve sheath fenestration she had mild bilateral optic atrophy. The average thickness of the peripapillary retinal nerve fiber layer, measured by optical coherence tomography, was 76 microns OD and 58 microns OS.

RESULTS

Of the seven subjects that met criteria for treatment failure, 5 were women and 2 were men. Overall, we enrolled 161 women and four men, and of the 144 subjects that reached the six month outcome all but 4 were women. Six of the seven treatment failure subjects were in the placebo group. All seven treatment failures had grade III to V papilledema in the study eye. Grades III – V papilledema comprised 49% of all study eyes in the acetazolamide group and 54% in the placebo group. In the placebo group, 6 of 41 subjects (14.6%) with high grade papilledema went to treatment failure; for acetazolamide it was 1 of 41 subjects or 2.4%.

All seven treatment failures occurred in Caucasians; this group represented 92 of the 144 subjects (64%) that reached the six month outcome.

Male gender, high papilledema grade and ETDRS acuity loss in the study eye were significant risk factors for treatment failure. Male patients (OR: 26.3; CI: 1.6, 5000; P value: 0.005), patients with stage III-V grade papilledema (OR: 8.6; CI: 1.7, infinite; p value: 0.025), and patients with worse ETDRS acuity (OR: 1.16; CI: 1.04, 1.30; p value: 0.005) in the study eye were more likely to have treatment failure. Other factors such as BMI, age at enrolment, weight gain or loss before randomization, baseline PMD, headache severity or number of headache days per month, pulse synchronous tinnitus or baseline CSF pressure were not significant predictors of treatment failure based on the logistic regression. Although there was a large difference in the numbers of TVO episodes per month between the treatment failure group and the non-failure group (30.9 vs. 83.6 TVO per month), the logistic regression failed to identify it as a significant predictor of treatment failure.

DISCUSSION

A variety of risk factors have been suggested for poor visual outcome in IIH. High-grade papilledema has been associated with more severe visual dysfunction in prior studies.[6-8] Orcutt et al. reported that patients with high grade or atrophic papilledema, or peripapillary subretinal hemorrhage, were significantly more likely to have had deterioration of visual function.[3] High grade papilledema was a major and significant risk factor for treatment failure in our cohort of IIHTT participants with mild visual loss.

Other significant risk factors for treatment failure in our cohort were decreased visual acuity in the study eye (the eye with the most visual field loss at baseline) and male gender. Others have also reported that men are at risk for poor visual outcome.[9-10] Bruce et al. reported that Black IIH patients were more likely than non-black IIH patients to have severe visual loss in at least one eye. [11] All seven treatment failures in our IIHTT subjects occurred in Caucasians, which represented 64% of our study population.

We found transient visual obscurations with an average of more than one per day to be useful in predicting treatment failure given the large difference in the numbers of TVO episodes per month between the treatment failure group and the non-failure group. Several authors have not found TVO to be associated with poor visual outcome.[1,16-19] Orcutt and coworkers, on the other hand, found a significant association between transient visual obscurations and visual loss. They found 88% of eyes with severe visual loss had transient visual obscurations while this symptom was present in 50% of all eyes. [3] The presence of optociliary collaterals, anemia, older age, and high myopia were other risk factors for visual loss that they reported.

Marked recent weight gain has shown to be significantly associated with poor visual outcome in a prospective study.[2] Patients with body mass index (BMI) over 40 have been reported to be more likely to have severe papilledema and have a trend toward more visual loss.[12] Baldwin and coworkers found no association between visual field deficits and BMI and/or weight gain.[13] In our treatment failure group, BMI as well as weight gain or loss before randomization were not significant predictors of treatment failure based on the logistic regression.

The IIHTT subjects on acetazolamide had lower risk for treatment failure. This may be due to finding in the IIHTT

that acetazolamide had a large and significant effect in reduction of papilledema with much of the effect in the first month.[14]Also, six of the seven treatment failures were in the placebo-plus-diet group (p = 0.06) of the IIHTT and only one in the acetazolamide-plus-diet group suggesting a protective effect of acetazolamide.

CONCLUSION

Seven IIHTT subjects met criteria for treatment failure. Risk factors for treatment failure in our cohort of IIHTT participants with mild visual loss are high-grade (Frisén grades III-V) papilledema, decreased visual acuity in the eye with the most visual field loss at baseline, and being a Caucasian male. IIH patients with these risk factors should be monitored closely for progressive visual loss and provided with appropriate treatment early in the course of their IIH. Treatment with the maximally tolerated dosage of acetazolamide appears to substantially reduce the risk of reaching IIHTT criteria of treatment failure.

Given the small number of treatment failures in the IIHTT along with the entry criteria of mild visual loss, these results should be interpreted with caution and may not be generalizable to all IIH patients.

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CME ANSWERS

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SAFETY AND TOLERABILITY OF ACETAZOLAMIDE: THE IIHTT EXPERIENCE

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LEARNING OBJECTIVES

1. Report the safety and tolerability of acetazolamide when used to treat Idiopathic Intracranial Hypertension
2. Review the evidence for acetazolamide dosing for the treatment of IIH
3. Review the experience of individuals treated with up to 4g/day of acetazolamide in the IIHTT

CME QUESTIONS

1. The following adverse events are commonly seen with acetazolamide:
    a. Hypokalemia
    b. Stevens Johnson syndrome
    c. Renal Calculi
    d. Fatigue
2. Which of the following statements about acetazolamide is false:
    a. Prevalence of adverse events is not proportional to dose
    b. Tetratogenicity is rare
    c. History of a previous sulphonamide allergy is a strict contraindication
    d. Hyponatremia is commonly seen

KEYWORDS

1. Acetazolamide
2. IIHTT
3. Safety
4. Tolerability

INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a disease of unknown etiology that occurs primarily in young obese women with an estimated incidence of 0.9/100,00 in the general population[1]. The current medical treatment paradigm for IIH aims to decrease intracranial pressure (ICP) by decreasing the production of Cerebrospinal Fluid (CSF)[2]. Conventional medical management of IIH with carbonic anhydrase inhibitors (CAIs) such as acetazolamide was first suggested by Lubow and Kuhr[3]. Clinically, resolution of optic disc edema has been demonstrated in IIH patients using acetazolamide at 1g/d[4]. In 1978, a case series of 4 IIH patients in which ICP was continuously monitored before and after treatment showed that in 2 of those cases, acetazolamide at 4g/d was effective in gradually reducing ICP[5] however data pertaining to safety or tolerability was not reported. In this syllabus, we examine the safety and tolerability data from the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), presenting evidence on the type, frequency, and relative risks of experiencing AEs in patients receiving acetazolamide up to 4g/d. A discussion of SAEs that occurred during the treatment phase of the trial is also presented.

BACKGROUND

The IIHTT used a dose escalation protocol of acetazolamide from 1g/d to 4g/d to determine whether there was any benefit in restoring or protecting vision in patients with mild visual loss due to IIH. The study collected all adverse and serious adverse experiences (AE/SAEs)[6]. The IIHTT is the only randomized controlled study to provide evidence-based treatment recommendations for the use of acetazolamide and to report on the safety and tolerability of Acetazolamide when used at doses of up to 4g/d.

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)-acetamide (acetazolamide) was synthesized in the early 1950s by T.H. Maren and approved by the US Food and Drug Administration for the treatment of seizures in 1953. Acetazolamide is considered a nonbacteriostatic sulfonamide based on chemical structure and pharmacological activity and is a classic noncompetitive reversible inhibitor of carbonic anhydrase. Carbonic anhydrase, the enzyme responsible for catalyzing the reversible reaction of carbon dioxide and water into protons and bicarbonate[7] is predominantly found in red blood cells, the luminal proximal tubule membrane of the kidney, plasma, and to a lesser extent the liver, the ciliary body of the eye and the choroidal plexus[8]. Acetazolamide is well absorbed orally from the GI tract and is excreted by

tubular secretion, at the proximal renal tubule. Excreted drug is principally unmetabolized. The action of blocking carbonic anhydrase activity induces sodium bicarbonate diuresis, which reduces whole body bicarbonate levels and increases chloride concentration, resulting in compensatory metabolic acidosis. Within the brain, eye, and choroidal plexus, acetazolamide produces an accumulation of carbon dioxide that is sufficient to prevent the tonic extensor component of the generalized seizure, reduces aqueous humour secretion and cerebrospinal fluid production, respectively making the use of acetazolamide effective in medically treating seizures, glaucoma and IIH.

TOXICITY, TERATOGENICITY AND ACETAZOLAMIDE USE

T.H. Maren first extensively studied acetazolamide toxicity in animals at a time when the effects of carbonic anhydrase inhibition were relatively unknown. Rabbits, exhibited some mild toxicity that was attributed to renal damage.. In dogs, single intravenous doses of 2000 mg/kg was tolerated (non-fatal) as were single daily oral doses of 100mg/kg. In growing rats, 900 mg/kg per day orally resulted in some growth and weight gain delays. In all these animals there was a marked metabolic acidosis, usually with a compensatory respiratory component. Moreover, sodium and potassium loss, observed following the initial dose was not continuous. Rather, a steady state deficit of ~10% was noted while on drug and the chemical changes reverted to normal when the drug was withdrawn. Plasma concentrations of calcium and phosphorous were unchanged[9]. In humans, there are many known systemic adverse experiences (AEs) in those who use oral acetazolamide. Paraguesias, paresthesias in the hands, feet and face, fatigue, nausea, diarrhea, abdominal cramps, loss of appetite, and polyuria are common[10]. Common metabolic changes include hypokalemia, hyponatremia, and metabolic acidosis. Uncommon but more severe AEs include anaphylaxis, Stevens-Johnson syndrome, renal stones[11], and blood dyscrasias[12]. Allergic reactions are uncommon and there is insufficient evidence to indicate there is any cross sensitivity in patients who are allergic to sulpha-based drugs[13, 14].

Given that IIH is common in young women of childbearing age, it is not surprising that 2-12% become pregnant during treatment.[15] The first study to report teratogenicity was performed in rats and found a teratogenic lesion[9]. Parturition was otherwise normal and no abnormalities were observed in the offspring. Subsequent studies indicate that acetazolamide use, at least in animals, is teratogenic[8, 16-21]. To date, there is no evidence of a direct association between acetazolamide and birth defects during pregnancy in humans. However, it should be noted that there are no adequately controlled data from human pregnancy. The retrospective Collaborative Perinatal Project (CCP) in which 12 of 50,828-monitored mother-child pairs exposed during the first or second trimester and a total of 1024 pairs who were exposed throughout the pregnancy, revealed no evidence between major or minor categories of defects to the use of acetazolamide[22]. More recently, Lee et al.,[23] reported unremarkable findings in 12 patients treated with acetazolamide for IIH during pregnancy and concluded, based on observed patients and an accompanying critical review, that there is little clinical or experimental evidence to support any adverse effect of Acetazolamide on pregnancy outcomes in humans. These conclusions are supported by others[24-26]. One published case of adverse pregnancy outcome has been reported; a woman who used acetazolamide (750 mg/d) during the first and second trimester gave birth to an infant with sacrococcygeal teratoma[27]. Given the associated teratogenic effects of drug use in animal reproductive studies and the lack of adequate and controlled human trials, acetazolamide has been assigned to a pregnancy category C by the US FDA. The use of acetazolamide in pregnancy therefore is cautioned during pregnancy and should only be prescribed when the benefits of taking the drug outweigh the risks of rare yet possible adverse outcomes.

ACETAZOLAMIDE USES

Acetazolamide is effective in the treatment of seizures [28] ,glaucoma[7, 29, 30], edema[31], altitude acclimatization, altitude sickness[32, 33], Meniere disease [34, 35], and IIH.

SEIZURES

Acetazolamide was approved for the treatment of epilepsy in 1953. For this indication, it is used primarily in combination therapy with other antiepileptic medications but also used as a monotherapy. The anticonvulsant properties associated with acetazolamide were first described by Bergstrom et al.,[36] and later reconfirmed in animals and humans[24, 37-39]. Since this time, acetazolamide has been used empirically in the treatment of refractory epilepsy[40]. An effective dose has not yet been reported in controlled clinical studies however reported doses range from 375mg-1g daily. [40, 41]

GLAUCOMA

Becker et al, was the first to show the IOP lowering effect of acetazolamide in glaucoma patients[29]. Since this time, acetazolamide is used an adjunctive treatment of open-angle or secondary glaucoma at doses from 250mg to 1g daily or every 4 hours in the case of acute angle closure glaucoma.

IIHTT TRIAL

Acetazolamide use (1g/d) for treatment of IIH was first suggested by Lubow and Kuhr[3] and subsequently supported by Tomsak et al to show a reduction in optic nerve edema[4]. Larger acetazolamide doses (4g/d), were used

by Gucer and Viernstein in 2 cases to maximally reduce intracranial pressure[5]. While the tolerability and safety of acetazolamide at 1g/d has been well documented, most studies lack scientific rigor. Beyond 1g/d there are no safety and tolerability studies.

PROTOCOL

In the IIH study, the acetazolamide dose was initiated at four 250mg tablets daily (1g/d) in 2 doses with subsequent dosage increases of 1 tablet/week up to maximum of 16 tablets daily (4g/d). The dosing range was selected based on common clinical practice where 1g/d is the usual starting dose, and 4g/d is the only dosage to show efficacy in reducing CSF pressure simultaneous with CSF pressure measurements[5].

Clinical evaluations were performed at screening, baseline, and 1,2,3,4.5, and 6 months after baseline. CBC with platelet count was performed at screening, month 3, and month 6 and a comprehensive metabolic profile including liver function and electrolytes was performed at screening and months 1, 2, 3, and 6. After the treatment phase, clinical laboratory tests were performed at the treating investigator's discretion. In addition, all adverse experiences (AEs) and serious adverse experiences (SAEs) were collected by recording all voluntary complaints of the subject and by assessment of clinical and laboratory findings. Participants were also queried directly regarding the occurrence of any AE/SAEs since their last visit.

One hundred sixty five participants were randomized to receive either placebo (n=79) or acetazolamide (n=86)[6].

TOLERABILITY

During the trial, if the participant had adverse experiences (AEs) that substantially interfered with activities of daily living, the highest dosage of study medication tolerated was given, with a minimum acceptable dose of 1/2 tablet (125mg) daily. Forty-two (49%) individuals in the acetazolamide group successfully reached the maximum study dose of 4g/day; the average time to attain this dose was 13 weeks (Min: 10; Max: 24). Forty-three individuals (46%) tolerated between 1.25g and 3.75g. Four individuals (5%) in the acetazolamide group did not progress beyond 1g/d. One participant in the acetazolamide group was not able to tolerate the 1g/d dose and was reduced to 0.75g/d at 1 week. Ten participants permanently discontinued the study drug during the trial, including 9 in the acetazolamide group (7 of whom completed follow-up) and 1 in the placebo group (who completed follow-up). Eight participants (4.8%) discontinued the drug due to AEs, and the remaining 2 (both in the acetazolamide group) were due to pregnancy and the desire to become pregnant[6].

SAFETY

Adverse Event (AE) was defined as any symptom, sign, illness, or experience, which develops or worsens during the course of the study whether or not the event is considered to be related to study drug. All AEs, whether volunteered or reported by the participant were included in the analysis. For each AE, the severity and causality was determined and recorded as either: unrelated, unlikely, possibly, probably.

Acetazolamide is well known to have a high incidence of AEs. The Compendium of Pharmaceuticals and Specialties reports over 10% of users experience malaise, diarrhea, anorexia, metallic taste and polyuria[42]. A further 1-10% of users will experience drowsiness, depression, and dizziness. In the IIHTT study, at least one or more AE was reported in 84% of the 165 participants (acetazolamide n=79, placebo n=60, Table 1) (see below). Given that some AEs may be dose related, it was anticipated that the IIHTT treatment group would report a larger number of adverse reactions. Indeed 92% of the treatment group experienced at least one AE (compared to 76% of the placebo group) and nearly two-thirds of the treatment group reported between 2 and 10 AEs over the course of the study.

In total, 675 AEs (acetazolamide n=479, placebo n=196; from 139 participants, Table 2) (see next page) were reported in the IIHTT. As expected, AEs associated with metabolic and nutrition disorders were significantly higher in the acetazolamide group. A relationship between these metabolic perturbations measured in the serum and systemic systems (such as malaise and gastric reflux) has been speculated but never demonstrated[43]. Renal and urinary disorders, nervous system disorders, and gastrointestinal disorders occurred more commonly in the acetazolamide group but did not reach statistical significance.

Number of AEs Reported Per Patient	Placebo N (%)	Acetazolamide N (%)	Total N (%)
0	19 (24)	7 (8)	26 (16)
1	13 (16)	9 (10)	22 (13)
2-4	33 (42)	24 (28)	57 (35)
5-10	13 (16)	32 (37)	45 (27)
>10	1 (1)	14 (16)	15 (9)
Total	79 (100)	86 (100)	165

Table 1. Frequency Of AEs Per Patient

TABLE 2. ALL AES REPORTED DURING THE IIHTT TRIAL

System Organ	Class	Placebo N*(%)	Acetazolamide N*(%)	z-value	p-value
Nervous		32 (16.3)	107 (22.3)	1.8	0.08
	Paresthesia	7	51		
	Paraguesia	0	13		
	Headache & Migraine	16	14		
	Dizziness	4	10		
	Fatigue	0	3		
	Other	5	16		
Gastroin-testinal		25 (12.8)	92 (19.2)	1.9	0.06
	Nausea	10	30		
	Diarrhea	4	14		
	Vomitting	3	12		
	Acid Reflux	2	12		
	Dry Mouth	0	3		
	Constipation	0	2		
	Other	6	19		
Investigations (e.g. Abnormal Laboratory Finding)		18 (9.2)	44 (9.2)	0	1
Infections (e.g. cold, flu, pneumonia)		43 (21.9)	43 (9.0)	4.6	<.001
Muscoluskeletal (e.g. Myalgia, Joint Pain)		13 (6.6)	27 (5.6)	0.8	0.63
Metabolic		1 (0.5)	23 (4.8)	2.5	0.01
	Metabolic Acidosis	0	6		
	Loss of Appetite	0	6		
	Hyperchloremia	0	4		
	Hyperkalemia	0	4		
	Dehydration	0	2		
	Increased Appetite	1	1		
Skin		5 (2.6)	19 (4.0)	0.6	0.53
	Rash	3	8		
	Hives	1	3		
	Acne	1	2		
	Pruritus	0	2		
	Other	0	4		
Eye/Vision		14 (7.1)	16 (3.3)	2.4	0.02
	Transient Visual	2			
	Obscuration	3	7		

(Continued on next page)

TABLE 2. ALL AES REPORTED DURING THE IIHTT TRIAL (CONTINUED)

	Permanent Visual	3			
	Obscuration	6	2		
	Flashes/Floaters		3		
	Other		4		
Respiratory (e.g. dyspnea, hypercapnia)		6 (3.1)	16 (3.3)	0	1
Psychiatric (e.g. depression, anxiety)		3 (1.5)	15 (3.1)	0.7	0.47
Ear (e.g. tinnitus, other)		5 (2.6)	15 (3.1)	0	1
General		12 (6.1)	36 (7.5)	0.9	0.37
	Fatigue	1	16		
	Other	5	12		
	Seasonal Allergies	1	3		
	Gynecologic Abnormalities	5	3		
	Allergic Reaction	0	1		
	Pelvic Pain	0	1		
Renal (e.g. polyuria, renal stones)		0 (0.0)	8 (1.7)	2	0.05
Vascular (e.g. blood pressure changes, other)		1 (0.5)	3 (0.6)	0	1
Pregnancy		0 (0.0)	3 (0.6)	1.4	0.16
Cardiac (e.g. palpitations, tachycardia)		0 (0.0)	3 (0.6)	1.4	0.16
Unrelated Surgery		1 (0.5)	1 (0.2)	2.2	0.03
Procedural complications (e.g. post LP complications, other)		17 (8.7)	10 (2.1)	4.2	<.001
***total number of AEs**		TOTAL AES	196	480	

When considered individually, the relative risk for experiencing paresthesia, paraguesia, vomiting, nausea, diarrhea, and fatigue were all significantly higher in the acetazolamide group (Table 3) (see next page). Common symptoms were more frequently reported at the lower dosages (0-2g/d); this may be a reflection that the symptoms were dose-limiting in the affected individuals. It is also plausible that carbonic anhydrase may be maximally inhibited at lower doses. An early study conducted in the 50s suggested that carbonic anhydrase inhibition is complete at 5-20 mg/kg in organs[9].

Common Adverse Experiences	Placebo (n)	Acetazolamide (n)	RR	95% CI	z-stat	P Value
Nervous Disorders						
Paresthesia	9	55	5.61	2.98-10.6	5.342	p<0.0001
Paraguesia	0	14	26.67	1.62-439.78	2.296	p=0.022
Gastrointestinal Disorders						
Vomiting	3	12	3.67	1.08-12.54	2.08	p=0.04
Nausea	10	31	2.85	1.5-5.42	3.19	p=0.001
Diarrhea	4	14	3.22	1.12-9.36	2.142	p=0.03
Metabolism and Nutrition						
Loss of appetite	0	6	11.95	0.68-208.83	1.7	p=0.09
Hypokalemia	0	2	4.6	0.22-94.33	0.99	p=0.32
Metabolic acidosis	0	5	10.12	0.57-180.04	1.58	p=0.12
Renal and Urinary Disorders						
Renal stone	0	2	4.6	0.22-94.33	0.99	p=0.32
Polyuria	0	3	6.44	0.34-122.69	1.238	p=0.22
Other						
Fatigue	1	19	17.45	2.39-127.37	2.82	p=0.005
CI=CONFIDENCE INTERVAL; RR=RELATIVE RISK; P VALUE=PROBABILITY VALUE; N=NUMBER OF AES.						

Table 3. Frequency and Relative Risk (RR) of common adverse experiences associated with acetazolamide use.

As expected, patients in the treatment group had significantly lower levels of CO2 at all time points after baseline. Similarly, the treatment group had significantly higher creatinine levels at most time points after baseline. The creatinine level was still well within normal limits at all points in time and deemed clinically insignificant. Serum bicarbonate fell below the lower limit of normal for many patients at multiple time points. Whether the observed low CO2 levels are responsible for some of the systemic adverse reactions that were reported (such as malaise, headache, and gastric reflux) is not known. Several authors have implicated low CO2 levels with paresthesia and dysguesias.

Serious Adverse Events (SAE) are defined as an AE that resulted in death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect. There are several known but rare SAEs associated with acetazolamide and CAI use.

Allergic reactions associated with acetazolamide use are rare but serious. Allergic reactions are generally but not always attributed to suspected cross reactivity in sulphonamide allergy although direct evidence for this is lacking[13, 14, 44-46]. Moreover, acetazolamide is a nonbacteriostatic sulphonamide which is distinct from the bacteriostatic sulphonamides thus an allergic reaction is not expected based on structure and pharmacologic activity. Despite the paucity of data supporting a suspected cross reactivity, it is still recommended not to prescribe acetazolamide to patients with a known sulphonamide allergy. Stevens-Johnson syndrome (SJS) is an immune-complex-mediated disorder, usually caused by a drug reaction, involving the skin and mucous membranes[47]. There have been 18 case reports of SJS in patients of Asian descent leading some to suggest that acetazolamide should be prescribed with caution in this population[48].

In the IIHTT, there was one reported allergic reaction. The participant was in the dose escalation phase and just increased to 5 tablets in the evening. The following morning, the patient woke with a generalized rash, facial, upper extremity and periorbital swelling. The participant had known penicillin and environmental allergies, was advised to remain permanently off the study drug but agreed to continue in the study.

Renal calculi are a common clinical problem affecting from 5-15% of the population worldwide with an estimated recurrence rate that is close to 50%. Risk factors for stone formation include age, male gender, family history, and multiple pathogenic factors. Hyperexcretion of calcium is a major contributor to stone formation. General incidence and prevalence of renal calculi is reported to be 164/100,000 and 5.2%, respectively and in the context of Acetazolamide therapy, patients are reported to have an 11 times higher risk of developing more than one kidney stone per year[11]. The mechanism of acetazolamide-induced stone formation is not fully understood however elevated citrate and magnesium have been implicated[49].

Two participants reported renal stones in the IIHTT. One required hospitalized due to complications (hydronephrosis; pyelonephritis) but were deemed not related to the study drug.

Aplastic anemia, agranulocytosis, and thrombocytopenia are documented blood dyscrasias in patients taking acetazolamide[50-53]. Fraunfelder et al., reporting on the Drug-Induced Ocular Side Effects in the National Registry showed 79 case reports of suspected hematopoietic toxicity to CAI use (not specifically acetazolamide)[54]. It was reported that the hematologic reactions occurred in 68% of patients within 6 months of initiating therapy. Thus, routine CBC monitoring of patients is recommended. There were no reports of aplastic anemia in the IIHTT.

Observed SAEs-IIHTT. SAEs were rare in the IIHTT. Eleven SAEs were reported (acetazolamide n=8; placebo n=3, Table 4) (see below). None of the SAEs resulted in persistent or significant disability. One participant with transaminitis required hospitalization. This participant was asymptomatic and liver function normalized after discontinuation of acetazolamide.

SAE #	Treatment	Event	Daily Dose	AE Related	Outcome
1	**Placebo**	Vision Loss	1g	Unrelated	Unknown
2	**Placebo**	Pneumonia & Bronchitis	2.25g	Unrelated	Recovered
3	**Placebo**	Vision Loss	1.75g	Unrelated	Recovered
4	**Acetazolamide**	Suicidal ideation	3g	Unrelated	Recovered
5	**Acetazolamide**	Decreased kidney function	4g	Related	Recovered
6	**Acetazolamide**	Transaminitis of unknown origin	4g	Related	Recovered
7	**Acetazolamide**	Allergic Reaction; lymphedema	2.5g	Related	Recovered
8	**Acetazolamide**	Acute Pancreatitis	1.5g	Related	Recovered
9	**Acetazolamide**	Hypokalemia	2.25g	Related	Recovered
10	**Acetazolamide**	Hydronephrosis; pyelonephritis	2g	Related	Recovered
11	**Acetazolamide**	Acute Diverticulosis	2.25g	Unrelated	Recovered

Table 4. Serious Adverse Experiences (SAEs) reported during the IIHTT.

CONCLUSIONS

The IIHTT protocol stipulated a slow dose escalation of acetazolamide from 1g/d to a maximum of 4g/d thus the generalizability of the expected safety and tolerability profile is restricted to those patients following the dose escalation protocol. It is not known whether the tolerability and the profile of adverse events changes upon deviation from the study protocol.

Most common adverse events were reported early in the dose escalation phase (0-2g/d), which may be a reflection that the symptoms were self-limiting in the affected individuals. Serious adverse events were rare and none resulted in persistent or significant disability.

Elevated liver function tests occurred in two participants who were asymptomatic and experienced normalization of hepatic enzymes after discontinuing acetazolamide. Based on their experience, we recommend routine monitoring of transaminases in the dose escalation phase of acetazolamide treatment. No participant experienced aplastic anemia. Reports of congenital defects in humans is rare however since IIH is seen predominately in women of child-bearing age, treating physicians should always enquire about the possibility of pregnancy in their patients before initiating therapy. In the IIHTT there were two such cases, one that became aware of a pregnancy while on treatment, the other who stopped treatment before becoming pregnant. In the first case, the participant delivered a healthy baby with no congenital defects.

The IIHTT is the first randomized double masked, placebo-controlled trial for the treatment of patients with mild visual loss from IIH and provides the first evidence-based treatment recommendations, showing the benefit of acetazolamide and weight loss for improving visual status in patients with mild visual field loss from IIH. Use of acetazolamide up to 4g/d in patients with IIH who experienced mild vision loss was effective, safe and well tolerated in most patients.

CME ANSWERS

1. d
2. c

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CHANGE IN BODY WEIGHT AFTER A 6-MONTH TELEPHONE-BASED WEIGHT LOSS INTERVENTION IN NORMAL WEIGHT, OVERWEIGHT, AND OBESE SUBJECTS WITH IDIOPATHIC INTRACRANIAL HYPERTENSION

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LEARNING OBJECTIVES

1. Understand the effectiveness of a phone based intervention for weight loss
2. Identify the % of body weight loss needed for improvement of IIH
3. Gain a general knowledge of effective weight loss strategies

CME QUESTIONS

1. True/False: Weight loss was achieved by diet alone in IIH.
2. What was the mean percentage of weight lost in all patients with IIH?
3. True/False: the acetazolamide treated group lost more weight than the placebo group

KEYWORDS

1. IIH
2. Weight Loss
3. Dietary intervention
4. Exercise intervention
5. Behavioral intervention

INTRODUCTION

OBJECTIVE: To measure the change in body weight after a 6-month telephone-based weight-loss intervention in normal weight, overweight and obese men and women with idiopathic intracranial hypertension (IIH) and mild visual loss randomized to either acetazolamide or placebo.

SUBJECTS: One hundred sixty-five men and women with IIH, aged 29.1 $\pm$ 7.5 (mean $\pm$ SD) and BMI 40.0 $\pm$ 8.3 kg/m^2, enrolled at 38 academic and private practice sites in North America.

DESIGN: Randomized, double-masked, placebo-controlled trial of weight change after a 6-month telephone-based weight loss intervention in subjects with idiopathic intracranial hypertension (IIH) and mild visual loss randomized to either acetazolamide or placebo.

OUTCOME MEASURES: Six-month change from baseline in body weight and quality of life.

RESULTS: Mean percent weight change at 6 months was -5.9% ± 6.7% of initial body weight overall, -3.5% ± 5.9% in the placebo group, and -7.8% ± 6.8% in the acetazolamide group. Subjects taking acetazolamide lost more weight over 6 months (mean -7.9 kg) than those on placebo (mean -3.7 kg) (treatment effect -4.1 kg, 95% CI -6.3 to -1.8 kg, $p < 0.001$).

CONCLUSION: Patients with idiopathic intracranial hypertension and mild visual loss assigned to either acetazolamide or placebo, all of whom received a 6-month telephone-based weight loss intervention, lost an average of 5.9% of initial body weight, consistent with NHLBI guidelines of 5% to 10% of body weight loss for clinically significant health benefit.

BODY

The weight loss intervention for the Idiopathic Intracranial Hypertension Treatment Trial was designed and implemented by the New York Obesity Nutrition Research Center (NYORNC). The information and counseling was provided by Weight Loss Coaches (WLC) located in New York via telephone calls to the subjects. The goal was 6% weight loss at 6 months and 10% weight loss at 1 year.

The WLC's included dietitians, certified life coaches, and social workers experienced with weight loss. They were hired locally and trained for the study by one of the NYORNC investigators to whom they reported. They also received additional training and support throughout the study. The calls consisted of a check-in on homework assignments, updates on any life events, review of previous information, new information when warranted, and a plan for achieving their upcoming goal.

A workbook was designed by the investigators at the NYONRC. It was based on the 52-week out-patient weight loss program at the NYONRC. Adjustments were made for telephone counseling and material was in a format appropriate for low vision and low reading skills. The content of the workbook and information covered during the calls is as follows:

Dietary intervention: The weight loss goal was to lose 1 to 2 lbs per week. Calorie needs were calculated using the Mifflin St. Jeor calculation. This calculation provides maintenance calories based on gender, age, height, weight, and activity level. To lose 1 lb per week, 500 calories per day was subtracted from their maintenance calories for a total defect of 3,500 calories per week. To lose 2 lbs per week, 1000 calories per day was subtracted from their maintenance calories for a total deficit of 1000 calories per week. The rate was determined by how much weight they had to lose and what they would be able to comfortably comply with. For subjects who were not overweight, their goal was to maintain while learning about balancing where their calories came from.

The goal was a balanced diet with about 20% of calories from protein (lean sources), 25-30% from fat (mono and polyunsaturated sources), and the remainder from carbohydrate (high fiber sources). Each of these nutrients was explained and reviewed throughout the year. Details were provided on limiting their sodium as much as possible. They were not instructed to stay below a certain level, but instead, encouraged to not add sodium to meals and choose low sodium options at home and when eating out. Subjects reported their compliance with restricting their sodium as either excellent (staying below recommendation majority of the time); good (staying close to recommendation most of the time); fair (25% to 50% more than the recommendation most of the time); poor (over 50% more than the recommendation most of the time); or unknown (not keeping track at all; no idea how much consuming).

Meal replacements, including shakes, bars, and frozen meals, were discussed in detail and strongly encouraged as a way to adhere to their calorie goals. They could be used for any of their meals and/or snacks. No one was following a full meal replacement diet. Subjects reported how often they used meal replacements for the previous week and when they were used (meals and/or snacks).

Other diet topics included volumetrics (low energy density), portion control, alcohol, eating out, food label reading, weight loss science, and environmental influences on eating, The WLC was able to cover a topic as often as needed in order to meet the subjects individual needs and personalize the plan. Homework would often be set based on the topic covered.

Exercise intervention: Each subject was encouraged to increase physical activity to reach a goal of 30-60 minutes of moderate-intensity exercise five or more days/week or 20-60 minutes of vigorous-intensity exercise five or more times/week[1]. Exercise topics included aerobic and resistance exercise, determining exercise intensity, increasing activities of daily living, goal setting, stretching, maintaining motivation, working out at a gym or at home, resistance exercise tubing, and walking tips and programs. Subjects received a pedometer and were encouraged to wear it daily. Subjects provided WLCs with weekly pedometer step counts and number of days the pedometer was worn to calculate the average number of steps per day.

Behavior intervention: Cognitive behavioral therapy (CBT) was the foundation of the behavior intervention. CBT involves identifying and challenging maladaptive thinking to change behavior (cognitive restructuring). Behavior topics included goal setting, relapse prevention, motivation, assertiveness, problem solving, stress management, managing cravings and urges, sleep habits, social support, and lifestyle balance. These topics could be covered individually or coupled with the diet or exercise intervention.

The phone sessions during the first six months were 30 minutes after an initial 1-hour session. For months 7 and 8 the calls were made every other week and then they changed to monthly for the remainder of the year. The session format was set by the WLC in order to feel more personalized for the subject. The initial 7 weeks had topics that were recommended to be covered, but adjustments were allowed if needed. The goal was for all of the topics in the workbook to be covered by 6 months and reviewed after that with an emphasis on managing weight loss throughout. By the end of each call information was obtained for the data that was then entered into an online database by the WLC. This would include current weight, frequency of weighing-in, use of meal replacements, diet compliance, sodium restriction compliance, exercise compliance, and homework compliance.

Results: The mean weight loss was 3.5% and 7.0% at 6 and 12 months, respectively, for the placebo group; 7.8% and 8.1% for the acetazolamide group; and 5.9% and 7.6% for both groups combined.

Attrition was 24% (n=39) at 6 months. Thirty-two were early withdrawals (including two pregnancies) and seven were treatment failures based on specific visual field criteria.

Overall, 80% of subjects (n=99) lost weight, 20% (n=25) gained weight, and two subjects had no change in weight. Sixteen subjects (28%) in the placebo group and 9 subjects (13%) in the acetazolamide group gained weight.

The phone calls allowed for a sense of privacy and comfort for many. There was a great deal of flexibility on when the calls could occur that helped subjects who had hectic schedules and/or limited ability to get to appointments. They also proved to be an issue for some who would have

preferred to meet in person or who did not have access to a phone for the calls. We had hoped for the subjects to connect online with each other on a message board. Unfortunately, this never managed to happen. Many had a sense of isolation with their diagnosis and would have benefited from being around other subjects during this trial.

The biggest weight loss challenge was the fact that the subjects joined the trial because of their IIH diagnosis and not for weight loss. Many felt that once their symptoms had improved and/or they met the 6 month mark that they were done. This would account for the decrease in compliance in calls and weight loss after 6-months. There also appeared to be a very high level of stress in their lives. Typically, major stressful life events are contraindicated for weight loss. These included, but are not limited to, moving, divorce, loss of a job, career changes, and/or death of a family or friend. The fear of losing their vision was the primary reason for agreeing to participate, but it did not provide results greater than we would see with this intervention without the IIH diagnosis.

CME ANSWERS

1. False
2. 5.9%
3. True

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ENDNOTES

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SAGGING EYE SYNDROME AND DISTANCE ESOTROPIA IN THE ELDERLY

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LEARNING OBJECTIVES

1. Describe the pathogenesis of cyclovertical strabismus in the sagging eye syndrome
2. Recognize the clinical differences between neuropathic strabismus and strabismus caused by sagging eye syndrome
3. Describe the surgical and non-surgical management of strabismus caused by sagging eye syndrome

CME QUESTIONS

1. Degeneration of what connective tissue structure is mainly responsible for age-related distance esotropia?

    a. Lateral canthal tendon
    b. LR-SR band
    c. Levator aponeurosis
    d. Peritoneal ligament
    e. Medial canthal tendon

2. Which clinical feature differs between hypertropia due to sagging eye syndrome, rather than due to superior oblique palsy?

    a. Excyclotropia in the hypotropic eye
    b. Vertical incomitance
    c. Excyclotropia in the hypertropic eye
    d. Vertical nystagmus
    e. Acute onset of diplopia

3. Which anatomic features are characteristic of the heavy eye syndrome, but not of sagging eye syndrome?

    a. High axial myopia
    b. Inferonasal displacement of the inferior rectus muscle
    c. Inferior displacement of the lateral rectus muscle
    d. a, b, and c
    e. a and b

KEYWORDS

1. Strabismus
2. Esotropia
3. Hypertropia
4. Magnetic Resonance Imaging
5. Orbit

INTRODUCTION

Purpose: Sagging eye syndrome (SES) causes strabismus because orbital connective tissue degeneration allows inferior shift of the lateral rectus (LR) extraocular muscle pulleys. This paper reviews this relatively common, non-neurological cause of diplopia in older adults.

Methods: High-resolution MRI of the orbits in patients with SES has been quantitatively compared with normal subjects age-matched to SES, and normal young adults. MRI has defined rectus pulley locations comparable to age-matched norms, and has quantified lengths of the LR-SR band ligament and rectus EOMs. These data have been correlated with facial and adnexal features, and ocular motility. Results of strabismus surgery have been systematically assessed in age-related distance esotropia (ARDE, "divergence paralysis") and cyclovertical strabismus (CVS) due to SES.

Results: Patients with SES commonly exhibit blepharoptosis and superior sulcus defect, and are likely to have previously undergone blepharoplasty or facelift surgery. The MRI hallmark of SES is significant inferolateral LR pulley displacement, with peripheral displacement of all other rectus pulleys, and lateral displacement of the inferior rectus pulley. Rectus muscles are generally elongated. Symmetrical LR sag is associated with ARDE, and asymmetrical LR sag >1 mm with CVS in which the hypotropic eye is also excyclotropic. The LR-SR band ligament is ruptured in the great majority of patients with SES. While there is no horizontal duction limitation or saccade slowing, patients typically have limited sursumversion due to medial rectus (MR) and LR sag. ARDE responds well to MR recession with augmented dosing, or to LR resection or plication. CVS may be treated by graded vertical rectus tenotomy or more conventional strabismus surgeries.

Conclusions: Rectus pulley displacement and EOM elongation, associated with connective tissue involution including LR-SR band rupture, causes acquired cyclovertical and horizontal strabismus in older patients.

Clinical Relevance: Small angle esotropia, hypertropia, and cyclotropia may result from common involutional changes in EOMs and orbital connective tissues that may be suspected from adnexal features.

INTRODUCTION

As at other anatomical sites, the orbital connective tissues change with aging,[1, 2] causing among other untoward effects aponeurotic blepharoptosis and limited supraduction due to inferior displacement of the horizontal rectus pulleys.[3-5] Similar to the way that the externally visible adnexa age, the internal connective tissues in the orbit also involute. Not all such involutional changes are homogeneous, however. A particularly significant involution occurs in the LR-SR band, a ligament originating on the lateral border of the superior rectus (SR) pulley and terminating on the superior border of the lateral rectus (LR) pulley. The LR-SR band vertically supports the LR pulley against the downward force of the inferior oblique muscle, whose orbital layer inserts on the LR pulley.[6] Degeneration of the LR-SR band permits inferior sag of the LR pulley, causing esotropia, or cyclovertical strabismus, or both.[2, 7, 8] Bilateral inferior shift of the LR pulley may mechanically produce age-related distance esotropia (ARDE), also variously known as divergence paralysis esotropia, "divergence insufficiency," "divergence insufficiency esotropia," and "divergence paresis esotropia." ARDE is characterized by esotropia at distance fixation, orthotropia or esophoria at near fixation, normal horizontal duction range, and normal horizontal saccadic velocities. [7, 8] Asymmetrical inferior shift of the LR pulley has been postulated to produce cyclovertical strabismus (CVS) because of unbalanced conversion of some of the forces of the two LR muscles from abduction to infraduction. Clinical strabismus patterns correlate closely with anatomical changes observable by orbital imaging. It is important to understand SES as a cause of acquired diplopia, because this diagnosis is not indicative of an acute neurological event, and does not require extensive or costly investigations as might be typically performed for acutely acquired diplopia due to neurological lesion.[9, 10] Moreover, the mechanical etiology of SES presents a favorable prognosis for appropriately designed surgical treatment.[11, 12]

This presentation reviews the quantitative anatomy of SES as revealed by high resolution magnetic resonance imaging (MRI) of the rectus EOMs, pulleys, and the LR-SR band ligament. Details of the studies have been published previously.[8, 13, 14]

METHODOLOGY

Detailed quantitative results were obtained by surface coil orbital MRI in 28 subjects (11 males, 17 females) of average age 69±12 years who had acquired horizontal or cyclovertical diplopia. Age-related distance esotropia (ARDE), defined as orthophoria or asymptomatic esophoria of ≤10□ at near, with distance esotropia measuring double or more the measured near esophoria, existed in 11 subjects.(12) CVS, defined as hypertropia exceeding 2△ with or without cyclotropia, existed in 17 subjects. Patients were excluded if they had superior oblique (SO) palsy, thyroid eye disease, trauma, prior strabismus surgery, or myopic degeneration suggestive of the "heavy eye" syndrome.(4)

Patients had attained mature age, with mean age for ARDE (3 males, 8 females) 72±11 years, and for CVS (7 males, 10 females) 68±2 years. Mean esotropia in ARDE was 12±11△ at distance and 1±3△ at near. ARDE was vertically comitant. Ten subjects had pure CVS, and 7 more had CVS with associated esotropia. Average hypertropia of these subjects was 10±10D. Fundus torsion was objectively determined by slit lamp measurement of the fovea to optic disc angle.[15, 16]

High resolution MRI was performed using surface coils in target-controlled central gaze by each scanned eye.[17, 18] Using 2 mm thick quasi-coronal images perpendicular to the orbit, cross sections of the rectus EOMs and the SO were analyzed in standard, oculocentric coordinates to identify rectus pulley positions for comparison with norms.[17, 18] Maximum SO cross sections were determined to exclude neurogenic SO atrophy due to SO palsy. Horizontal rectus EOM path lengths were determined from axial images, and vertical rectus EOM path lengths from quasi-sagittal images. Lengths of the superior (SR) and inferior rectus (IR) muscles were determined in 18 orbits of 9 patients with SES (average age 64±4years), and compared to 64 orbits of 34 normal young (average age 24±4 years) and 15 orbits of 9 normal older controls (average age 62±5 years).

QUANTITATIVE FINDINGS

EXTERNAL FEATURES IN SES. Adnexal sag was highly prevalent in SES. Retraction of the upper eyelid into the superior orbit (superior sulcus deformity) was evident in 64% of subjects with SES; 29% exhibited aponeurotic blepharoptosis and high upper eyelid crease. Previous blepharoplasty, brow or facelift surgeries had been performed in 29% of patients with SES.

RECTUS PULLEYS IN ARDE. Both the MR and LR pulleys were both significantly displaced centrifugally from the orbital center (P<0.005). The LR pulley was 4 mm more lateral than in younger control orbits, while also being bilaterally symmetrically inferoplaced by a significant average of 5.9 mm. The MR pulley was about 2.4 mm more medial than in younger control orbits, while also

being significantly inferoplaced by 3.4 mm. The IR pulley was displaced about 5 mm temporally and about 3 mm inferiorly than in young and older normal subjects.

RECTUS PULLEY POSITIONS IN CVS. The MR pulley of the hypotropic eye was 2.6 mm inferior and 1.6 mm temporal to younger normal (P< 0.005), but not significantly different from older normal subjects. The SR pulley in CVS was about 1 mm inferior to that of normal younger subjects (P<0.005), but similar to normal older subjects. The MR and SR pulleys in the hypertropic eyes of subjects with CVS were normally located.[17] The LR pulley in the hypotropic eye in CVS was about 4 mm temporal and 6 – 8 mm inferior to that of younger and older controls (P<0.005 for both), while the LR pulley in the hypertropic eye was only about 4 mm inferior. The LR pulley in the hypertropic eye in CVS was about 4 mm more lateral than in both younger and older controls (P<0.005). The inferior rectus (IR) pulley was displaced temporally from both younger and older controls by 4–5 mm in both the hypotropic and the hypertropic eyes in CVS (P<0.005).

As noted above, inferior LR pulley displacement was bilaterally symmetrical in ARDE, differing from right to left on average only 0.3±0.1 mm (P=0.8). Quite different was CVS, in which binocular LR displacement asymmetry averaged 2.6±1.8 mm (P=0.04). For individuals with ARDE, asymmetry of LR sag was always less than 0.5 mm, while in CVS, LR pulley infraplacement in the hypotropic orbit always exceeded that in hypertropic orbit by at least 1 mm. No other difference in pulley positions between hypertropic and the hypotropic eyes was statistically significant (P>0.05). This difference is mechanistically consistent with hypotropia in the eye with greater LR pulley infraplacement, and also consistent with observations of fundus cycloposition. The eye that exhibited greater hypotropia and greater LR sag exhibited 12±6° excycloposition, more than the hypertropic fellow eye that exhibited 7±5° excycloposition (P=0.01.)

RECTUS MUSCLE PATH LENGTHS. The LR path was markedly elongated in SES. In younger controls, LR path length averaged 33±6 mm, similar to 31±14 mm in older people without strabismus. The LR path was approximately 40% longer, at 45–47 mm, in both ARDE and CVS (P<0.005). The MR path was not as elongated as the LR in SES (P < 0.000002), but nevertheless was about 25% longer, at 38–39 mm, in both ARDE and CVS than the length of 31±6 mm in younger and older controls (P<0.005). Path length of the SR in both ARDE and CVS was 3–6 mm longer than in younger and older controls, but IR length was not abnormal.

PATHOLOGY OF LR-SR BAND. Reflecting age-related degeneration, the LR-SR band was elongated by about ~12 mm in non-strabismic older than younger controls (P < 0.005), but no control exhibited rupture of the LR-SR band. The superior pole of the LR was angulated laterally from the vertical by 6±9° in younger controls, but significantly more so at 18±7° in older normal subjects ($P=2.1 \times 10^{-8}$). Patients with SES exhibited LR-SR band attenuation, stretching, or often even rupture. There was superotemporal bowing of the LR-SR band in milder cases, and abrupt termination of an attenuated remnant in severe cases. The LR-SR band was ruptured in 14/22 orbits with ARDE, and in CVS, it was ruptured in 31/34 orbits; these proportions are statistically similar. In subjects with ARDE having intact LR-SR bands, band length and LR angulation were all significantly exceeded by values observed in normal young controls. From these findings it is inferred that LR-SR band ligament rupture is associated with asymmetrical LR sag that causes hypotropia, because the difference in combined LR plus MR sag in the hypotropic and hypertropic eye in CVS is significantly correlated with the magnitude of hypotropia (P<0.02).

TREATMENT OF ARDE. Base-out spectacle prism has been the historical mainstay for treatment of ARDE, particularly for small angles of esotropia in patients whose refractive errors demand corrective lenses for adequate visual acuity.[19] Since convergence fusional amplitudes are typically robust in ARDE, base-out prism in the entire spectacle lens typically does not induce convergence insufficiency exotropia during near viewing. It often does not even induce exophoria at near. However, continuing refinement of refractive and cataract surgical technique has now created a population of patients with ARDE who are not dependent on corrective lenses for visual acuity, and who are loathe to wear spectacles merely for their prismatic effects. Spectacle prisms also suffer from disadvantages of weight and optical aberrations, and cannot be tailored to lateral incomitance. Strabismus surgery, probably of any sort that reduces esodeviation, is effective for ARDE as long as convergence fusional amplitudes at near exceed the surgically-induced exoshift; this criterion is very commonly fulfilled in clinical practice. While LR resection has been preferred historically[20-22] based upon the now-discredited presumption that LR surgery is more effective for distance than near viewing,[23] comparative study demonstrates that MR recession is effective,[24-26] and equally so to LR resection if performed using modestly augmented dosage targeted, using conventional tables, to twice the esotropia angle measured at distance.[8] Lateral incomitance deserves therapeutic consideration. Even historical descriptions of ARDE noted that distance esotropia might be present mainly or even exclusively in lateral gazes; the angle need not be the same in both dextroversion and levoversion. Because recession of one MR has maximal effect on distance esotropia in contralateral gaze, with little or no effect in ipsilateral gaze, most cases of ARDE treated by MR recession require the procedure bilaterally.

TREATMENT OF CVS. Of course, vertical spectacle prism has long been effectively employed for cases of small vertical heterophoria due to SES, and this remains a reasonable approach. Lens weight is seldom a serious disadvantage. A more serious problem is vertical gaze incomitance, with

heterotropia often varying significantly with vertical gaze direction. Vertical rectus recession or resection, even with adjustable sutures, typically produces larger changes in vertical alignment than the heterophorias associated with SES. A more suitable therapy is partial vertical rectus tenotomy at the insertion.[14] When performed in progressively graded fashion under topical anesthesia, partial vertical rectus tenotomy at the insertion can precisely connect hypertropia of 1 - 8D[14]. Moreover, partial IR tenotomy from the temporal side produces incycloduction helpful to treat the excyclotropia usually encountered in the hypotropic eye in CVS due to SES; the mechanism can be considered similar to nasal transposition of the IR insertion, since only the nasal IR tendon fibers remain intact. Partial SR tenotomy from the nasal side also produces incycloduction in a manner analogous to temporal transposition of the insertion, since only the temporal SR tendon fibers remain intact. Of course, for hypertropia exceeding 8D, more conventional oblique or vertical rectus muscle surgery may be effective.

DISCUSSION

Key to the pathogenesis of SES is degeneration of the LR-SR band ligament interconnecting the SR and LR pulleys so as normally to maintain the LR pulley's vertical position [11, 27] against inferior traction exerted by the inferior oblique (IO) muscle, whose orbital layer inserts on the LR pulley.[28, 29] In serially-sectioned autopsy orbits, quantitative densitometry has demonstrated progressive collagen and elastin loss, associated with attenuation and rupture of the LR-SR band ligament with age. This phenomenon is associated with gross LR pulley sag, presumably because downward IO force becomes unopposed after LR-SR band rupture. In a 93-year old post-mortem orbit, the LR-SR band was ruptured and its remnants severely attenuated.[11] Rutar and Demer first proposed that three elderly, non-myopic patients who presented with unilateral hypotropia and divergence paralysis type esotropia exhibited a previously unrecognized entity they termed SES, and noted association with orbital connective tissue degeneration manifested by prominent eyelid fat pads, superior sulcus deformity, aponeurotic blepharoptosis, and proclivity towards blepharoplasty or similar surgery.[11]

Subsequent quantitative imaging has confirmed and extended original suppositions about SES.[13] Inferior LR pulley displacement is a universal feature of SES. All subjects with CVS, with or without associated esotropia, exhibited highly significant asymmetrical inferior LR pulley displacement, characteristically greater in the hypotropic and more excyclopositioned eye. A useful additional observation is that the rectus muscles are elongated in SES. Although even non-strabismic older subjects exhibit appreciable lengthening of the otherwise-intact LR-SR band, the ligament was ruptured in two-thirds of orbits with ARDE and nearly all with CVS. This high prevalence for LR-SR band rupture supports occasional patient accounts of sudden, painful onset of diplopia in SES. Presumably, catastrophic LR-SR band rupture creates a sudden horizontal and/or vertical LR force imbalance sufficient to cause diplopia. The inferred causal connection is supported by the quantitative observation that magnitude of vertical strabismus is correlated with magnitude of horizontal rectus pulley sag.

Muscle length, as embodied in the classical length-tension curve, is a parameter implicit to all physiologic studies of muscle behavior, yet with the only very recent application of in vivo imaging has extraocular muscle length received scientific or clinical attention. Rectus muscle length, as uniformly assessed in central gaze position, does not change appreciably in concomitant esotropia[30] and exotropia.[30, 31] However, rectus muscle lengths are abnormal in SES, corresponding to displacement of the rectus pulleys. All four rectus pulleys are significantly displaced by 2 to 14 mm from the orbital center in SES. Although normal aging is also associated with some centrifugal pulley displacement, the changes in SES greatly exceed those in non-strabismic subjects of comparable age.

Since the shortest distance between points is a straight line, centrifugal pulley displacements necessarily imply that the muscles passing through the pulleys from origin to scleral insertion must traverse greater than normal paths, and at least in this sense these muscles are abnormally long. Thus, MRI measurements demonstrate horizontal EOM lengths in SES that are ~40%, or 14 mm, longer than the EOMs of normal young and older controls. These elongations are large in comparison to resections and recessions performed typically performed for strabismus surgery. What would happen if otherwise normal muscles were suddenly stretched to the lengths observed here? Computational modeling using the Orbit 1.8 program predicts significant exotropia, unless muscle rest length is commensurately increased to conform to increased muscle path length.[32] One can suppose that many of the changes in pulley position and corresponding changes in muscle lengths develop gradually over a long period of time by chronic remodeling, perhaps including addition of sarcomeres, or insertion of passive connective tissue in series with sarcomeres. This remodeling would likely have other consequences for treatment of strabismus. It is possible that the marked rectus EOM elongation in ARDE explains the observed requirement for atypically large dosages of MR recession for surgical correction.[12] Widespread anatomical changes in the orbits in SES probably also impact the effects of other forms of strabismus surgery. Adaptive remodeling may at least in part result from orbital connective tissues thinning that allows both pulley shifts and orbital fat migration, as well as secondary adaptive and pathological changes in muscles and central innervation patterns. It is indeed remarkable that the extreme EOM elongations and pulley shifts observed in normal older subjects do not more frequently cause strabismus, and that

patients with SES do not exhibit more severe strabismus than typically observed. Fusional vergence mechanisms are likely protective against symptomatic diplopia, as evidenced by a longitudinal observational study demonstrating progressive increase in distance esophoria in ARDE, but with development of diplopia only when esophoria exceeded fusional divergence amplitude.[19]

The foregoing studies of SES excluded well-understood causes of strabismus such as orbital trauma, thyroid ophthalmopathy, restriction, and EOM paralysis. After these clinical exclusions, the remaining cases proved to be SES. In one specialty strabismus practice in Florida, for example, 17% of 200 cases of adult acquired esotropia were attributed to ARDE, and 96% of these were successfully treated by strabismus surgery[33]. The clinician can thus infer that many cases of similar acquired adult DPE and CVS are likely to be caused by SES, and are likely to exhibit the characteristic adnexal signs including blepharoptosis and superior sulcus defect. However, many subjects with SES had previously undergone blepharoplasty or facelift, so some of the orbital findings may have been partially iatrogenic.

Patients with SES are recognizable from their external appearances and motility patterns. Typical findings include generalized elongation of the levator aponeurosis, resulting in a superior sulcus deformity, aponeurotic ptosis, or lid crease elevation compensated by frontalis recruitment. Most patients with SES exhibit symmetrically limited supraduction, although all exhibit full horizontal ductions and normal horizontal saccadic eye velocities that should be clinically required to exclude abducens palsy. If these conditions are met, do patients with clinical evidence of SES require orbital imaging? If such patients present with horizontal binocular diplopia for distant but not near targets, and report no associated neurological complaints, further etiological investigations are probably unnecessary even if the onset of diplopia is acute. Patients presenting with acute or chronic onset of vertical binocular diplopia in clinical circumstances suggestive of SES may also be spared neurological investigations when no evidence exists of cranial neuropathy or other acute neurological deficit.

Neuro-ophthalmologists should be aware that CVS due to SES can mimic features of SO palsy. The 3-step test, heretofore considered the gold standard for diagnosis of SO palsy, has now been demonstrated to have only about 70% sensitivity[34] and 50% specificity for deficits of SO structure or function that can be demonstrated by high resolution MRI[35]. Since even normal subjects adapted to wearing of a vertical prism develop an hyperphoria that varies with head tilt[36], head tilt dependence of hypertropia should probably be regarded as a non-specific concomitant of any vertical heterophoria, not as the signature of SO palsy[34]. Because all subjects with CVS contributing to the foregoing data exhibited normal SO size by MRI, SO palsy due to denervation could not have been a confounding factor here. The busy clinician might well be faced with a more difficult diagnostic dilemma. A clinical finding that may be helpful is that while in SES, the hypotropic eye is excyclotropic, in SOP the hypertropic eye is excyclotropic. If cyclotropia is not a sufficiently clear diagnostic sign and the clinical situation warrants, then high resolution orbital imaging may be helpful in confirming or excluding SO palsy based upon the presence or absence or SO muscle atrophy, and in confirming or excluding SES based upon LR position.

CME ANSWERS

1. b. LR-SR band
2. a. Excyclotropia in the hypotropic eye
3. e. a and b

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PATHOLOGICAL PROCESSES OF EYE MUSCLES

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LEARNING OBJECTIVES

1. List the most common causes of restrictive strabismus due to pathological processes of the eye muscles
2. Know several examination techniques to differentiate restrictive strabismus from neurological causes of strabismus
3. Understand how various infiltrative, inflammatory, and neoplastic diseases cause strabismus

CME QUESTIONS

1. Which diagnostic test is most likely to differentiate thyroid eye disease from a sixth nerve palsy?

    a. Ocular alignment
    b. Ocular rotations
    c. Slit lamp examination
    d. Forced-duction testing

2. Which MRI sign is most commonly seen with orbital myositis?

    a. Extraocular muscle enlargement with tendon involvement
    b. Extraocular muscle enlargement with tendon sparing
    c. Focal nodular enlargement of a single muscle
    d. Abnormal signal in the pons

3. Which ocular alignment would be most consistent with left medial rectus metastasis from breast cancer?

    a. 45 prism diopters exotropia in all directions of gaze
    b. 10 prism diopters of esotropia in primary position, orthotropic in right gaze and 25 prism diopters of esotropia in left gaze
    c. 25 prism diopters of esotropia in all directs of gaze
    d. Orthotropic in all positions of gaze except for 8 prism diopters of right hypertropia in upgaze

KEYWORDS

1. Infiltrative extraocular muscle disease
2. Inflammatory extraocular muscle disease
3. Thyroid eye disease
4. Restrictive strabismus
5. Extraocular muscle metastases

INTRODUCTION

Pathological processes involving the extraocular muscles are some of the most common causes of acquired, non-neurologic strabismus. Although thyroid eye disease is most frequently encountered, other infiltrative, metastatic, and myotoxic processes must be considered. In general, the pathologic processes involving the eye muscles that will be discussed herein (Table) present with a restrictive strabismus that can involve any of the six extraocular muscles. Common presenting signs and symptoms as well as clinical tests can be helpful to the clinician in distinguishing extraocular muscle disease from neurologic causes of strabismus.

BODY

Although the various etiologies of restrictive strabismus present in differing ways, there are many clinical signs and tests that can help clinicians to differentiate these disorders from neurologic causes of strabismus and diplopia. In evaluating patients for restrictive strabismus, special attention should be given to the following features of the eye examination: (1) Orbital signs and eyelid signs, (2) Ocular rotations and saccades, (3) Forced-duction and forced-generation testing, and (4) Imaging findings. The use of these examination features will be described below, followed by detailed descriptions of some of the more common pathological processes affecting the extraocular muscles.

In all patients with acquired strabismus, the following examination features are useful in differentiating pathological processes of the extraocular muscles from other neurologic and non-neurologic etiologies. These examination techniques are easily performed and may preclude the need for more expensive neuroimaging and other laboratory work-up.

Orbital Examination

All patients should be observed for abnormalities of the eyelid. For example, *eyelid retraction* and *periorbital edema* can be seen in patients with thyroid ophthalmopathy. The presence of eyelid retraction and periorbital edema may indicate the presence of thyroid eye disease in a patient with acquired esotropia and diminished abduction, thereby differentiating from an abducens palsy. *Periorbital edema* and focal or diffuse *conjunctival injection* can also be seen in inflammatory disorders that cause orbital myositis. In addition, a Hertel's exophthalmometer should be utilized in all patients with acquired strabismus in order to determine if there is unilateral or bilateral proptosis. In most pathological processes that affect the extraocular muscles, one can find some degree of proptosis since the extraocular muscles often become enlarged, thereby placing posterior pressure on the globe and forcing the globe more anteriorly within the orbit. Similarly, the orbit can be palpated for resistance to retropulsion, which may be more commonly seen in processes that cause extraocular muscle enlargement.

Ocular Rotations and Saccades

Testing of ocular rotations and saccades can be very useful in differentiating neurologic from non-neurologic strabismus. In pathological processes that affect the extraocular muscles, the affected muscle often becomes restricted due to infiltration, inflammation, or mass effect. A restricted muscle can mimic a paresis of the opposing muscle (for example, a restricted medial rectus muscle can be mistaken for a paretic lateral rectus muscle). *Restriction of ocular ductions in multiple directions* that is not consistent with a specific cranial nerve palsy should raise suspicion for a non-neurologic cause of strabismus. However, occasionally, a patient with restrictive strabismus will present with a motility pattern that can mimic a cranial nerve palsy if the appropriate combination of muscles are affected. In these cases, *testing of saccades* can be very useful. It is important to test saccades in the field of maximal function. In patients with restrictive, non-neurologic strabismus, the saccade speed is normal in the field of unrestricted gaze. For example, if a patient has limited abduction, the patient should have normal saccade speed from full adduction to the point where the limitation becomes apparent. However, in extraocular muscle paresis from cranial nerve palsy, saccades will be "floating" when compared to the fellow eye that has full movements.

Forced-Duction and Forced-Generation Testing

Forced-duction and forced-generation tests are under-utilized and are of utmost importance in differentiating restrictive processes due to extraocular muscle disease from neurologic disease. Both of these tests can be done in an office or clinic setting with minimal side effects or complications. These tests are best performed in patients over the age of 8 years and are short and relatively painless. To perform both tests, one can instill topical anesthetic (such as Tetracaine) and then instruct the patient to look in the direction of the muscle suspected of having limited rotation (ie. the muscle that may be palsied in a neurologic scenario). The clinician can then grasp the limbus at a point opposite the side with the gaze limitation. Force is used to push the eye in the natural arc of globe rotation – if the eye can easily be moved past the point that the patient is able to rotate, then a paresis is most likely. However, if the globe cannot be moved beyond the point of the patient's rotation, then a restrictive or pathological process in the extraocular muscle should be suspected.

Forced-generation testing can also be performed as part of the test described above. After the forced-duction testing is performed, clinicians can then ask patients to continue to look in the desired direction, but the force from the forceps is directed in the opposite direction (away from the possible palsied muscle). If the clinician can easily move the eye away from the direction that the patient is looking, then a palsy is most likely. However, if the patient produces force against the clinician's forcep movement, then a palsy is less likely, and restrictive strabismus should be suspected.[1]

An example of forced-duction and forced-generation testing would be a patient with esotropia and limited abduction. In this case, medial rectus restriction vs. abducens palsy could be suspected. For this patient, a clinician would grasp the limbus near the medial rectus muscle after instructing the patient to maximally abduct the eye. The clinician would then attempt to further abduct the eye. If the eye can be fully abducted beyond the patient's best attempt to abduct, than a lateral rectus paresis is more likely. If the clinician cannot move the eye beyond the patient's maximal abduction, then restriction from the medial rectus is more likely. Then, with the patient continuing to attempt abduction, the clinician will attempt to adduct the eye. If it can be easily adducted, the lateral rectus is not producing normal force, and a paresis is more likely. If it cannot be easily adducted, then the lateral rectus is producing force, and a medial rectus restriction is the more likely etiology.

Imaging

Orbital ultrasound, CT and MRI scans can also be useful in demonstrating pathological processes of the extraocular muscles. B-scan ultrasonography is the easiest and least expensive modality that can be employed to recognize extraocular muscle abnormalities. Typically in thyroid eye disease and many infiltrative diseases of the extraocular muscles, the muscles appear enlarged. In thyroid eye disease, the muscles are typically hyperechoic while in orbital myositis, the muscles show low reflectivity.[2] Ultrasound may be useful in determining disease activity as well, with lower echogenicity related to higher likelihood of treatment response.[3,4] CT and MRI scanning are typically more disease specific than ultrasonography and can show extraocular muscle enlargement along with other features of the underlying disease, such as lacrimal gland infiltration, scleral thickening, proptosis, and bony changes. Involvement of the extraocular muscle tendon can help differentiate thyroid eye disease (spared) from acute

Table: Summary of Pathological Processes that May Affect the Extraocular Muscles and Cause Strabismus

Category	Typical Etiologies
Infiltrative	Thyroid eye disease, Amyloidosis
Inflammatory	Orbital Myositis, IgG-4 disease, Sarcoidosis, SLE, Rheumatoid Arthritis, Wegener's granulomatosis
Infectious	Contiguous spread from sinusitis or orbital absecess, parasitic or fungal abscesses
Neoplastic	Metastatic disease, lymphomatous or leukemic infiltration, primary orbital tumors
Post-Surgical	Inadvertant injection of retrobulbar anesthesia
Miscellaneous	Secondary contracture of antagonist muscle in long-standing strabismus, congenital fibrosis syndromes, vascular malformations, acromegaly

orbital myositis (involved). In addition, MRI may show irregular muscle margins in inflammatory diseases such as myositis, amyloidosis, or lymphomatous infiltration, while it will show smoother muscle margins in thyroid disease, primary muscle tumors, and intramuscular abscess or cyst. More recently, MRI has been used to estimate disease activity in thyroid eye disease. Prolonged T2 relaxation times have been shown to indicate increased edema and inflammation, and may be more diagnostic than several clinical or laboratory factors.[5]

With regard to neoplastic disease, imaging is particularly useful in defining the extent of metastatic disease and in diagnosing this etiology in patients with new onset strabismus and known neoplastic disease elsewhere in the body. MRI typically shows fusiform or nodular enlargement of a single extraocular muscle with well-defined margins and any level of intensity (depending on the tumor type) when the lesion is due to a solid tumor metastasis. In cases of lymphomatous infiltration, muscle enlargement is typically more diffuse, and is isointense on T1 and T2 sequences.[6]

OVERVIEW OF SPECIFIC PATHOLOGICAL PROCESSES OF THE EYE MUSCLES

Thyroid Eye Disease

Thyroid eye disease is the most commonly encountered pathological process of the extraocular muscles that results in restrictive strabismus. The etiology of thyroid dysfunction in this disease is related to stimulatory autoantibodies directed against the thyrotropin receptor, yet the mechanism of orbital involvement is still not well-understood.[7] Recent research has pointed to a combination of factors, including a genetic predisposition,[8-10] epigenetic factors,[11] and environmental factors such as infectious agents[12] and cigarette smoking[13] all combining to predispose a patient to the disease.

Patients with diplopia due to thyroid eye disease often present with periorbital edema, eyelid retraction, proptosis, chemosis, and exposure keratopathy. All patients with new onset of strabismus should be evaluated for these signs so that the clinical diagnosis can be made without the need for expensive ancillary testing. Diplopia is typically associated with inflammation and subsequent fibrotic changes in the extraocular muscles. These changes typically take up to three years to stabilize. Given that the medial rectus and the inferior rectus are most typically involved in thyroid eye disease, patients may present a diagnostic dilemma and may appear to have a neurologic cause of strabismus such as a sixth nerve palsy, partial third nerve palsy, or skew deviation. However, the diagnostic tests described above, including the orbital examination and forced duction testing should allow clinicians to easily determine the true cause of a patient's diplopia. In addition, MRI of the extraocular muscles has been used with increasing frequency to evaluate for extraocular muscle enlargement as well as to look for more advanced signs to demonstrate clinical activity level. As mentioned above, prolonged T2 relaxation time on MRI provides information related to clinical activity level and prognosis, with higher relaxation times correlated to increased disease activity, inflammation, and edema.[5, 14] In addition, increased signal intensity on STIR sequences has been correlated with disease activity as well as response to steroid treatment.[15, 16] Finally, somatostatin receptor scintigraphy is also being evaluated as a method by which to evaluate clinical disease activity. Indium-labeled octreotide has been shown to accumulate in the orbit of patients with active thyroid eye disease and may be detected with CT-SPECT as a marker of disease activity, with several studies showing good correlation with clinical disease activity.[17-19]

Surgical treatment of strabismus related to thyroid eye disease should be reserved for patient's whose ocular deviation has remained stable for at least six months and in those patients with low clinical activity profiles. In addition, if an orbital decompression is planned, it should

be performed prior to any strabismus procedures, due to the potential of orbital decompression to change ocular alignment. Similarly, any procedures related to eyelid position should be reserved for after strabismus surgery, since strabismus surgery can alter the eyelid position. Methods for strabismus surgery in Graves' disease vary although reported results are acceptable using adjustable suture techniques,[20] the "intraoperative relaxed muscle positioning" technique,[21] or standard fixed sutures.[22] However, over-corrections are common, especially with the use of absorbable and adjustable sutures.[23, 24] For this reason, many authors recommend the use of a semi-adjustable suture or using permanent, non-absorbable sutures when operating on the inferior rectus muscle for a hypotropia.[23, 25] Historically, rectus muscle resections have been avoided in patients with Grave's disease due to concerns related to increasing inflammation and restriction; however, recently this dogma has been brought into question and rectus muscle resection may be an acceptable procedure in certain situations, such as patients who have persistent esotropia despite maximal medial rectus recession and patients with unilaterally poor vision.[26]

Infiltrative and Inflammatory Extraocular Muscle Disease
The most commonly encountered inflammatory and infiltrative diseases of the eye muscles include orbital myositis (either idiopathic or due to autoimmune processes), neoplastic disease (such as lymphomatous infiltration), infection, or cicatricial diseases like scleroderma.[27] Specific etiologies that can rarely causes infiltrative extraocular muscle disease include sarcoidosis, Wegener's granulomatosis, Crohn's disease, Whipple's disease, amyloidosis, and infections such as cysticercosis.[27-29] Infiltration of the extraocular muscles by any of the above listed disorders may cause enlargement of the muscle, which can lead to a mass effect causing displacement of the ocular and orbital structures, as well as a mechanical restriction to ocular rotations.

The clinical presentation of infiltrative extraocular muscle disease varies depending on the underlying etiology. For example, the presentation of strabismus may be of acute onset in cases that are associated with infection or intramuscular hemorrhage. In these cases, patients may have minimal premonitory symptoms and may present with sudden onset of pain and diplopia. In these cases, patients may present with a red eye, increased intraocular pressure, and limited ocular rotations in the field of gaze contralateral to the affected muscle. Patients with orbital myositis or IgG-4 related disease may present with a subacute onset of conjunctival injection, eyelid swelling, proptosis and enlargement of multiple extraocular muscles. In contrast, patients who are affected by chronic infiltrative diseases such as sarcoidosis, amyloidosis, or scleroderma may describe a gradual onset of strabismus. These patients often present with a white and quiet eye, and clinicians will note progressive limitation to ocular rotations in the field contralateral to the affected muscles.

Recently, IgG-4 related disease has been gaining attention amongst clinicians. IgG-4 related disease is a systemic inflammatory process with an unknown underlying etiology that manifests in most of the human organ systems. There have been multiple case reports detailing orbital involvement in IgG-4 related disease, with the lacrimal gland, infraorbital nerve, and extraocular muscles all reportedly at risk for involvement.[30] Most patients initially present with painless eyelid swelling. In the largest series of patients with IgG-4 related orbitopathy, 89% of the 27 included subjects had extraocular muscle involvement. Most commonly, the lateral rectus was involved (71%) and the disease was bilateral in 88% of the patients.[30] Co-existent lacrimal gland, infraorbital nerve, and paranasal sinus disease were present in the majority of patients, thereby helping to clinch the diagnosis in this difficult disease. Interestingly, the propensity to affect the lateral rectus may be quite useful to clinicians attempting to differentiate IgG-4 disease from thyroid eye disease.

Other forms of myositis related to connective tissue disease are rare. However, recent reports of myositis of the extraocular muscles from Wegener's granulomatosis,[29] lupus,[31] Behcet's disease,[32] Crohn's disease,[33] and celiac disease[34] should serve to remind clinicians to have a high level of suspicion for autoimmune diseases in patients presenting with restrictive strabismus and a red, painful eye.

Treatment for infiltrative and inflammatory diseases of the extraocular muscles is disease-specific. Anti-inflammatory or anti-infectious agents are typically the first line of treatment. However, the use of radiation therapy, biologic agents, and strabismus surgery is also warranted in certain cases.

Metastatic Disease
The most commonly encountered tumor types encountered within the extraocular muscles include both primary ocular/orbital tumors such as choroidal melanoma or retinoblastoma, as well as distant metastatic tumors such as breast carcinoma, cutaneous melanoma, gastrointestinal adenocarcinoma, or carcinoid tumors.[6, 35-37] In addition, leukemic and lymphomatous infiltration of one or more extraocular muscles has also been reported.[6] In a single-center study, the prevalence of orbital muscle involvement in all carcinomas over a 10-year period was 0.1% (7 or 6,668 patients). The prevalence was higher for plasmacytomas (1 in 303, 0.3%) and Non-Hodgkins Lymphomas (3 in 774, 0.4%).[6] Whether due to local infiltration or metastatic disease, neoplastic disease of the extraocular muscle causes muscle enlargement, restricted eye movements, and most commonly proptosis (although enophthalmos may be more commonly seen in breast cancer). The propensity of certain tumors to proliferate within the extraocular muscles gives credence to the "seed and soil" hypothesis of metastatic disease.[36] This hypothesis posits that certain tumor-types proliferate better in specific tissues most likely due to tissue adhesion molecules.

The clinical presentation of patients with metastatic extraocular muscle disease is usually an indolent, gradual onset of diplopia that often commences in an eccentric position of gaze and increases such that diplopia is eventually present in primary position. Most often, patients already have a primary tumor diagnosis, but rarely patients may not yet be diagnosed with cancer.[38] Lacey *et al.* reviewed the literature and found that the medial rectus is involved in 39% of reported cases, followed by the lateral rectus (33%), superior rectus (16%), and inferior rectus (12%).[27]

It may be difficult to determine whether a new onset case of strabismus is due to extraocular muscle metastatic disease unless there is a known history of metastatic cancer. Forced duction and forced generation testing can be useful in ruling out paralytic causes of strabismus, but it may be difficult to differentiate patients with extraocular metastases from those with other causes of restrictive strabismus, especially Grave's disease. In these cases, periorbital signs such as eyelid edema, conjunctival injection, and eyelid retraction may be helpful; however, orbital imaging is the best method by which to rule out metastatic disease. MRI findings in lymphomatous infiltration usually reveal unilateral or bilateral homogeneous enhancement of one or more muscles after contrast administration without tendinous involvement.[6] These lesions are often difficult to differentiate from other infiltrative lesions such as amyloidosis and sarcoidosis and biopsy may be necessary. In addition, T2-weighted images may be helpful since many infiltrative diseases are typically hypointense on T2-weighted sequences, unlike lymphomatous infiltration which are typically iso-intense to hyperintense.[6] Unlike lymphoma, solid tumor metastases are typically more focal and nodular areas of enhancement within one or more muscles. These lesions must be differentiated from intramuscular abscesses, which typically have a rim of enhancement on post-contrast images.

Given that metastatic disease is typically a harbinger of poor prognosis, treatment of extraocular muscle involvement is often palliative. Occasionally, extraocular muscle biopsy is required for diagnostic purposes. Biopsies can be performed using an open technique or via fine-needle aspiration. In certain cases, strabismus surgery can be considered. In addition, radiotherapy is often useful in shrinking the orbital mass and improving patient comfort.

CME ANSWERS

1. d. Forced-duction testing
2. a. Extraocular muscle enlargement with tendon involvement
3. b. 10 prism diopters of esotropia in primary position, orthotropic in right gaze and 25 prism diopters of esotropia in left gaze

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MECHANICAL STRABISMUS FOLLOWING OCULAR SURGERY

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LEARNING OBJECTIVES

1. Describe the mechanism and recognize the clinical course of strabismus due to anesthetic myotoxicity
2. Describe three causes of strabismus following implantation of ocular devices
3. List three ways to prevent the occurrence of postoperative strabismus
4. Understand appropriate indications for surgery to treat iatrogenic strabismus following ocular surgery

CME QUESTIONS

1. Which of the following best portrays the incidence of involvement of extraocular muscles in anesthetic myotoxicity in decreasing order?

    a. Superior rectus, inferior rectus, lateral rectus, inferior oblique
    b. Inferior rectus, inferior oblique, superior rectus, lateral rectus
    c. Inferior rectus, superior rectus, inferior oblique, lateral rectus
    d. Inferior oblique, inferior rectus, superior rectus, lateral rectus

2. A patient undergoes a scleral buckling procedure OD under peribulbar anesthesia with bupivacaine. The buckle is placed for 200 degrees superiorly. One day postoperatively he notices binocular vertical diplopia with the image from the operated eye lower than that of the fellow eye. This slowly improves over a few weeks but one month postoperatively he demonstrates a right hypotropia of 15 PD with an elevation deficit of the right eye. Which of the following is the most likely cause of the diplopia?

    a. Anesthetic myotoxicity to the right inferior rectus
    b. Anesthetic myotoxicity to the right superior rectus
    c. Restrictive strabismus from the scleral buckle
    d. Intraoperative stretch trauma to the right superior rectus

3. What is the most common cause of isolated unilateral inferior oblique paresis?

    a. Anesthetic myotoxicity
    b. Implantation of a glaucoma drainage implant
    c. Direct surgical trauma during lower lid blepharoplasty
    d. Fat adherence syndrome following orbital decompression

KEYWORDS

1. Diplopia
2. Mechanical Strabismus
3. Anesthetic Myotoxicity
4. Ocular Surgery
5. Bupivicaine

INTRODUCTION

Strabismus or diplopia after ocular surgery, particularly one that is otherwise uncomplicated, is a distressing situation for patients and physicians alike. Multiple mechanisms play a role in this phenomenon, including decreased visual acuity leading to sensory deviations, defects in the supranuclear fusion system resulting in manifest deviations, and changes in refractive error resulting in fixation switch or aneisokonia/anisophoria. The focus of this presentation is postoperative strabismus secondary to iatrogenic mechanical causes.

MECHANICAL STRABISMUS AFTER CATARACT SURGERY

The most common cause of mechanical strabismus following cataract surgery is myotoxocity from local anesthesia, which occurs in 0.1% to 1% of cases using peribulbar or retrobulbar blocks[1]; although much less common, sub-Tenon's delivery of local anesthesia can also produce a similar result.[2] In addition to direct injury from the needle itself, myotoxicity from either lidocaine or bupivacaine (the latter more severe) also occurs.[3] It is important to realize that direct injection of the agent must occur in order for myotoxicity to develop; mere exposure to drug does not produce any muscle damage.

Use of hyaluronidase in the injection cannula may help to spread the anesthesia more evenly and avoid higher concentrations of drug, thus diminishing the incidence of myotoxicty.[3]

The typical sequelae of anesthetic myotoxicty of the extraocular muscles are an initial paresis which is replaced by progressive segmental fibrosis and hypertrophy of the muscle over a period of 3-8 weeks; the segmental nature of the cicatricial response may produce a true overaction of the affected muscle. Thus, damage to the inferior rectus will immediately result in an ipsilateral hypertropia followed over several weeks by improvement of the hyperdeviation and an eventual hypotropia with the greatest deviation in downgaze. The temporal profile of this reversal of deviation is almost pathognomonic for anesthetic myotoxicty.[3]

By virtue of the location of the retrobulbar or peribulbar injection (generally given inferiorly), the most common muscle involved is the inferior rectus.[1,3,4,5] However, Capo and associates have demonstrated via cadaver studies that the superior rectus may also be affected in such injections, bypassing the optic nerve and injecting the muscle very posteriorly in the orbit, although approximately 5 times less frequently than the inferior rectus.[5] Other authors have also demonstrated involvement of the horizontal rectus and oblique muscles.[6,7,8]

Over the years, the frequency of this post-cataract mechanical strabismus has progressively diminished, primarily due to use of topical anesthesia for cataract surgery. Discontinuation of a bridle suture around a muscle to stabilize the globe has also contributed as well. Anesthetic myotoxicity is also finding a new role in the treatment of strabismus[9,10] to increase muscle contractile strength and elastic stiffness, often in conjunction with injection of botulinum toxin to the direct antagonist; preliminary reports demonstrate that an average of 20 PD of strabismus may be treated with such an approach.

MECHANICAL STRABISMUS FOLLOWING SURGICAL INSERTION OF OPHTHALMIC DEVICES

Although in decreasing use in some areas, ***scleral buckles*** still remain in the therapeutic armamentarium of retinal detachment with retinal breaks. Transient postoperative strabismus and diplopia may occur in 50-60% of cases[11,12], but persistent symptoms remain in approximately 5-10% of cases. Mechanical etiologies are numerous, and include direct muscle damage from myotoxicity, surgical traction, necessity of muscle release and reattachment to insert the buckle, and motility restriction from the exoplant itself or adhesions between it and muscles or surrounding connective tissue.[11,12, 13] Involvement of the muscle pulley systems by insertion of any ophthalmic device is an increasingly recognized cause of postoperative strabismus as well, and, in part because of such changes, removal of a scleral buckle frequently has little effect on induced strabismus;[14] although in some cases very early postoperative removal may be helpful, additional surgery is required to address the retinal detachment . Avoidance of strabismus may be enhanced by meticulous surgical technique, taking care to avoid encountering orbital fat, excessive muscle traction, and poorly placed buckles.

Insertion of ***glaucoma drainage devices*** is another important cause of mechanical strabismus.[15,16,17] Strabismus is possible regardless of the type or brand of glaucoma drainage device, with motility restriction from the device and/or underlying bleb and direct muscle damage being the most common causes. As with scleral buckles, adhesions can develop between the devices between muscles and surrounding tissue. Because many devices are implanted superotemporally, a typical strabismus pattern is ipsilateral exotropia and/or hypertropia.[15] Although removal of the device seems to improve strabismus more than removal of a scleral buckle, results are unpredictable, and removal is often contraindicated due to the severity of the glaucoma. Treatment thus consists often of removal of scar tissue, prisms for smaller deviations, or surgery on yoke muscles of the fellow eye.[17] In addition, use of the smallest plate possible is recommended during initial surgery to minimize risk of postoperative diplopia.[17]

Strabismus following ***episcleral plaque brachytherapy*** for uveal melanoma is also well documented in 1-2% of patients.[18] The pattern of motility deficit varies with location of the plaque, and treatment involves a combination of prisms, surgery and chemodenervation.

MECHANICAL STRABISMUS FOLLOWING OTHER OCULAR PROCEDURES

Although seemingly a fairly straightforward procedure, strabismus following ***pterygium surgery*** is not uncommon[19,20,21]. Significant scar tissue in the medial fornix may result in abduction deficits and an incomitant esotropia that is extremely difficult to treat. Alternatively, disinsertion of the medial rectus during intraoperative dissection produces a large exotropia with loss of adduction.

Whether for functional or cosmetic indications, diplopia after ***blepharoplasty*** is well documented[22,23,24,25]. Paretic strabismus is more common, thus, upper lid blepharoplasty may result in superior oblique paresis and lower lid surgery in paresis of the inferior oblique or inferior rectus. Although no large studies are reported, consensus is that the inferior oblique is likely the most commonly involved muscle, with blepharoplasty being the number one cause of isolated inferior oblique palsy. Less commonly, a Brown syndrome or inferior rectus fibrosis occur. Medial rectus restriction has also been reported.[24] Most cases result from direct surgical trauma to the muscle, although injection of local anesthesia may contribute as well.

While pre-existent strabismus from thyroid orbitopathy, orbital masses, or inflammatory disease is often present in patients undergoing ***orbital decompression***, the procedure itself may cause or worsen strabismus.[1] The incidence of new-onset diplopia/strabismus seems to increase with the number of walls decompressed, ranging from 10% after single wall surgery to 20% with three. In addition, decompression surgery often alters vector forces of all muscles as well as globe position, further complicating the etiologic factors involved.

OTHER CONSIDERATIONS IN PREVENTION AND MANAGEMENT

As noted earlier, use of topical or general anesthesia for ocular surgery precludes post-operative strabismus from anesthetic myotoxicity. When peri- or retrobulbar anesthesia is needed, use of lidocaine over bupivacaine should be considered, as the latter is more toxic to the extraocular muscles. In all cases, careful surgical technique to minimize tissue disruption, muscle displacement, and postoperative scarring can aid in prevention, with avoidance of orbital fat and significant bleeding paramount.

An important principle in treatment is to avoid surgery until the deviation has stabilized. As noted earlier, the temporal profile of anesthetic myotoxicty evolves over weeks to months, and many cases of postoperative strabismus can improve or resolve spontaneously. For smaller deviations, prisms may be helpful, but for large or incomitant ones, monocular occlusion may be necessary. When surgical correction is indicated, judicious attempts to relieve restriction are indicated. Surgical treatment of anesthetic myotoxicty after otherwise successful cataract surgery is generally good, although removal of scleral buckles or other devices generally yields unimpressive results. Performing surgery on the uninvolved eye is often required to maximize alignment and improve incomitance. As in any case of vertical strabismus, careful assessment of the patient's torsional status is required to ensure that the surgical approach to the vertical misalignment does not worsen the cyclodeviation. Surgical doses must be highly individualized, and standard formulas or tables are not applicable in these cases. Treatment of strabismus with bupivacaine and botulinum toxin may have an increasing role in these patients. However, the complicated nature and etiology of the motility disruption, as well as problems with sensory fusion in patients with loss of visual acuity or visual field, often contribute to residual diplopia.

CME ANSWERS

1. c. Inferior rectus, superior rectus, inferior oblique, lateral rectus
2. a. Anesthetic myotoxicity to the right inferior rectus
3. c. Direct surgical trauma during lower lid blepharoplasty

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CONGENITAL PROCESSES THAT CAUSE INCOMITANT STRABISMUS

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LEARNING OBJECTIVES

1. Recognize the clinical features that characterize congenital processes which result in restrictive or incomitant strabismus
2. Gain exposure to the genetic basis of complex strabismus
3. Develop an understanding of the surgical management of congenital incomitant strabismus

CME QUESTIONS

1. What clinical characteristics may help to distinguish Type I Duane syndrome from a 6th nerve palsy?
2. What type of anomalous head posture do patients classically adopt in order to maintain binocularity in Type I Duane syndrome, CFEOM1, and congenital Brown syndrome?
3. Which of the CFEOM subtypes is associated with cognitive delay and later onset peripheral neuropathy?

KEYWORDS

1. Congenital Fibrosis of the Extraocular Muscles (CFEOM)
2. Duane Syndrome
3. Brown Syndrome
4. Incomitant Strabismus
5. Congenital Strabismus

INTRODUCTION TO CONGENITAL CRANIAL DYSINNERVATION DISORDERS (CCDDs)

Congenital cranial dysinnervation disorders or CCDDs comprise a group of complex strabismus disorders that result from aberrant innervation or dysinnervation of extraocular muscles. Historically, many CCDDs were thought to be the result of a primary myopathic process that generated incomitant strabismus. Our current understanding, which has been greatly enhanced by the identification of the genetic basis for many of these conditions, is that the underlying etiology for the CCDDs is a primary disruption of innervation of the extraocular muscles with consequent restrictive strabismus.[1-3] The ability to recognize the salient clinical features of the CCDDs is essential for appropriate management both non surgical and surgical, for prognosis, and for work up of associated systemic findings when relevant.

CCDDS WHICH MANIFEST PRIMARILY WITH LIMITATION OF HORIZONTAL MOVEMENT

DUANE SYNDROME

Duane Syndrome is the most frequently observed CCDD and accounts for approximately 4-5% of all strabismus. Familial cases account for 10% of Duane syndrome with a reported range of 5-22%. The underlying pathogenesis stems from a hypoplastic or absent abducens nerve with subsequent aberrant innervation of the lateral rectus by branches of the oculomotor nerve.[5-6] Primarily, Duane syndrome occurs sporadically. In familial cases, Duane syndrome is dominantly inherited with the possibility of significant phenotypic variability within families.[7] Two Duane associated genetic loci have been identified: the DURS1 locus at 8q13 and the DURS2 locus at 2q31. Mutations in the *CHN1* gene (*alpha-1-chimerin*, OMIM 118423) are responsible for DURS2; the gene encodes a signalling molecule shown to be important for axonal pathfinding in mice.[8] The number of genetic syndromes associated with Duane syndrome are myriad. The more commonly encountered associated syndromes are listed in **Table 1**. (see next page)

Table 1. Clinical Characteristics of Syndromic Duane Syndrome

Syndrome	Clinical Features	Gene
Duane Radial Ray syndrome (Okihiro, acro-renal-ocular)	Radial defect/ Hypoplasia of thenar eminence, deafness, renal dysplasia	*SALL4* (OMIM 607343)
Holt-Oram syndrome	Upper limb/hand anomalies, congenital heart defects	*TBX5* (OMIM 601620)
Townes-Brocks syndrome	Thumb malformation, deafness, imperforate anus	*SALL1* (OMIM 602218)
Bosley-Salih-Alorainy syndrome	Bilateral Type 3 Duane syndrome, deafness, cardiac anomalies, developmental delay Patients of Middle Eastern origin	*HOXA1* (OMIM 142955)
Wildervanck syndrome	Deafness, Klippel-Feil anomaly (cervical vertebrae)	unknown

CLINICAL FEATURES

The clinical characteristics typical of Duane syndrome include: complete, less often partial, limitation of abduction, variable limitation of adduction, globe retraction on adduction, narrowing of the palpebral fissure with attempted adduction, and abnormal vertical movements in adduction (**Figure 1**)(see below).[9] These vertical movements may be described as an upward or downward (upshoots/ downshoots) deviation of the eye on attempted adduction. Other aberrant movements such as synergistic divergence or abduction of the eye on attempted adduction have been described.

Huber provided a classification scheme which is helpful in clinically stratifying patients with Duane syndrome.[10] In Type I Duane syndrome, the affected eye shows limited abduction with typically normal adduction. In Type II Duane syndrome, the affected eye shows limited adduction with typically normal abduction. In Type III Duane syndrome, the affected eye demonstrates limitation of both abduction and adduction. These limitations of movement result in incomitant strabismus. Type I Duane syndrome will demonstrate an esodeviation worse in the field of action of the eye which cannot abduct. Type II Duane syndrome will demonstrate an exodeviation worse in the field of action

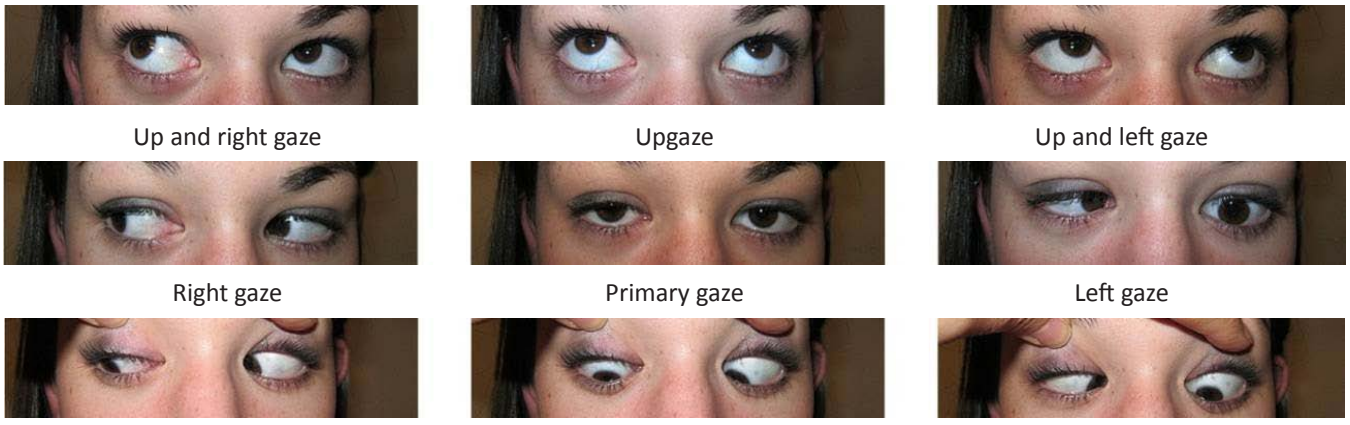


Figure 1. External photographs of a 17 year old girl with Duane syndrome Type I affecting the left eye. Nine fields of gaze are shown. There is inability to abduct the left eye with narrowing of the palpebral fissure on adduction.

of the eye which cannot adduct. The incomitance for Type III Duane syndrome will vary depending on the degree of limitation. Patients often will have an anomalous head posture to achieve a position of gaze that allows them to see binocularly. Strabismus may or may not be present when the head is in the primary position.

In general, we do not routinely obtain neuroimaging in both pediatric and adult patients with a clear history of a congenital strabismus and with the salient clinical features of Duane syndrome on exam. For infants in whom it may be more difficult to establish whether there is a change in eyelid position with horizontal movement of the eye or globe retraction, and therefore difficult to distinguish between Duane syndrome and an acquired 6th nerve palsy, neuroimaging may be pursued in some cases. Typically, congenital 6th nerve palsy is rare.

MANAGEMENT

Patients with Duane syndrome will often present with uncorrected refractive error and amblyopia.[11] In particular, anisometropia and astigmatic error are often present. A thorough eye examination which includes a cycloplegic refraction in children or manifest refraction in adults is an important aspect of the non surgical treatment of patients with Duane syndrome.

Surgery is generally considered when there is a horizontal deviation in primary gaze, when there is a significant anomalous head position or torticollis, and when there is concern regarding the cosmesis associated with up/downshoots or marked globe retraction of the affected eye. There are a number of treatment strategies which have been proposed for the management of Duane syndrome. Recession of a horizontal rectus muscle, primary transposition of the vertical rectus muscles, combined recession of a horizontal muscle with transposition of the vertical rectus muscles and botulinum toxin injection of a horizontal rectus muscle have all been employed in the treatment of Duane syndrome.[12] Recessions are more commonly performed rather than resections. The preferred approach at Boston Children's Hospital is medial rectus recession combined with superior rectus transposition for Duane Type I as opposed to the traditional vertical rectus transposition surgery. This approach allows the surgeon to relieve medial rectus restriction while also expanding the field of binocular vision by improving abduction of the eye. Addressing the medial rectus restriction is particularly important for adult patients for whom the muscle will often appear tighter than in pediatric patients given the contracture of the medial rectus over time. Although only the superior rectus muscle is transposed, hypertropias post-operatively are relatively uncommon.[13-14]

ADDITIONAL CCDDS WITH PRIMARY LIMITATION OF HORIZONTAL MOVEMENT

In addition to Duane syndrome, there are several additional CCDDs that manifest primarily with limitation of horizontal movement. The clinical features of these conditions are summarized in **Table 2** (see below). In contrast to classic, non-syndromic Duane syndrome, these conditions are associated with significant systemic findings. Recognition of the systemic associations and appropriate referral for these findings is essential. Often the broader evaluation may be initiated by the treating ophthalmologist who may be the first to establish the underlying diagnosis in these patients.

Table 2. Congenital Cranial Dysinnervation Disorders with Limited Horizontal Movements and their Associated Genes

Syndrome	Clinical Features	Gene
Horizontal Gaze Palsy with Progressive Scoliosis	Limitation of horizontal gaze and aggressive scoliosis	*ROBO3* (OMIM 608630)
Athabaskan Brain Dysgenesis syndrome	Limitation of horizontal gaze, deafness, developmental delay, central hypoventilation, cardiac anomalies Patients of Native American ethnic origin	*HOXA1* (OMIM 142955)
Hereditary Congenital Facial Paresis	Esotropia, bilateral facial palsy	*HOXB1* (OMIM 142968)

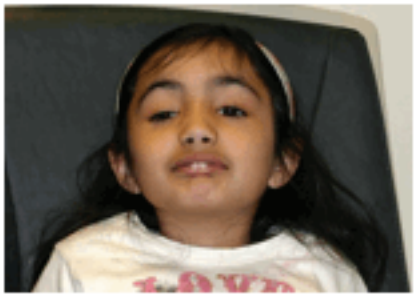
CCDDS WHICH MANIFEST PRIMARILY WITH LIMITATION OF VERTICAL ± HORIZONTAL MOVEMENT

CONGENITAL FIBROSIS OF THE EXTRAOCULAR MUSCLES (CFEOM)

Congenital fibrosis of the extraocular muscles refers to several rare strabismus disorders characterized by non-progressive ophthalmoplegia and blepharoptosis. This condition is hypothesized to result from dysinnervation of the extraocular muscles innervated by the oculomotor and/or trochlear nerves.[2-4, 15] Three dominant (FEOM1, 3, 4) and one recessive (FEOM2) CFEOM genetic loci have been mapped. The kinesin family member *KIF21A* (OMIM 608283), the homeodomain gene *PHOX2A* (OMIM 602078), and a b-tubulin gene *TUBB3* (OMIM 602661) have been identified as the FEOM1, FEOM2, and FEOM3 genes, respectively. These genes contribute to neuronal differentiation, axonal trafficking, and axonal pathfinding.[16-18] Genetic testing for each of these genes is commercially available. The clinical features of the subtypes of CFEOM are described below.

CFEOM 1

CFEOM 1 is the most common and is inherited in an autosomal dominant manner from mutations in *KIF21A* and rarely *TUBB3* genes.[17, 3] These mutations affect innervation by the superior division of oculomotor nerve. Clinical features include bilateral blepharoptosis and eyes infraducted with limited vertical movement (**Figure 2**) (see below). Consequently, many patients will adopt a chin-up head posture. Horizontal movement may be unaffected. Associated features include Marcus-Gunn jaw winking.[19] Optic nerve abnormalities have been reported including excavation of the optic nerve or optic nerve hypoplasia.[20-21] High resolution MRI imaging of the orbit has revealed hypoplastic oculomotor and abducens nerves and atrophy of the levator and superior rectus muscle complex.[21]



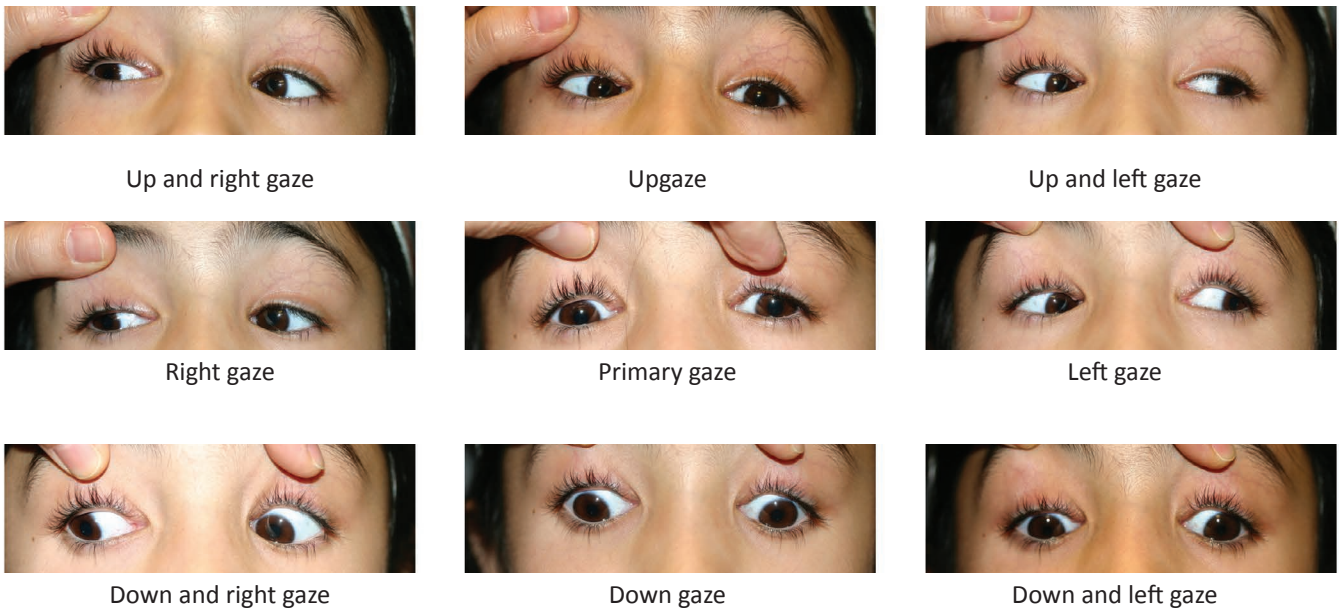


Figure 2. External photographs of a 6.5 year old girl with CFEOM1. Note the marked chin up position. Nine fields of gaze are shown. The eyes are fixed in downgaze with inability to elevate the eyes. Horizontal movement of the eyes is intact.

CFEOM 2

CFEOM2 has autosomal recessive inheritance secondary to mutations in the *PHOX2A* gene[16] and affects both the superior and inferior divisions of the oculomotor nerve. Clinical features include a large angle fixed exotropia with blepharoptosis of varying severity. There is phenotypic heterogeneity with respect to the degree of vertical misalignment ranging from full vertical movements to unilaterally or bilaterally supra/infraducted eyes. A distinguishing feature of CFEOM2 is the presence of pupillary abnormalities both in size and also in responsiveness.[22-23] Neuroimaging findings of absent oculomotor and trochelar nerves and enlarged lateral rectus muscles have been reported.[22]

CFEOM 3

CFEOM 3 is autosomal dominantly inherited from mutations in *TUBB3* and rarely *KIF21A* genes[18, 24] Clinical features of this subtype are more variable and may include unilateral or bilateral blepharoptosis and ophthalmoplegia with heterogeneity in the limitation of vertical eye movements.[3,18] Optic nerve anomalies may be present.[20] Importantly, CFEOM 3 may have associated systemic findings including developmental delay and late onset peripheral neuropathy.

Neuroimaging findings including hypoplasia of the oculomotor nerve with variable atrophy of extraocular muscles.[3] Tukel syndrome describes a condition characterized by a CFEOM3 phenotype with hand anomalies; the genetic basis for Tukel syndrome has not been identified to date.[25]

CFEOM WITH INTELLECTUAL DISABILITY

A novel phenotype of CFEOM co-segregating with polymicrogyria and cognitive dysfunction has been described. This is secondary to mutations in a b-tubulin gene *TUBB2*.[26]

SURGICAL MANAGMENT OF STRABISMUS IN CFEOM

Literature regarding surgical approach and detailed surgical outcomes are limited.[27-31] Surgery may include large recessions with/without adjustable suture technique, resections, tenotomies, myectomies, fixation of a muscle to the orbital wall, and botulinum toxin injection. More specifically, for the marked restriction of elevation of the eyes, at Boston Children's Hospital, we typically perform a weakening procedure of the superior oblique muscles (tenotomy) coupled with large recessions of the inferior rectus muscles. We have found resection of the superior rectus muscle to be less useful in treating the vertical misalignment. Although classically for restrictive strabismus, resections are generally avoided, in the management of CFEOM, large resections of the horizontal rectus muscles may be necessary. Patients should be counseled that multiple strabismus procedures may be needed as undercorrection is common in spite of an aggressive surgical approach. In our experience, adult patients undergoing surgery have tighter and more friable muscles than the pediatric patients who are being treated surgically for CFEOM. Therefore, we counsel our patients that earlier surgery may be more beneficial.

MANAGEMENT OF BLEPHAROPTOSIS IN CFEOM

The primary consideration in repair of blepharoptosis in this condition is the risk of post-operative exposure keratopathy given the limitation of vertical eye movements.[32] The frontalis sling procedure is an effective, conservative method of ptosis repair for these patients.

CONGENITAL BROWN SYNDROME

Congenital Brown syndrome is characterized by limitation of elevation of the eye in adduction passively or actively (**Figure 3**).[33] (see next page) There may be a downshoot of the eye in adduction and an associated chin up posture to maintain binocularity however, a true superior oblique overaction is not generally observed. The underlying etiology is unclear and the congenital form of this condition may fall into category of CCDDs[34-35] Traditionally, the mechanism of Brown syndrome is considered to be secondary to restricted movement of the superior oblique tendon or trochlear abnormalities and consistent with this, forced duction testing is positive with adduction and elevation of the eye. Whether this occurs secondarily as a consequence of aberrant innervation is unclear. Spontaneous resolution of congenital Brown syndrome is uncommon.[36]

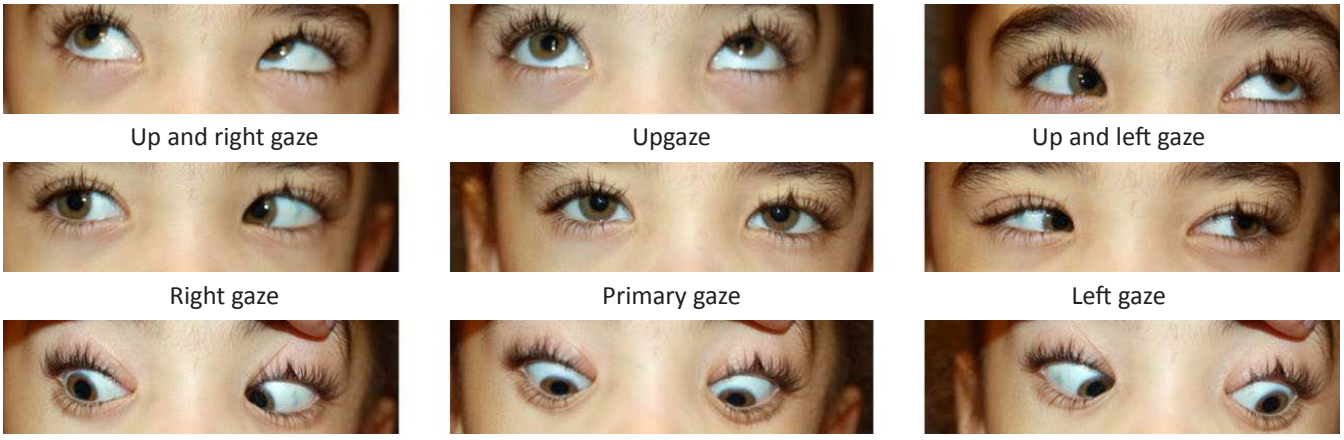


Figure 3. External photographs of a 6 year old girl with congenital Brown syndrome right eye. Nine fields of gaze are shown. There is limitation of elevation of the right eye in adduction.

In comparison to patients with congenital Brown syndrome, the etiologies for acquired Brown syndrome are myriad including inflammatory causes associated with systemic disease, traumatic causes, and iatrogenic causes after orbital or ocular surgery.[36] In a study of 85 patients with congenital and acquired Brown syndrome, Wright[36] observed several features which appeared to distinguish congenital from acquired causes of Brown syndrome: acquired cases are more likely to have a large hypotropia in primary position compared with congenital cases and this is more pronounced in those cases secondary to a trauma. Further in this cohort, amongst the acquired cases, excluding traumatic cases, 16% of patients experienced spontaneous resolution of their strabismus.[36] Amongst some of the patients with spontaneous resolution were pediatric patients diagnosed with idiopathic acquired Brown syndrome.

SURGICAL MANAGEMENT OF CONGENITAL BROWN SYNDROME

The mainstay of treatment involves a weakening procedure of the superior oblique without creating a secondary superior oblique palsy. Complete tenotomy of the superior oblique tendon is likely to result in an iatrogenic superior oblique palsy therefore more a conservative expansion of the superior oblique tendon is preferred. Techniques to elongate the superior oblique tendon may include split thickness lengthening of the tendon, z-myotomy of the tendon, or placement of a tendon expander including the Wright silicone expander or suture spacer. Our preferred technique involves the use of a non-absorbable polyethylene suture suture spacer.[37-38]

CME ANSWERS

1. Globe retraction on adduction, narrowing of the palpebral fissure with attempted adduction, and abnormal vertical movements in adduction are clinical features associated with Duane syndrome as distinct from a 6th nerve palsy. Further, a congenital 6th nerve palsy is rare and therefore a history of a limitation of abduction since infancy in addition to the above clinical findings would support the diagnosis of Type I Duane syndrome.
2. Duane syndrome Type I- head turn towards the affected side; CFEOM1- chin up head position; Brown syndrome- chin up head position
3. CFEOM3

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ORBITAL AND PERIORBITAL DISEASE CAUSING MECHANICAL STRABISMUS

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LEARNING OBJECTIVES

1. Describe the important anatomic relationships between the eye, orbital adnexa and paranasal sinuses
2. Describe successful strategies for managing mechanical diplopia
3. Recognize the typical patterns of mechanical strabismus that develop after orbital fractures and with paranasal sinus disease and surgery
4. Be familiar with paranasal sinus mucocoeles and how they cause diplopia

CME QUESTIONS

1. All of the following are true concerning acquired browns syndrome except:
    a. A similar motility pattern can be seen after inferior blow out
    b. Has not been described to result from mucocele
    c. Is rarely seen with systemic rheumatologic conditions
    d. Can be painful as a result of inflammation of the tendon trochlear complex
2. What is the reason that both medial and lateral rectus muscle recession might be performed in a patient with persisting large esotropia after medial wall fracture?
    a. No reason, would never do it
    b. Recession of contralateral lateral rectus may be necessary after recession of involved medial rectus to prevent exotropia
    c. Recession of ipsilateral lateral rectus may be necessary because of secondary contracture
    d. Recession of ipsilateral lateral and medial rectus muscle may be necessary to improve the impaired vertical eye movements
3. Mucocoeles commonly develop in the setting of previous history of all of the following except:
    a. Allergic sinusitis
    b. Orbital tumor
    c. Trauma/fractures
    d. Chronic infectious sinusitis
    e. Previous surgery

KEYWORDS

1. Diplopia
2. Mucocele
3. Orbital Fracture
4. Sinus Surgery
5. Brown's Syndrome

INTRODUCTION

The ocular adnexa, orbital structures and paranasal sinus and associated diseases can mechanically impair eye movements though a variety of different mechanisms. These conditions can both physically prevent the eye from moving to a certain position, and can limit eye movement by entrapping or impairing the movement of an eye muscle. In addition, these same processes can impair eye movements through direct effect on cranial nerves 3,4 and 6. These clinical presentations will generally be identified based on the circumstances of the patient's presentation and the associated orbital symptoms and signs that usually accompany their presentation. Conditions generally fall into four broad categories: 1) infections and tumors of the orbit or paranasal sinuses 2) inflammatory conditions affecting the orbit 3) trauma to the orbital bones and 4) iatrogenic in association with surgery of the paranasal sinuses. The most common scenarios are processes that affect the paranasal sinuses and then either extend into the orbit or otherwise affect orbital bones, eye muscles or soft tissues (orbital fractures). Other common scenarios for mechanical strabismus include processes that infiltrate the orbital fat and connective tissue or affect the trochlear.

RELEVANT ANATOMY

Conditions that impair the movement of the eye and result in mechanical strabismus are most commonly primary disorders of the extraocular muscles (i.e thyroid eye disease, discussed elsewhere). Other mechanical issues result in strabismus by either affecting the healthy eye muscle and therefore limiting eye movements or by directly taking up space and preventing the eye from moving. All four of the primary paranasal sinuses (frontal, maxillary, sphenoid and ethmoid) are separated from the orbit by a layer of bone (sometimes "paper" thin, lamina papyracea) and periorbita. The bony structure of the orbit is necessary to support the position of the eye and eye muscles and although significant changes in orbital volume are often well tolerated without impaired eye movement, mechanical effects can often develop (ie silent sinus syndrome). Increasing orbital volume can also worsen restrictive strabismus by allowing the disease to shift further away from the globe (ie worsening of esotropia after medial wall decompression in thyroid eye disease). The periorbita functions as a very effective barrier to infectious, inflammatory and neoplastic processes but can be transgressed by these conditions when chronic, untreated or behave in an aggressive fashion. The periorba is an ineffective barrier to the high speed instruments of the sinus surgeon and often gets entrapped with orbital soft tissues (muscle and fat) in the setting of traumatic orbital fractures. In particular the proximity of the inferior rectus and inferior oblique muscles to the orbital floor and the medial rectus to the lamina papyracea make these eye muscles particular vulnerable to entrapment. The trochlear is a loop of cartilage attached to the medial orbital roof (wall of the frontal sinus) thrus which the tendon of the superior oblque passes. This proximity to the frontal sinus as well as the unique nature of the soft tissue of the trochlear make it uniquely vulnerable to conditions and trauma of the frontal sinus as well as autoimmune inflammation. Orbital fat surrounds the extraocular muscles and the fat and muscles share connective tissue therefore both neoplastic and inflammatory conditions that are either "scirrhous" (metastaic breast cancer) or sclerosing" (orbital inflammation) frequently result in mechanical strabismus.

CLINICAL PRESENTATION

The clinical presentation of mechanical causes of strabismus is unique for each of the conditions described below but there are common features that should be considered in all patients being evaluated for diplopia to suggest the process is first mechanical and then to suspect an etiology or localization to structures other than processes primarily involving the extraocular muscles (which are the commonest localization for mechanical problems affecting eye movements i.e. thyroid eye disease). During history taking the examiner should concentrate on any previous history of sinus disease or history of previous trauma which could be the setting of subsequent development of a mucocele. Also a history of a previous primary tumor with the potential to metastasize should be sought. The most obvious would be associated proptosis. The confined space of the boney orbit, given the significant amount of fat, can allow a space occupying process, especially one that develops indolently, to cause relatively little proptosis. However, the majority of patients with tumors or mucoceles for example, will have proptosis in association with their mechanical strabismus. The position of the globe should also be noted. Globe ptosis or physical shifting of the globe inferiorly can be an important sign of superiorly located tumors and mucoceles or inferior fractures. Similarly ptosis may be present. Processes associated with enophthalmos generally either have enlarged the orbital volume or caused contraction or fibrosis of the orbital fat. These conditions may be associated with an exaggerated superior sulcus. On the physical examination one should attempt to identify resistance to retrodisplacement of the globe or pain on palpation of the orbit or the region of the supratrochlear notch. A careful sensory exam looking for abnormalities in the function of the first and second division of the fifth cranial nerve should be performed.

The pattern of double vision and eye movement impairment is most notable for the fact that it does not fit with dysfunction of a specific cranial nerve, although depending on specific localization of condition, the presentation can closely mimic dysfunction of the 3rd, 4th or 6th nerve. One common feature that can often be identified is that mechanical strabismus will usually be associated with normal forced generations (the initial saccade speed will look (and feel) normal) and then mechanical limitations will subsequently limit the eye movement with positive forced ductions. Forced ductions should be performed whenever mechanical strabismus is suspected. Finally interpretations of impaired eye movements can by difficult because of simultaneous loss of function of the mechanically limiting muscle.

ORBITAL FRACTURE

The most common form of mechanical strabismus related to the adnexa and sinuses are the eye movement impairments that develop after orbital fractures and in particular inferior and/or medial wall blow out fractures. These typically develop after an object (fist, ball) strikes the orbit and eye, suddenly increasing the pressure in the orbit resulting in a "blow out" of orbital tissue into the nearby sinus. Immediately after the pressure stops the broken bones and soft tissue move back toward the orbit and this trap door will often result in trauma to the muscle and soft tissues being physically stuck between bones.

Orbital fractures and resulting entrapment of extra ocular muscle or other orbital soft tissues are generally easy to recognize on CT scans of the orbit, with direct, thin section (1.5 -3mm), non enhanced axial and coronal views. Varying amounts of impairment or paresis of the eye muscles's function combined with entrapment can create a wide

variety of patterns of strabismus acutely.[1] Initially the associated swelling and hemorrhage can make accurate assessment of eye movements difficult. The most common inferior blowout with both entrapment and dysfunction of the inferior rectus can mimic the pattern of a third nerve palsy with both impairment of elevation and depression of the globe. The absence of ptosis, exotropia and papillary findings, along with the CT findings will generally distinguish the two conditions. Fractures can occasionally be hard to recognize clinically when presenting as a "white eye" with minimal swelling and a small fracture or "trap door" with entrapment of the inferior or medial rectus. In these cases, where the orbital trauma is less obvious patients can present with what appears to be a cranial nerve palsy (third or sixth) based on impaired eye movements and may also have syncope or confusion secondary to the oculcardiac reflex and bradycardia suggesting a more serious intracranial injury.[2] Severe orbital trauma has been reported to cause actual transection of the inferior rectus muscle.[3-5]

The most typical presentations of orbital fractures are of the inferior and/or medial walls. With inferior wall fractures and entrapment there is typically a hypotropia and impaired/limited upgaze. The actual tissue entrapped or area of the inferior rectus muscle involved may depend on the position of the eye at impact. Often there is an associated hypertropia on downgaze secondary to injury to the muscle or its innervation and more rarely because of a reverse leash restriction. Medial fractures typically involve the medial rectus and only very rarely affect the superior oblique. Medial rectus entrapment presenting with an esotropia worse in abduction of the affected eye and once again, not uncommonly with some exotropia when adducting the affected eye secondary to nerve or muscle injury or from a tethering resulting in a reverse leash phenomenon. Interestingly, mechanical strabismus is less often a consequence of superior and lateral fractures. The strong zygomatic arch makes these bones less like to result in a blow out/entrapment scenario since the medial and inferior walls are likely to give first. Exceptions perhaps occur with very lateral blows and fractures that extend to the rim and orbital roof fractures and their repair have been associated with injury to the trochlear and an acquired Brown's syndrome,[6] or actual entrapment of the superior oblique muscle in a superomedial fracture.[7] Prompt surgical repair is indicated in these situations.

MECHANICAL STRABISMUS AFTER ORBITAL FRACTURE

A wide variety of presentations are possible and the pattern of eye movement impairment will almost certainly evolve over time and may have a combination of restrictive and paretic strabismus. Mechanical strabismus can result from actual muscle entrapment or entrapment of attached connective tissue and fat. Further increasing the difficulty of interpreting finding is the possibility that restriction can affect the eye muscle in both the field of gaze away from the entrapped or damaged muscle (leash effect) and as well, particularly with the medial rectus, in the direction of the muscle's action (reverse leash). This phenomenon is important to recognize in distinguishing multiple cranial nerve palsies (3rd and 6th) from complex mechanical strabismus. In the end, much of this exercise is thought provoking but not high stakes until it becomes important to the strabismus surgeon as he/she plans surgery to improve ocular alignment. Acutely the examiner, armed with a good history and informative CT scans of the orbit will not have difficulty identifying mechanical strabismus in the appropriate setting of orbital trauma. It is however critical to recognize any restrictive strabismus acutely since prompt repair (within 2 weeks) is always indicated for acutely entrapped muscles or soft tissues. On the other hand, it is equally important through review of post operative imaging and testing of forced ductions and forced generations to recognize when entrapment has been adequately addressed and residual eye muscle dysfunction is on the basis of edema and or muscle or nerve injury to avoid unnecessary reattempts and fracture repair or repositioning of orbital implants. A systems based challenge can also arise acutely when the surgeon repairing the fracture is not an ophthalmologist and therefore may not easily understand or address your concerns when motility defects persist.

In many instances, successful surgical repair of the fracture and relief of the entrapment will result in the return of eye movements to normal as edema and hemorrhage resolve. In other circumstances, even with successful initial surgery and clearing the fracture of entrapped tissue a combination mechanical and paretic strabismus can persist and ultimately may require strabismus surgery. First several weeks should be allowed for swelling, edema and hemorrhage to resolve. Many early problems will spontaneously resolve as these acute processes clear. Inferior oblique underaction can present after blow out fractures and resolve over time in conjunction with resolution of swelling hemorrhage or nerve injury.[8, 9] One study reported a rate of 60% improvement (either complete resolution or only mild non bothersome diplopia persisting) in patients who initially had diplopia after the orbital repair.[10] Even with successful early repair of these fractures a residual pattern of extraocular muscle dysfunction and in particular hypertropia, can occasionally be difficult to distinguish from traumatic fourth nerve palsies or even mild traumatic third nerve palsies. The distinction ultimately may not be important as long as residual entrapment has been excluded then after a period of timed allowed for spontaneous improvement, strabismus repair can be performed to address the residual deviation and any abnormalities in the forced ductions.

The principles used to repair strabismus in this setting are similar to other restrictive problems and often involves a combination of recession of the affected muscle and recession and/or fadenoperation (posterior fixation suture)

to the contralateral yoked muscle. The fadenoperation or posterior fixation suture is an operation which generally does not change the primary position affect of a muscle but weakens it in its field of gaze thereby expanding the field of single vision by matching the weakness in the contralateral eye.[11] Using a combination of observations concerning primary position alignment, forced ductions/generations the surgeon can plan repair. Generally the greater the restriction the less likely a simple recession of that muscle will be adequate since the necessary recession to improve the eye movement will invariably lead to underaction of the recessed muscle. For instance with a right hyotropia after inferior blowout and significant residual restriction, a large recession of the inferior rectus to improve the extent of the upward eye movement will result in a right hypertropia in down gaze. This is generally less of an issue in vertical strabismus compared to medial fractures and horizontal strabismus because we are often willing to sacrifice upgaze (therefore a smaller recession can performed) and allow persisting diplopia in upgaze (generally well tolerated) and aim for realignment in primary position and downgaze. We generally do not have that luxury with the medial rectus where the necessary recession of the medial rectus to relieve restriction will often result in an exotropia in the opposite direction. In this case the surgeon might simultaneously recess the contralateral (yoke) lateral rectus. The situation of impaired function of the recessed muscle and consecutive hypertropia could be increased if there is also a component of muscle injury or paresis. Identifying restriction and eye movement limitation, testing forced ductions and generations and the primary position deviation will generally inform this decision. Various other patterns for restrictive strabismus have been described with perhaps the third most common being entrapment and or injury to the inferior oblique. A specific pattern in which restriction and downgaze limitation, worse in adduction, with resulting hypertropia has been described with inferior oblique fibrosis/injury.[12] The patients with diplopia limited to downgaze represent a unique group of patients. Fadenoperation and slab off prism can be excellent options for these patients and there are excellent summaries describing the management of diplopia limited to downgaze.[13-15] Kushner also reported successful results through a combination of recession of both superior and inferior rectus muscles on the affected side.[16] A posterior tenotomy of the contralateral superior oblique tendon has been described as an effective treatment for inferior rectus weakness after blowout fracture.[17]

ORBITAL TUMORS

Diplopia is a common symptom in patients with both primary and secondary orbital tumors. These tumors can also be associated with visual dysfunction from concurrent optic nerve dysfunction and a unique form of transient vision loss associated with eye movements (gaze evoked amaurosis). This commonly develops with optic nerve sheath meningiomas (which are uncommonly associated with double vision) but can develop with other tumors based on movement of the eye being transiently associated with compression of the optic nerve or compromise of blood flow to the optic nerve. Proptosis is the rule and the tempo of symptom development depends on the nature of the tumor. Protracted presentations over months or even years can occur with more benign primary tumors such as pleomorphic adenoma or the various fibrous tumors of the orbit. More rapid presentations would be expected with the more aggressive secondary tumors either malignancies extending directly from the paranasal sinuses or metastatic tumors to the orbital fat or eye muscles. The most common primary orbital tumor are cavernous hemangiomas and these only very rarely are associated with diplopia and are often detected based on insidious onset of proptosis or incidently on imaging study done for other reason. The most common tumors to extend from the paranasal sinuses into the orbit are squamous cell tumors. The most common metastaic tumors to the orbit are breast and lung carcinoma.

Diplopia primarily develops when two firm structures (eye and tumor) compete for a limited fixed amount of space. Most commonly double vision will not develop in this setting until the eye tries to move into the area of the mass. For example, an esotropia only present in lateral gaze in a patient with a lateral orbital mass. Similarly restrictive problems problems can result from associated tissue edema and or infiltration (scirrhous breast metastases). Generally these process involve the extraocular muscle directly but occasionally they result from infiltration or restriction of the adnexal structures. This is distinct from the pattern which is usually seen with orbital apex lesions which generally cause paretic problems.

ORBITAL INFLAMMATORY SYNDROME

Diplopia is a common acute finding and often persisting sequelae in many patients with idiopathic orbital inflammation. This can result both in cases of what has presented initially as a primary myositis as well as in conditions in which there is more generalized involvement of the orbital fat and connective tissue. Generally prompt treatment (steroids) of acute orbital inflammation will result in resolution of all motility impairments. However, when the treatment effect is incomplete and or the conditions is associated with fibrosis or sclerosing inflammation of the orbital soft tissue, a persisting primarily restrictive strabismus can develop. Both orbital inflammatory syndrome variants, (sclerosing orbital inflammation and IgG 4 related inflammation may be more likely to be associated with persisting restrictve strabismus.

A unique form of mechanical strabismus can develop in association with inflammation of the trochlear causing an acquired Browns syndrome or Superior oblique tendon sheath syndrome. Generally this falls on the spectrum

of idiopathic orbital inflammatory syndrome but can arise more specifically in the setting of specific systemic autoimmune conditions such as psoriasis and rheumatoid arthritis.[18-21]

In the end treatment is designed as in all cases of orbital conditions leading to diplopia to a combination of weakening where restriction is present and match weakness in the affected eye thru muscle recessions or fadenoperations on the contralateral eye when indicated. A mixed series of of patients that included several patients with hypertropias after orbital inflammatory disease was reported and the authors noted a high degree of success with botulinium toxin injections in to the inferior rectus muscle.[22] Four of their six patients with inflammatory cause of the strabismus improved and this was true with both small and large deviations.

MUCOCELES

A wide variety of presentations of patients with impaired eye movements and mechanical strabismus have been reported in the setting of mucoceles of the paransal sinuses.[23-30] Mucoceles are fluid filled epithelial lined cysts containing sinus secretion that expand and/or extend through the walls of the sinus/orbit into the orbital space. They are notorious for their presentation to the ophthalmologist because of orbital signs and symptoms. They generally result when there is obstruction of the normal outflow of mucus into the normal nasal drainage channels. They develop most commonly in the setting of chronic infectious or allergic sinusitis and previous trauma to the sinus bones (iatrogenic surgical trauma as well). The most common location for mucoceles are the frontal and ethmoid sinuses. They develop insidiously and present much like other slow growing mass lesions that affect the orbital contents by either compressing important structures (nerves or muscles) or taking up space. Because these lesions develop by eroding bone or causing bone to resorb at any point in the orbit, they can present in a wide variety of ways. Occasionally the presentation is more dramatic in association with infection developing in the fluid inside the cystic cavity (mucopyocele). Again as with any of these processes affecting the orbit the diagnosis is often not difficult provided the suspicion exists, orbital signs are present and the examiner obtains appropriate radiographic studies which can identify the mucocele.

Various presentations have been reported including limitation of upgaze secondary to fontal sinus mucoceles,[27] downgaze issues from maxillary sinus lesions,[29] either Brown's syndrome or superior oblique paresis from ethmoidal or frontal sinus lesions,[23, 28] and finally they have also been reported to present with cranial nerve palsy when they involve the orbital apex.[25, 31]

COMPLICATIONS OF ENDOSCOPIC SINUS SURGEY (ESS)

Despite the extraordinary number of procedures performed and the fact that a very high speed drill is proximate to the thin medial wall of the orbit, the incidence of orbital complications of functional ESS is quite low.[32-37] When inadvertent entry occurs into the orbit, the drill most commonly encounters either the structures in the orbital apex including the optic nerve and cranial nerves three four and six, the mdial rectus muscle and or the orbital fat. Cases of complete blindness have been reported as well as motility patterns consistent with cranial nerve palsy. Complete transection and removal of part of the medial rectus can also occur. In these patients prompt attempts to identify the cut end of the muscle and reaatach it to the eye should be attempted.[36] In other patients, the orbital entry is less severe and there is only involvement of the orbital fat and connective tissue. This can create a pattern of severe secondary restrictive strabismus. Smaller fractures or defects in the medial wall of the orbit after sinus surgery can be a sight of medial rectus entrapment.

Surgical management of this often mixed pattern strabismus (weakness and restriction) is complex and several series and reports describe varying degrees of success often including improving on adhesions and vertical muscle transpositions to create an adducting force in the case of a severed medial rectus.[38-40]

SILENT SINUS SYNDROME

The silent sinus syndrome is a unique condition associated with chronic maxillary sinus dysfunction, chronic negative pressure and erosion of the orbital floor. Ultimately there is sufficient anatomic change from bony destruction to alter the normal "convex up" appearance of the orbital floor changing it to a "concave down configuration". The resulting increase in orbital volume and downward shift of the globe and inferior rectus causes enophthalmos, hypoglobus and an ipsilateral hypotropia with mild limitation of upgaze. The clinical presentation is generally insidious onset with progressive development of enophthalmos, an exaggerated superior sulcus and diplopia in upgaze although acute presentations have been reported.[41] It is generally a condition that develops in adults but pediatric cases have been reported.[42] A recent review identified 84 reported cases in the literature and summarized findings.[43] Other presentations of this unusual entity include a pattern that mimics a cyclovertical strabismus, hypotropia and relatively excyclotortion, that mimics a contralateral fourth nerve palsy and in one case was successfully treated with contralateral inferior oblique myectomy.[44] Generally treatment of the underlying sinus/orbital floor abnormality can improve the strabismus.[45, 46]

CME ANSWERS

1. b. Has not been described to result from mucocele
2. b. Recession of contralateral lateral rectus may be necessary after recession of involved medial rectus to prevent exotropia
3. b. They arise in the setting of conditions that chronically affect the integrity of the orbital bones such as previous surgery, inflammation and trauma

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North American Neuro-Ophthalmology Society

41st Annual Meeting

February 21-26, 2015
Hotel del Coronado • San Diego, California

Program Schedule

THURSDAY, FEBRUARY 26, 2015

6:30 a.m. – 12:30 p.m.	**Registration**	**Ballroom Foyer**
7:00 a.m. – 8:00 a.m.	**Breakfast**	**Crown Room**
8:05 a.m. – 12:32 p.m.	**Glaucoma: The Other Optic Neuropathy [4 CME]** *Moderators: Helen V. Danesh-Meyer, MD, PhD, FRANZCO & Mark L. Moster, MD*	**Ballroom**

This symposium is a combined program of AGS (American Glaucoma Society) and NANOS aiming to clarify the relationship between glaucoma and other optic neuropathies.

The structure of the symposium is divided into 3 sections: 1) Establishing whether there is a difference between high tension glaucoma and normal tension glaucoma. This section will explore the contribution of intraocular pressure to glaucoma as well other factors that might be contributory; 2) Differentiating glaucoma from other optic neuropathies and deciding whom to image with MRI; and 3) Looking at glaucoma as a neurodegenerative disorder and reviewing issues of neuroprotection and neuroregeneration.

Upon completion of this course, participants should be able to: 1) Identify important contributions to glaucomatous damage other than intraocular pressure; 2) Identify which glaucoma patients should be evaluated for other causes of optic neuropathy; and 3) Identify areas of research ripe for collaboration between glaucoma and neuro-ophthalmologic researchers.

		PAGE
8:05 a.m. – 8:10 a.m.	**Introduction**	
8:10 a.m. – 9:44 a.m.	**IOP and Other Issues in Glaucoma**	
8:10 a.m. – 8:17 a.m.	**Case: Is it Glaucoma?** *Marlene R. Moster, MD*	
8:17 a.m. – 8:25 a.m.	**What is Glaucoma: Clinically, Functionally, and Pathologically?** *Paul L. Kaufman, MD*	**487**
8:25 a.m. – 8:33 a.m.	**The Role of IOP in Glaucoma** *M. Roy Wilson, MD, MS*	**493**
8:33 a.m. – 8:41 a.m.	**Phenotypic Differences in Normal vs. High Tension Glaucoma** *Jonathan S. Myers, MD*	**497**
8:41 a.m. – 8:49 a.m.	**Is Normal Tension Glaucoma Different than High Tension Glaucoma? Vascular and Autonomic Dysfunction** *Louis R. Pasquale, MD, FARVO*	**501**
8:49 a.m. – 8:57 a.m.	**Is Normal Tension Different from High Tension: Genetic/Epidemiological Factors** *Janey Wiggs, MD, PhD*	**509**
8:57 a.m. – 9:05 a.m.	**Role of Intracranial Pressure in Glaucoma** *Timothy McCulley, MD*	**513**

9:05 a.m. – 9:13 a.m. **Is Normal Tension Different than High Tension Glaucoma: Other Possible Factors** **517**
Martin B. Wax, MD

9:13 a.m. – 9:29 a.m. **Pro and Con Debate: We Should Eliminate the Normal Tension in Glaucoma** **525**
Pro: *Robert N. Weinreb, MD;* Con: *Robert Ritch, MD*

9:29 a.m. – 9:44 a.m. **Discussion**

9:44 a.m. – 10:14 a.m. **Break** **Crown Room**

10:14 a.m. – 11:15 a.m. **Clinical Differences Between Glaucoma and Other Optic Neuropathies**

10:14 a.m. – 10:22 a.m. **The Morphological Difference Between Glaucoma and Other Optic Neuropathies** **527**
Claude Burgoyne, MD

10:22 a.m. – 11:15 a.m. **Case Presentations**
Helen V. Danesh-Meyer, MD, PhD, FRANZCO and *Mark L. Moster, MD*
Panel: *Peter Savino, MD, Valérie Biousse, MD, Anne L. Coleman, MD, PhD,* and *Richard Lee, MD, PhD*

11:15 a.m. – 12:32 p.m. **The Neurology of Glaucoma**

11:15 a.m. – 11:23 a.m. **Glaucoma as a Neurological Disease** **543**
Helen V. Danesh-Meyer, MD, PhD, FRANZCO

11:23 a.m. – 11:31 a.m. **The Brain in Glaocomatous Optic Neuropathy: Evidence for Trophic-Factor Mediated Self-Repair** **547**
David J. Calkins, PhD

11:31 a.m. – 11:39 a.m. **What are the Common Neurodegenerative Pathways Relevant to Glaucoma?** **555**
Stuart J. McKinnon, MD, PhD

11:39 a.m. – 11: 47 a.m. **Neuro-Protection in Glaucoma: Where are We Going?** **559**
Leonard A. Levin, MD, PhD

11:47 a.m. – 11:55 a.m. **Neuro-Regeneration for Glaucoma and other Optic Neuropathies** **563**
Jeffrey Goldberg, MD, PhD

11:55 a.m. – 12:03 p.m. **Mitochondrial Disease and Glaucoma** **565**
Alfredo A. Sadun, MD, PhD

12:03 p.m. – 12:19 p.m. **Debate: Non-IOP Lowering Therapies will be the Future of Glaucoma Management.**
Pro: *Harry Quigley, MD* **569**
Con: *Christopher A. Girkin, MD, MSPH, FACS* **573**

12:19 p.m. – 12:32 p.m. **Q & A**

2:00 P.M. – 5:30 P.M. AGS/NANOS AFTERNOON SESSION **Ballroom**

AGS will lead the afternoon collaboration with NANOS. The scientific session will feature the following topics: 1) The Pathogenesis of Optic Neuropathy: Glaucoma vs. The Rest and; 2) Optic Nerve Imaging: New Parameters and Techniques, a platform presentation session, poster viewing and an afternoon break.

**Please note that the CME credits for this session will be provided through AGS.

WHAT IS GLAUCOMA: CLINICALLY, FUNCTIONALLY, PATHOLOGICALLY?

Carol A. Rasmussen, MS and Paul L. Kaufman, MD

University of Wisconsin-Madison
Madison, WI

LEARNING OBJECTIVES

1. Describe clinical aspects of glaucoma
2. List functional deficits associated with glaucoma
3. Define aspects of glaucoma pathology

CME QUESTIONS

1. By the time glaucomatous optic neuropathy can be diagnosed with currently available clinical technologies, approximately what percentage of retinal ganglion cells will have been lost?

   a. 5-10%
   b. 10-20%
   c. 25-35%%
   d. >50%
   e. None of the above

2. How many people are affected by glaucoma worldwide?

   a. 1 million
   b. 10 million
   c. 50 million
   d. 70 million

3. The earliest clinically detectable sign of glaucomatous optic neuropathy is presently

   a. Thinning of the RNFL as measured by OCT
   b. An arcuate scotoma demonstrated by SAP
   c. Characteristic cupping of the ONH
   d. Characteristic alterations of the electroretinogram
   e. In a state of flux

KEYWORDS

1. Glaucoma
2. Optic Nerve
3. Retinal Ganglion Cells
4. Trabecular Meshwork
5. Retinal Nerve Fiber Layer

INTRODUCTION

The glaucomas are a collection of progressive optic neuropathies that can lead to irreversible damage to retinal ganglion cells (RGC) and their axons and eventual loss of vision if inadequately treated. In the early stages the disease is largely asymptomatic and it is estimated that only half of glaucoma patients are aware that they have the disease. Clinically, glaucoma patients show characteristic optic nerve head (ONH) and retinal nerve fiber layer (RNFL) changes. These include thinning of the neuroretinal rim, increased cup-to-disk ratio, peripapillary atrophy and attenuated RNFL (Figure 1). Visual field deficits, especially in the periphery, are also a hallmark of glaucoma presentation. The clinical utility of imaging devices is growing as the technology rapidly evolves. Instruments are faster, resolution is increasing, computational algorithms are more refined and normative databases are expanding to include a wider range of patients. A current trend in glaucoma clinical care is the development of metrics that combine information from multiple testing modalities.[13, 14, 15] Pathologic changes noted in glaucoma include ONH, RNFL and macular (ganglion cell-inner plexiform layer) deficits as well as atrophy of the lateral geniculate nucleus (LGN) and visual cortex. A potential biomarker for glaucoma involves imaging apoptosis of RGCs. Glaucoma is a disease with multifactorial mechanisms. Advances in diagnostic instrumentation and out understanding of the pathology of the disease will benefit patients. An individualized treatment approach will result in improved patient outcomes.

Indeed, in aggregate the glaucomas are the most common optic neuropathy, affecting ~70 million people worldwide.[1] The number of people (aged 40-80 years) with glaucoma globally is estimated to increase to 76 million by 2020 and 112 million by 2040.[2] Three-quarters

of these have primary open-angle glaucoma (POAG) and women are affected more than men (55% of POAG, 70% of primary angle closure glaucoma (PACG), and 59% of all glaucoma)[1]. The prevalence of POAG is highest in Africa, while the prevalence of PACG is highest in Asia. People of Japanese ancestry have a higher incidence of normal-tension glaucoma (NTG), in which damage occurs to the optic nerve without intraocular pressure (IOP) exceeding the statistically normal range. (generally between 10-20 mm Hg).[2] Of concern is that while glaucoma prevalence is increasing globally, in resource poor areas access to ophthalmologists is severely limited[3] It is estimated that in sub-Saharan Africa there are less than 3 ophthalmologists per million people while there are approximately 79 ophthalmologists per million in high-income countries.[4] The major risk factors for POAG include older age, Black or Latino race, higher IOP and lesser central corneal thickness (CCT). In the early stages the disease is largely asymptomatic, so many people are unaware they have glaucoma until significant loss of vision occurs. It is estimated that only half of glaucoma patients are aware that they have the disease.[5] Vision deficits in glaucoma patients are associated with worse on-road driving performance[6] and an increased risk of falls.[7]

Stereo fundus photos, long the gold standard for assessment of a patient's ONH morphology, have been a key part of glaucoma diagnosis and evaluation of progression. These photos reveal much about the condition of the eye but grading is subjective and inter observer variability can be high.[8, 9] Techniques using computer assisted digital analysis of the ONH have been developed to improve intra and inter observer reproducibility.[10, 11, 12]

There are several different visual field tests: standard automated perimetry (SAP), Swedish interactive threshold algorithm (SITA), frequency-doubling technology (FDT), matrix frequency-doubling technology, short-wavelength automated perimetry (SWAP), and high-pass resolution perimetry (HPRP). These tests provide valuable information about a patient's visual function and are required in clinical trials for glaucoma therapeutics. The FDA requires functional testing in clinical trials in an effort to provide patients with drugs that offer meaningful changes in, or preservation of, visual function. Critics of visual field tests point to their subjectivity and the patient learning effects that make evaluation of disease progression difficult.

Imaging instruments, such as confocal scanning laser ophthalmoscopy (HRT), scanning laser polarimetry (GDx), and optical coherence tomography (OCT), can provide objective quantitative measures of the optic disc, retinal nerve fiber layer (RNFL) and macula. Confirming structural damage can help in the initial glaucoma diagnosis but a critical aspect of glaucoma management is follow-up. Imaging systems offer the prospect of detecting progression early so that changes to a patient's treatment plan can be made to prevent visual impairment. Imaging tests also provide more objective measurements of glaucoma-relevant structures and can be compared from visit to visit but are not necessarily diagnostic themselves. They are intended to provide information that can be used in conjunction with clinical examinations and visual fields. [13, 14, 15]

Positive correlations exist between functional data from visual fields tests and structural data from imaging devices such as optical coherence tomography (OCT). RNFL thinning measured by OCT is associated with visual field loss.[16] Additionally, OCT studies demonstrate that thinning in the macular layers (ganglion cell and inner plexiform layers) also occurs in glaucoma, can occur early in the disease and

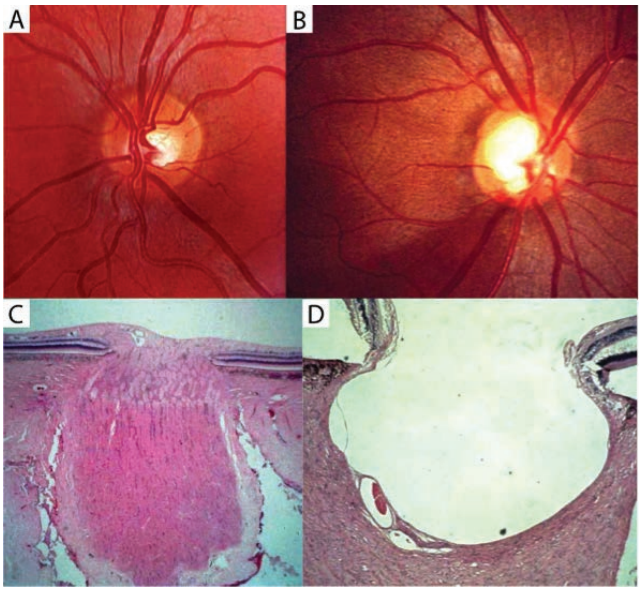

Fig 1: Normal optic nerve (A and C). Glaucomatous optic nerve (B and D) with characteristic changes including 1) Thinning of the neuroretinal rim, 2) Increased cup-to-disk ratio, 3) Vertical elongation of the cup, 4) Pitting or notching of the rim, 5) Quick angulations in the course of the exiting blood vessels, 6) Wedge-shaped dark areas - retinal nerve fiber layer damage, 7) Undermined disk margins, 8) Peripapillary atrophy, 9) Attenuated nerve fiber layer. Panels A and B with permission from Atlas of Ophthalmology; panels C and D courtesy of Dr Morton Smith, Washington University.

is also associated with visual field loss.[17, 18, 19] A recent study indicates that a combined thickness value derived from the RNFL, ganglion cell layer (GCL), and inner plexiform layer (IPL) is the most useful parameter to evaluate structure and function within the central 10° in glaucoma.[19] There is a school of thought that imaging provides better information early in the disease while visual fields are better later. Metrics that include data from both may be the most useful at most stages.

The effect of glaucoma on the inner and outer retina and macula has also been documented by studies using electrophysiology tests, notably the photopic negative response of the multifocal electroretinogram (mfERG)[20], the full-field photopic negative response (PhNR)[21] and pattern ERGs (PERG). [22] Electrophysiology testing has some advantage over visual field testing since it is less subjective and not as dependent upon patient "performance". Newer iterations of electrophysiology instruments have improved discriminatory ability but are not as commonly available as perimetry instruments and not as widely used. In experimental glaucoma models, electrophysiology deficits correlate with decreases in RNFL and both inner and outer retinal thickness.[23, 24] Highlighting the benefit of experimental models, the structural changes can be confirmed by histology.[24,25,26] Of importance in evaluating structure /function data is that substantial structural loss occurs before functional loss is detected using existing visual field-methods as has been reported by several groups. Comparing the number of RGCs topographically mapped to specific test points in the visual field in the same eyes among glaucoma patients, a 25% to 35% RGC loss was associated with statistical abnormalities in automated visual field testing.[27] In an observational cohort study estimates of RGC numbers were made in eyes converting to glaucoma versus healthy eyes using a model that combines SAP sensitivity thresholds and retinal nerve fiber layer (RNFL) thickness measurements with spectral domain optical coherence tomography (SD-OCT). [28] Compared with the average number of RGCs in the healthy group, glaucomatous eyes had an average RGC loss of 28.4%. [29] In a prospective cross-sectional study using automated perimetry (Humphrey) field analyser and spectral domain OCT (Cirrus) HD-OCT, a structural loss of ~17% was necessary for functional loss to be detectable.[30] Also, structure/structure and structure/function relationships can change with age as well as glaucoma status.[31]

Pathologic changes noted in glaucoma include the ONH, RNFL and macular (ganglion cell-inner plexiform layer) deficits described above as well as atrophy of the lateral geniculate nucleus (LGN) and visual cortex, which includes layer shrinkage and reduced neuron size and numbers.[32] Experimental models of glaucoma have established the correlation between axon size, number of remaining axons and LGN atrophy[33, 34] LGN atrophy may have potential as a biomarker of visual system injury or glaucoma progression in some patients, especially those with media clarity issues.[35, 36]

Another potential biomarker for glaucoma involves imaging apoptosis of RGCs. Several systems are in development, hoping to identify early cellular degeneration; perhaps even before permanent vision loss occurs. One system uses a wide-angle confocal laser scanning ophthalmoscope (cLSO) and fluorescently labeled annexin V to non-invasively visualize single retinal cells undergoing apoptosis in vivo. This has been given the acronym DARC (Detection of Apoptosing Retinal Cells).[37] A series of in vivo studies using experimental models has been performed using DARC technology to evaluate RGC apoptosis.[38] A second system in development for serial, non-invasive imaging of apoptosis is TcapQ488, which uses a cell-penetrating caspase- activatable peptide probe.[39] Highly specific uptake by RGCs was noted following intravitreal injection of fluorophores conjugated to a modified cell-penetrating peptide sequence. Subsequent localization of apoptosing cells using retinal flat mounts from a rat model of NMDA-induced RGC degeneration helped validate the technology.[40, 41] The results from both imaging systems demonstrate the potential of this type of technique; clinically for direct assessment of retinal ganglion cell health in neurodegenerative diseases such as glaucoma and Alzheimers, but also in clinical trials to provide an assessment of the potential neuroprotective effects of novel drug candidates and their therapeutic efficacy. The development of a novel clinical endpoint would help fill an unmet need in glaucoma research and the development of therapeutics.[42]

Advances in imaging instrumentation have facilitated the development of new models aimed at understanding the etiology of glaucomatous pathologic changes in the lamina cribrosa[43] and clinical correlates of those changes.[44] Trabecular meshwork (TM) changes in glaucoma are well documented histologically.[45, 46] Imaging technologies are being developed to quantify TM change serially and non-invasively, aiming to develop metrics for what constitutes meaningful change in glaucoma.[47, 48]

Glaucoma is a disease with multifactorial mechanisms. Advances in diagnostic instrumentation and out understanding of the pathology of the disease will benefit patients. An individualized treatment approach will result in improved patient outcomes.

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CME ANSWERS

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THE ROLE OF IOP IN GLAUCOMA

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LEARNING OBJECTIVES

1. Describe the evolving role of IOP in relation to primary open-angle glaucoma
2. Measure the relative strength of IOP as a risk factor for glaucoma development and progression

CME QUESTIONS

1. The size of the general population with intraocular pressure of 21 mmHg or less is greater than the population with intraocular pressure 22 mmHg or higher by how much?

   a. 3 to 4 times
   b. 6 to 8 times
   c. 10 to 12 times
   d. 15 to 17

2. According to data from the Early Manifest Glaucoma Trial, every mmHg higher IOP corresponds to higher risk of glaucoma progression at what level:

   a. 0%
   b. 3%
   c. 11%
   d. 16%

3. True/False: The absolute risk reduction for developing glaucoma achieved with treatment of elevated IOP in ocular hypertension is of the same magnitude as the absolute risk reduction of a cardiovascular event achieved with treatment with statin therapy.

KEYWORDS

1. Intraocular Pressure
2. Primary Open-angle Glaucoma
3. Risk Factor
4. IOP Variability
5. Glaucoma Progression

INTRODUCTION

That IOP is intricately linked with primary open-angle glaucoma is well established. A historical perspective on the evolving role of IOP as synonymous with glaucoma to being a risk factor for glaucoma is explored. The predictive ability of IOP as a risk factor for POAG is calculated and compared with risk factors for cardiovascular disease, a disease for which there exists considerable data.

That intraocular pressure (IOP) and primary open-angle glaucoma (POAG) are intricately linked is well established. Yet, the IOP- POAG relationship has arguably been the subject of more controversy than any other topic in glaucoma, and our understanding of it continues to evolve. Several decades ago, IOP, specifically 21 mmHg, defined glaucoma. Subsequent observations that some patients continue to lose vision despite well-controlled IOP has led to the assertion that IOP independent mechanisms may play a role in the glaucomatous process. Recent research on optic nerve related factors that are potentially involved in the glaucomatous process lends further credence to this view. As our knowledge of pathogenic mechanisms in glaucoma advances, IOP will undoubtedly be considered to play a less prominent role than in the past. Thus, in addition to IOP-lowering strategies, novel therapies to protect retinal and central visual system neurons are increasingly being investigated.

IOP had historically been considered the primary therapeutic endpoint. It has been argued that IOP is not in itself the primary variable of interest but should rather be considered as an intermediary factor that may affect the endpoint[1]. Glaucoma comprises a continuum of disease states from undetectable disease, characterized by ganglion cell death and axonal loss at one end of the spectrum, to total loss of sight at the other end. Since the outcome of importance to the patient is symptomatic disease, particularly blindness, visual functioning is beginning to supplant IOP as the primary indicator of success or failure of treatment.

Despite shifting perspectives on IOP, what remains incontrovertible is that IOP is the most important risk factor for glaucoma development and progression. Population-based studies have repeatedly and consistently documented that elevated IOP is associated with higher prevalence and incidence of POAG[2,3,4,5,6,] that progressively higher IOP is

associated with progressively greater risk of POAG[7], and that elevated IOP is associated with greater progression of POAG[8].

The fact that a substantial proportion of subjects with POAG have initial IOPs below 21 mmHg does not diminish the strength of this IOP-POAG relationship. The size of the general population with IOPs less than or equal to 21 mmHg is ten to twelve times the size of the population with IOPs greater than 21 mmHg[9]. Because of the sheer size of the at-risk population with IOPs in this lower range, this group can be expected to have a considerable number of subjects with glaucoma. However, according to data from the Baltimore Eye Survey, the relative risk of having glaucoma in eyes with higher IOPs (22 mmHg or higher) was 8.6 times that of eyes with lower IOPs (21 mmHg or lower)[9]

A causal relationship between IOP and glaucoma would be strengthened if incidence data were used rather than prevalence data. Unfortunately, only a few population-based incidence studies have been attempted due to the large cohorts and long follow-up periods necessary to obtain a sufficient number of newly diagnosed cases to ensure valid estimates. The Rotterdam Eye Study found the risk of developing POAG increased by 16% per 1 mmHg in highest baseline IOP; the risk of developing glaucoma was three times higher if baseline IOP was greater than 21 mmHg[10]. The Barbados Eye Study also found baseline IOP to be a significant risk factor for subsequent development of POAG[11]. Causal inference is also strengthened considerably when a dose- response relationship can be demonstrated. The Collaborative Glaucoma Study demonstrated that among subjects with baseline IOP of less than 16, 0.8 percent subsequently developed glaucoma; the corresponding percentages for those with baseline IOPs of 16-19 mmHG, 20-23 mmHg, and 24 mmHg and higher were 1.4, 3.1, and 8.4[12].

Elevated IOP is not only a glaucoma risk factor but also a prognostic factor for glaucoma progression. In fact, this assumed relationship between elevated IOP and glaucoma progression has been the underpinning upon which glaucoma treatment has historically been based. A number of studies, most notably the Early Manifest Glaucoma Trial (EMGT)[13], have provided scientific validation. The EMGT followed a cohort of patients with early glaucoma in a clinical trial in which patients were randomized to IOP lowering treatment or no treatment. One finding from the study was that each higher millimeter of mercury of IOP on follow- up was associated with an approximate 10% increased risk of glaucoma progression. That every millimeter of mercury of IOP lowering reduces the risk of glaucoma progression by some specific percentage amount that is quantifiable over the entire spectrum of IOPs has been called into question by Wilson and Singh[14]. Nonetheless, that there is an association between elevated IOP and glaucoma progression is not contested and is confirmed by other studies.

Because IOP is the only known risk factor amenable to modification, it can be argued that it is the most important risk factor for POAG. One way to assess the strength of a risk factor is to calculate the treatment effect using measures such as *Absolute Risk Reduction* (ARR) and *Relative Risk Reduction* (RRR). Absolute risk reduction is the absolute difference in outcome between the control and treatment groups: untreated group disease risk minus the treatment group disease risk. Relative risk reduction measures how much the risk is reduced in the treatment group compared with the untreated group. It is measured as one minus the relative risk, in which relative risk equals the treated group disease risk (numerator) over the untreated group disease risk (denominator). Both absolute risk and relative risk measures have their advantages and disadvantages; in both, the higher the number the more effective the treatment.

Risk calculations have routinely been used with cardiac risk factors for predicting cardiac events. Although the epidemiology of POAG is not nearly as advanced as that of cardiovascular disease, some useful lessons can be learned from considering assessment and prevention strategies developed for coronary heart disease. For example, reduction of plasma low-density lipoprotein cholesterol levels has long been a therapeutic goal to prevent coronary mortality and morbidity, and a clinical trial evaluated the three year risk of a cardiovascular event with or without statin therapy[15]. Using data from recently completed glaucoma clinical trials, the five year risk of glaucoma development (Ocular Hypertension Treatment Study)[16] and the six year risk of glaucoma progression (Early Manifest Glaucoma Trial)[13] with and without treatment can be calculated and compared with the statin therapy trial.

Statin trial (3 yr)	12.5%	49%
OHTS (5 yr)	5.1%	54%
EMGT (6 yr)	17%	27%

Because of the different time lines, a direct comparison is difficult. However, it is clear that the greatest reduction in risk is with the statins in cardiovascular disease. Over a three year period, for every 100 subjects who received statin in the trial, 12.5% averted a bad cardiovascular event (ARR). Also, a cardiovascular event was reduced by 49% in the statin group compared to the control group (RRR). Nonetheless, the benefit from reduction of IOP is substantial for both the development of glaucoma and progression of glaucoma. Over a six year period, for every 100 subjects who received IOP lowering treatment, 17% had progression of glaucoma averted; over a five year period, the development of glaucoma was reduced by 54% in the IOP lowered treatment group versus non-treatment group.

A number of questions regarding the IOP-POAG relationship remain unanswered. Among these is the age-specific trend of intraocular pressure among the Japanese population, in which a very low prevalence of ocular hypertension and very high prevalence of POAG with IOPs in normal range are noted. Most American and European population-based studies that measured IOP have demonstrated an increasing IOP with increasing age. Though the magnitude of the IOP increase with age is small, this positive IOP-age correlation is at least consistent with the positive POAG-IOP correlation noted universally. However, several population-based studies have shown a negative correlation between IOP and age among the Japanese[17,18]. Population differences in potentially confounding factors such as blood pressure and body mass index have been postulated, but reasons for this peculiarity are not well understood. This suggests that there are other factors at play in the glaucomatous process besides IOP, and that these other factors may be relatively more important than IOP in causing glaucoma in elderly Japanese.

From initially defining glaucoma to defining glaucoma treatment success to being an intermediate factor for vision-related glaucoma endpoints, IOP's role in glaucoma has become increasingly limited. The large numbers of patients with POAG and normal IOP, particularly among the Japanese, have even called into question the primacy of IOP in the pathogenesis of glaucoma. Focus on other factors such as decreased ocular perfusion pressure and ischemia, excitotoxicity, neurotrophic factor deprivation, oxidative stress, immune modulation, and exposures to potential biomarkers such as nitric oxide and endothelin have increased over recent years. Undoubtedly, the actual mechanism of glaucomatous damage is multifactorial and IOP is likely only one of many contributory factors.

Yet, IOP is unequivocally an important risk factor for the development of glaucoma and it is strongly prognostic of glaucoma progression. Lowering of IOP currently remains the only therapeutic option for mitigating the visual deficits associated with advancing disease, and the effect of treatment is substantial. Though diminished, IOP's role in glaucoma is firmly established and the two will forever be inextricately linked.

CME ANSWERS

1. c. 0 to 12 times
2. c. 11%
3. b. False

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PHENOTYPIC DIFFERENCES IN NORMAL VS HIGH TENSION GLAUCOMA

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LEARNING OBJECTIVES

1. Describe differences between normal tension glaucoma and primary open angle glaucoma in optic nerve and visual field findings
2. Cite studies reporting on optic nerve and visual field changes in normal tension and primary open angle glaucoma
3. Define the broad overlap in findings in most patients with normal tension glaucoma and primary open angle glaucoma

CME QUESTIONS

1. Focal Notching of the optic nerve is
    a. Always associated with normal tension glaucoma
    b. More often associated with primary open angle glaucoma
    c. Found in normal tension and primary open angle glaucoma
    d. Indicative of a non-glaucomatous optic neuropathy
    e. Rarely seen in glaucoma
2. Visual field defects in normal tension glaucoma
    a. May be more focal in some cases than in primary open angle glaucoma
    b. May be closer to fixation in some cases than in primary open angle glaucoma
    c. Are often identical to those seen in primary open angle glaucoma
    d. All of the above
    e. None of the above
3. Normal Tension Glaucoma and Primary Open Angle Glaucoma
    a. Are easily distinguished in individual cases based on optic nerve findings
    b. Are easily distinguished in individual cases based on visual field findings
    c. Are distinct entities with little overlap in research studies on optic nerve and visual field parameters
    d. Have not been adequately studied and compared in regards to their associated optic nerve and visual field findings
    e. Show broad overlap clinically and in studies, but have slight differences in the frequency of various findings

KEYWORDS

1. Normal Tension Glaucoma
2. Primary Open Angle Glaucoma
3. Optic Nerve
4. Visual Field

INTRODUCTION

Normal tension glaucoma (NTG) and high tension open angle glaucoma (HTG), are associated with characteristic patterns of optic nerve findings and associated patterns of visual field loss. In the past, most clinicians viewed NTG and HTG as distinct entities, with separate underlying pathophysiologies and often different clinical presentations and courses. Optic nerve and visual field findings in NTG have been reported to be different than those in HTG. There has been increasing recognition of the shared features NTG and HTG. In more recent years, there has been a trend to consider these two entities as part of a spectrum of glaucoma with overlapping pathophysiology and clinical characteristics.

NTG and HTG are both primary open angle glaucomas, without evidence of other associated pathologies. Thus the clinical findings, other than the elevated pressure in HTG, are confined to the optic nerve and visual field. Both NTG and HTG are characterized by optic nerve cupping, notching, larger disc size, RNFL loss, peripapillary pigment changes, lamina cribrosa thinning or defects, and disc hemorrhages. Visual field findings for both may include the full range from nasal step to arcuate defects, to central and temporal islands. However, some researchers have found significant differences in the associations of each of these with these two clinical entities, NTG and HTG.

Larger optic nerve size has been associated with a greater risk of the development of open angle glaucoma in some but not all studies.[1] Disc size was not associated with the development of HTG in a subset of subjects in the Ocular Hypertension Treatment Study[2] In the Blue Mountains Eye Study, significant differences were not found between the disc size in NTG and that in HTG.[3] However, in some studies in Asian populations larger discs were found in NTG vs HTG.[4, 5] In another study of Japanese patients this was not found.[6] In all of these studies, the range of disc sizes of subjects with NTG significantly overlaps that of HTG; there is no single value that serves to separate these populations by disc size.

Concentric cupping is another feature seen in glaucomatous eyes. Concentric cupping has been reported to be more prevalent in HTG than NTG.[7, 8] Focal thinning of the neuroretinal rim has been reported to be more common in NTG.[9] In this study of patients matched for degree of VF loss, inferior or inferotemporal thinning was more pronounced in the NTG group. In each of these studies, both focal thinning and concentric cupping were seen in individual eyes in both group.

Studies of the optic nerve by confocal laser scanning, confocal scanning laser ophthalmoscopy (Heidelberg Retinal Tomography (HRT)) not shown differences between NTG and HTG in some studies[6], however RNFL loss was found to be greater in NTG by HRT in two studies.[10, 11] It is worth noting, however, that RNFL loss as measured by the HRT is derived from topographic data, and is not a direct measure.

More recently, spectral domain optic coherence tomography (SD-OCT) has shown differences in NTG vs controls and HTG. Firat et al found greater macular thickness and ganglion cell complex values in the NTG group, even in early field loss similar among the HTG and NTG groups.[12] However, there was broad overlap in the range of values of all parameters. In a study by Kim et al, comparing SD-OCT of the nerve head and macula in about 50 normal, HTG, and NTG eyes, no differences were seen in optic nerve head measures. Differences were seen in the macular thickness and ganglion cell complex measures suggesting more focal loss in NTG and diffuse loss in HTG. These findings were of high statistical significance, but with broad overlap of the HTG and NTG groups.[13]

Peripapillary pigment changes in the retina pigment epithelium has been correlated to progression in HTG but not NTG.[14] In this large prospective study of 289 patients with HTG and 178 patients with NTG followed on average 4 years, a larger area of beta zone atrophy was associated with progression in the HTG group but not the NTG group. Disc hemorrhage was a factor associated with progression in the NTG group.

Several studies have looked at the lamina cribrosa with enhanced depth imaging in HTG and NTG. NTG eyes with disc hemorrhage have been reported to have thinner lamina cribrosa in the mid superior and mid inferior regions compared to normal and HTG eyes.[15] In another study of 148 eyes, focal lamina cribrosa defects were associated with NTG and more frequent disc hemorrhages.[16]

Disc hemorrhages have been associated with progression in a multitude of prospective studies, including the Collaborative Normal Tension Glaucoma Study, the Canadian Glaucoma Study, the Early Manifest Glaucoma Treatment Study, and others (eg17). Additionally, some studies have found disc hemorrhages to be more common in NTG vs HTG.[18, 19]

Visual field defects are a hallmark of glaucoma, and, of course, follow a variety of patterns related to optic nerve damage. Focal defects have been reported to be more common in NTG than HTG.[20, 21] In the study by Hitchings et al., 30 eyes with NTG were compared with 30 eyes with HTG in terms of location and steepness of defect edge on Goldmann perimetry. More NTG eyes had steeper defects and defects closer to fixation. However, many eyes with HTG had steep sided defects close to fixation as well. In a similar but larger study (79 NTG eyes, 106 HTG eyes) Caprioli et al. also found NTG eyes to have more focal defects, closer to fixation on automated perimetry.[22] Chauhan et al. studied 40 pairs of eyes with NTG or HTG were compared, and the NTG eyes had more clusters of normal points, suggesting more focal defects on average.[23]

In summary, NTG and HTG are both characterized by typical optic and visual field findings. There is ample evidence showing significant differences in the patterns of nerve and field damage, with the most common being more focal nerve and field damage in NTG compared to HTG. Statistically significant differences between the averages of these traits for the two populations have been reported, in some but not all studies. Additionally, the range of findings for each these entities is 80-90% shared with the other. Thus, there is great overlap in the features of these two conditions, such that most patients fall in a middle zone in which their findings could be associated with either condition. The appearance of the optic nerve or visual field in any one patient cannot be reliably distinguished as normal or high tension glaucoma in the vast majority of cases.

CME ANSWERS

1. c
2. d
3. e

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IS NORMAL TENSION GLAUCOMA DIFFERENT THAN HIGH TENSION GLAUCOMA? VASCULAR AND AUTONOMIC DYSFUNCTION

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LEARNING OBJECTIVES

1. Define the nature of vascular dysfunction in primary open angle glaucoma across the spectrum of intraocular pressure
2. Describe what is meant by autonomic dysfunction as it relates to primary open angle glaucoma across the range of intraocular pressure

CME QUESTIONS

1. All of the following aspects of endothelial cell dysfunction may be important in primary open-angle glaucoma pathogenesis **except**:
    a. Increased endothelin-1 production
    b. Impaired nitric oxide signaling
    c. Sub-vascular endothelial plaque formation
    d. Reduction of circulating endothelial progenitor cells
2. Which of the following vascular beds exhibit abnormalities in primary open-angle glaucoma?
    a. Brachial artery
    b. Cerebral vasculature
    c. Retinal and choroidal vasculature
    d. Nail fold capillaries
    e. All of the above
3. Which of the following statements about autonomic dysfunction in primary open-angle glaucoma is true?
    a. Excessive sweating is a well-documented aspect of primary open-angle glaucoma
    b. Autonomic dysfunction is specific to normal-tension glaucoma and is not seen in high-tension variant of primary open-angle glaucoma
    c. Intraocular pressure is not under autonomic nervous system control
    d. An important feature of autonomic dysfunction in primary open-angle glaucoma is the reduced variability in heart rate.
    e. Normal tension glaucoma patients have a more profound dip in nocturnal blood pressure compared to age-matched controls

KEYWORDS

1. Primary Open-Angle Glaucoma
2. High-Tension Glaucoma
3. Normal–Tension Glaucoma
4. Vascular Dysfunction
5. Autonomic Dysfunction

INTRODUCTION

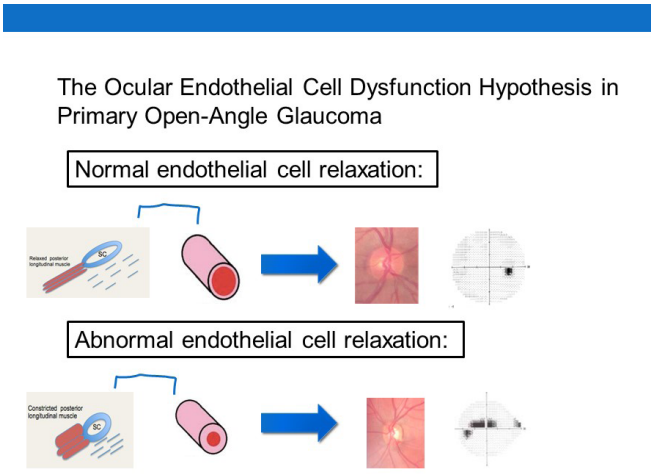
Primary open-angle glaucoma (POAG) is a progressive optic neuropathy that is often arbitrarily stratified by the intraocular pressure (IOP) level associated with initial damage into high-tension glaucoma (HTG) and normal–tension glaucoma (NTG) subtypes. Patients with both POAG subtypes exhibit a variety of ocular and non-ocular vascular abnormalities and there is no evidence these abnormalities predominate in one subtype or the other. Interestingly common genetic variation in *NOS3* and the *CAV1/CAV2* genomic regions, which code for proteins involved in setting vascular tone, are associated with POAG but these markers seem to stratify with POAG subtypes by sex or pattern of initial visual field loss. Overall it is clear that there is also cardiovascular autonomic dysfunction in HTG and NTG but it is unclear if this dysfunction is more common in NTG compared to HTG. It is largely unknown if other physiologic processes that are under autonomic control are abnormal in POAG. Overall POAG is likely a heterogeneous disease but stratifying cases by IOP level associated with initial optic nerve damage may be less useful than using other endophenotype approaches. Embracing the evidence suggesting systemic endothelial and autonomic dysfunction are operative in POAG will help move beyond an IOP-centric view of the disease and facilitate "tearing down the wall" that divides treating physicians and a better understanding POAG pathogenesis.

In primary open angle glaucoma (POAG), there are no obvious anterior segment abnormalities and the filtration angle is physically open but the optic head is excavated and the neuroretinal rim is eroded. There are no obvious clinical clues as to why the intraocular pressure (IOP) might be elevated in the subset referred to as high-tension

glaucoma (HTG) cases. Furthermore, it is unclear why optic nerve pathology develops in patients whose IOP is in the statistical normal range (the so called normal-tension glaucoma (NTG) cases). The ultimate goal in POAG is to define the disease in terms of biochemical pathways as opposed to describing it as an IOP-related optic neuropathy without obvious secondary cause. It is likely that the term POAG encompasses several disease mechanisms produced by distinct biochemical pathways. On an interim basis, it is reasonable to stratify POAG into HTG and NTG subtypes and ask if candidate disease mechanism are operative at lower or higher IOP at presentation. In fact, from an experimental perspective, it makes sense to first compare NTG patients to controls with comparable IOP in order to explore whether any putative mechanism makes the optic nerve vulnerable to degeneration in POAG. Here we will discuss whether two pathophysiologic processes – vascular dysfunction and autonomic dysfunction – are related to POAG stratified by the IOP level associated with optic nerve degeneration.

VASCULAR DYSFUNCTION IN POAG

Broadly speaking, vascular dysfunction refers to an inability of endothelial cells to transmit cellular and chemical signals from luminal surfaces to nearby tissues in a physiologic manner. Normally endothelial cells function to maintain normal vascular tone but they also play a role in immune processes, platelet adhesion and other functions. One hypothesis is that POAG is categorized by impaired endothelial signaling between both: a) the inner wall Schlemm's canal endothelial cells as well as endothelial cells located in the ciliary body and the posterior longitudinal muscle that helps to set outflow resistance and b) the ocular vascular endothelial cell and underlying luminal smooth muscle for vessels that supply the RGCs (**Figure 1, see below**). This hypothesis could explain why POAG can occur across the spectrum of IOP but it does not consider the role of systemic endothelial cell dysfunction in the disease.



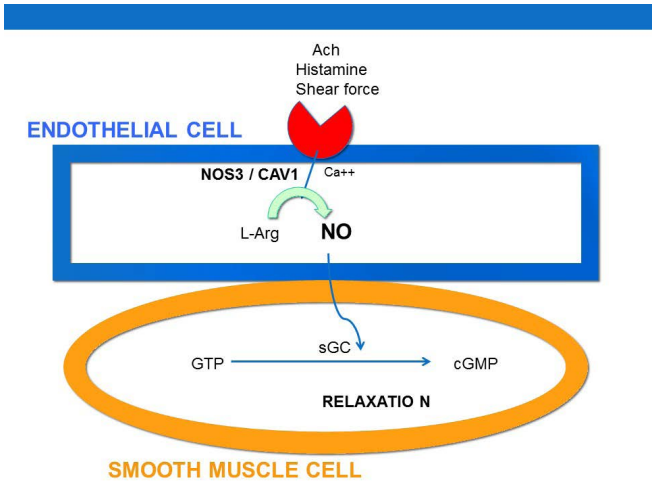
(Figure 1)

Figure 1: The ocular endothelial cell dysfunction hypothesis in primary open-angle glaucoma (POAG). The outflow pathway contains classical vascular endothelial cells in the ciliary body that contributes to setting tone in the outflow pathway while the retina is rich in vessels that supply the optic nerve and retinal ganglion cells. When endothelial cell function is normal, as illustrated in the upper panel, vascular endothelium can transmit signals that cause posterior longitudinal smooth muscle relaxation and low resistance in the outflow pathway. Furthermore retinal vessels can dilate as needed to supply a healthy optic nerve. When endothelial cell function is impaired, as illustrated in the lower panel, there can be simultaneous constriction of posterior ciliary muscle and retinal / optic nerve vasospasm that contributes to glaucomatous optic neuropathy and visual field loss. This hypothesis allows for glaucomatous optic neuropathy to occur across a spectrum of IOP on the basis of vascular endothelial cell dysfunction.

What is the evidence for impaired endothelial cell dysfunction in POAG and what are biological mediators of this impairment? A pharmacologic intervention study in untreated NTG patients found that forearm blood vessels failed to dilate in the presence of exogenous acetylcholine.[1] These findings suggest there is a generalized abnormality of vascular endothelium in POAG. Various researchers studied flow-mediated vasodilation in the brachial artery and found that both HTG and NTG patients had impaired responses compared to controls.[2-4] One group provided evidence that impaired flow mediated vasodilation was related to reduced circulating endothelial progenitor cells, which are a small group of cells partially derived from the bone marrow that serve to replace and repair the endothelial cell lining.[3] Evans et al compared the changes in retrobulbar ocular blood flow in POAG patients with normal subjects during supine and upright posture.[5] They concluded that posture change exposes a vascular autoregulatory abnormality in the vessels distal to the central retinal artery. Feke et al confirmed these results in HTG and NTG cases.[6,7] In fact, in open-angle glaucoma (OAG), there is evidence for vascular dysregulation in the choroidal circulation,[8,9] the optic nerve head circulation,[10,11] the central retinal artery,[12] and the perifoveal macular capillaries.[13] In fact there is evidence that this vascular dysregulation extends to the cerebral vasculature.[14]

Since compromised endothelial cell signaling plays an important role in POAG, an important question regards what are the biological mediators of this impairment? The answer to such question could translate into more rational treatments for POAG. There is compelling evidence that impaired nitric oxide (NO) signaling plays an important role in the endothelial cell dysfunction in POAG and this evidence comes from human genetics and laboratory studies. One study with no controls found no difference in two functional *NOS3* (the gene coding for the enzyme responsible for NO generated by vascular endothelium) between HTG and NTG cases.[15] On the other hand, several research group[16-23] that have evaluated genetic polymorphisms in *NOS3* have implicated this system in POAG pathogenesis. In fact, the evidence is fairly strong

that at least one *NOS3* variant (-786 C/T) is associated with HTG and that the association is particularly strong in women. In addition, polymorphisms in the genomic region corresponding to the caveolin genes, which code for proteins that reciprocally control NOS3 activity in endothelial caveolar membranes,[24] are also associated with POAG.[25] The association between *CAV* variants and POAG was particularly strong for cases with early paracentral vision loss. While one study found that the maximum untreated IOP in early paracentral visual field loss cases (21.6 mm Hg) was lower than in early peripheral visual loss cases (28.3 mm Hg), it was still above the statistical norm.[26] Another study did not find more paracentral visual loss in NTG versus HTG, suggesting there is a range of IOP at presentation for this pattern of glaucomatous damage.[27] When soluble guanylate cyclase (sGC is the intracellular receptor for NO) is knocked out in a murine model, IOP increases nominally (~1-2 mm Hg), there is abnormal retinal vascular reactivity to NO donators, and optic nerve degeneration ensues.[28] Interestingly, a subset of female POAG patients with early paracentral visual loss tended to harbor a polymorphism (rs11722059) in the genomic region between *GUY1A3* (codes for the sGC alpha 1 subunit of sGC) and *GUY1B3* (codes for the sGC beta 1 subunit of sGC). This locus is in high linkage disequilibrium with another *GUCY1A3 / GUYC1B3* variant (rs13139571) linked to blood pressure in a large European consortium.[29] *What emerges is that a biochemical pathway that starts with activation of acetylcholine receptors on endothelial cells and concludes with smooth muscle cell relaxation plays an important role in POAG pathogenesis* **(Figure 2, see below)**.

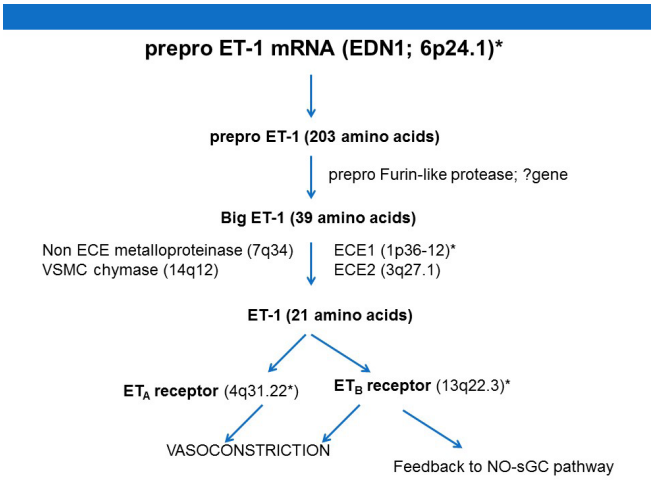


(Figure 2)

Figure 2: Simplified schematic of endothelial cell mediated smooth muscle cell relation mediated by nitric oxide. The vascular endothelial cell (blue) receives signals which activate NOS3 leading to formation of nitric oxide (NO). NO permeates into the smooth muscle cell (orange) and binds to sGC to mediate relaxation via biomarkers not shown.

Endothelin-1 (ET-1), a 21 amino acid peptide made by vascular endothelium throughout the body including tissues relevant to glaucoma (non-pigmented ciliary epithelium, ciliary body muscle and iris[30]), is a potent vasoconstrictor and serves to balance endothelial cell NO mediated vasodilation. Considerable interest in ET-1 emerged when perineural optic nerve delivery in rabbits produced optic nerve excavation and retinal ganglion cell loss without elevated IOP.[31] However excitement that ET-1 might be a NTG biomarker was curbed when appropriately designed studies found that plasma ET-1 levels were not necessarily higher in NTG compared with HTG or CACG.[32-34] In fact not every study shows that ET-1 levels are higher in glaucoma subtypes versus controls,[33,34] but ET-1 is abluminally directed from the endothelial cell to the underlying smooth muscle and assessing serum levels may not be sufficiently sensitive to understand the role this peptide plays in glaucoma pathogenesis. Nonetheless interventional studies with NTG patients clearly implicate the endothelin processing system in POAG pathogenesis. For example the physiological increase in ET-1 plasma levels after shifting from supine to standing was absent in NTG patients.[33] After cold-pressor challenge associated with donning a cooling head vestment for 30 minutes, POAG patients experienced a 34% increase in plasma ET-1 levels compared to only a 7% increase in controls.[35] Patients with progressive POAG had higher ET-1 levels compared to those regarded as having stable disease.[36] Interestingly, while untreated NTG patients had a normal systemic vasoconstriction when exposed to intra-arterial ET-1, intra-arterial injection of a selective endothelin A (ET_A) receptor antagonist (BQ123) produced less forearm vasodilation than in controls.[37] This is a critical experiment because there are two endothelin receptors—ET_A and ET_B – and antagonism of ET_A unmasks ET_B related activation of the NO-sGC pathway that produces vasodilation. Therefore, antagonizing ET_A could expose an impaired NO-mediated response via ET_B activation, although other explanations must also be considered such as increased ET_B- receptor mediated vascular tone or pre-existing poor ET_A-receptor mediated tone. The cardiology literature indicates that ET_A-receptor antagonist-mediated vasodilation is inhibited by blocking NO synthesis.[38] Overall interaction with ET_A and ET_B receptors is intertwined with NO production, which is key for physiologically appropriate vascular regulation. It is clear that endothelin processing is abnormal in POAG, especially in NTG patients, but the problem is complex and may point more to NO than to endothelin itself. To complicate matters further the problem with NO may involve how NOS3 interacts with caveolin as retinal blood flow tends to respond passively to posture change in POAG.[6,7] The possibility that genes involved in endothelin processing (see **Figure 3 on next page** for the ET-1 processing) are related to POAG has not been fully explored. The available studies show no relation between various endothelin processing variants and POAG after controlling for multiple comparisons but not every possible gene involved has been studied and small sample sizes could obscure real associations (see **Figure 3 on next page** for references regarding the relation between endothelin processing genes and POAG). This is in contrast

to the evidence of replication for associations between a functional variant in the NOS3 promoter region (-786C), which is adversely associated with HTG in women.[16,22,23] and between CAV1/CAV2 variants and POAG.[39,40]



(Figure 3)

Figure 3: Endothelin-1 (ET-1) processing with chromosomal locations for processing enzymes. ET-1 is formed prepro ET-1 which is cleaved by a protease to big ET-1 which in turn is converted to the active 21 amino acid peptide that binds either ET_A or ET_B receptors. Receptor binding triggers vasoconstriction but ET_B receptor activation also leads to compensatory endothelial cell relaxation. *Common gene variants in ET-1, ECE1, ET_A and ET_B receptors have not been associated with POAG after accounting for multiple comparisons.[72-74]
Abbreviations: ET-1; ECE= endothelial converting enzyme

How do we reconcile the impaired NO signaling paradigm in POAG with the observed increased disc hemorrhages which represents an important biomarker of glaucoma progression? First we must revisit optic nerve anatomic features that would make it vulnerable to damage in the face of vascular dysregulation. It is important to remember that central retinal artery occlusion produces selective retinal ganglion cell layer dropout, a feature shared with glaucoma. Furthermore a subset of POAG patients with paracentral loss will develop fairly profound loss of retinal sensitivity in a discrete visual field zone resembling vascular injury (see **Figure 1**). The optic nerve can be considered a neurovascular pedicle where vessels make acute turns as they emerge onto the retinal surface. This creates opportunity for large shear forces to develop in the smaller vessels if significant alterations in blood flow develop. If shear forces exceed the loading capacity of the vessel wall, then the vessel will rupture and bleed. Second, the scleral ring of Elschnig serves to create a compartment syndrome in the pre-laminar portion of the optic nerve head. Thus optic nerve hemorrhages can act like space occupying lesions and compress RGC axons in the optic nerve head. Simple positional changes such laying down prompts physiologic increases in ocular perfusion pressure (blood pressure minus IOP) of ~ 30 mm Hg.[6] Such hemodynamic changes must be accompanied by changes in vascular tone that keep ocular blood flow relatively constant. Studies of postural changes in ocular blood flow in POAG patients suggest that these vessels behave like passive sieves and that blood flow can paradoxically increase as much as 100% when patients recline for 30 minutes.[41] It is suspected that some complex interaction between ET-1, NO and CAV1 is responsible for this aberrant retinal hemodynamic response to posture change. Such increases in retinal blood flow could translate into the kind of shear forces necessary to induced hemorrhaging in lamina cribrosa capillaries. In the Ocular Hypertension Treatment Study,[42] the Normal Tension Glaucoma Study[43] and the Early Manifest Glaucoma Study,[44] disc hemorrhage was associated with disease progression in multivariable models that also account for IOP. Nonetheless disc hemorrhage does occur in chronic angle closure glaucoma, suggesting that it could also be a secondary event after IOP-induced optic nerve damage.[45] The reason why disc hemorrhages might occur more commonly in NTG than HTG may relate to the fact that there is more of an opportunity to tamponade the micro-bleeding that occurs in HTG cases.

If disc hemorrhages in POAG reflect the workings of an impaired NO signaling system, then stopping disc hemorrhages should have therapeutic effect in this disease. Interestingly the Low Pressure Glaucoma Treatment Study[46] found that brimonidine, an alpha 2 agonist that has vasomodulatory activity mediated through nitric oxide signaling,[47] was effective in reducing visual field loss in NTG patients. Brimonidine use was also associated with less frequent occurrence of disc hemorrhages.[48] The counter view that the study did not demonstrate the neuroprotective effect of brimonidine but rather the deleterious effect of timolol seems unlikely. First the disease progression in the timolol arm of the study (39% in 3 years) was comparable to the untreated arm of the CNTGS (35%).[49] Second, in the EMGT, patients with OAG across the spectrum of IOP achieved neuroprotective benefited from treatment consisting of laser trabeculoplasty plus betaxolol versus observation.[50]

AUTONOMIC DYSFUNCTION IN PRIMARY OPEN-ANGLE GLAUCOMA

The autonomic nervous system (ANS) is housed in the medulla oblongata with the hypothalamus serving as an integrator. The ANS has parasympthetic, sympathetic and enteric arms that controls many bodily functions such as: body temperature, heart rate, breathing rate, perspiration, digestion, salivation, swallowing, coughing, sneezing, vomiting, sexual arousal and function, pupil diameter, and accommodation. The parasympathetic and sympathetic arms of the ANS have been the targets of therapeutic drugs used to treat glaucoma for over a century. The level of IOP may itself be partially controlled by the ANS. In fact, chemical stimulation of the dorsomedial and perifornical hypothalamus where central autonomic regulatory neurons are housed, causes marked rises in IOP.[51] This is interesting

because diurnal variation in IOP is more variable in POAG patients compared to controls.[52] This wider fluctuation in IOP coupled with instability of blood flow regulation probably contributes to POAG, regardless of IOP level. It should be pointed out that the ability to regulate retinal blood flow is not a pure autonomic function; rather, it is partially under local paracrine control (especially in the retina where vessels are not innervated[53]) with a neurovascular component in the retrobulbar optic nerve vessels.

Patients with Familial Dysautonomia (FD) who exhibit a wide array of autonomic function abnormalities uniformly exhibit an optic nerve phenotype. The optic nerve pathology seen in FD predominately involves the maculopapillary bundles, pathologic features shared by some POAG patients (as discussed above) and by patients with mitochondrial disease.[54,55] Another disease with well known vasomotor and autonomic abnormalities is Nail Patella syndrome,[56] a condition that represents a familial form of NTG[57] caused by the *LMX1B* gene.[58] Interestingly common variants in *LMX1B* are linked to both HTG and NTG.[59] At this juncture the link between LMX1B and autonomic dysfunction is not entirely clear. What is quite remarkable is that three cardiovascular autonomic studies shows reduced low frequency heart rate variability in NTG patients versus controls and these changes are not accompanied by dramatically different blood pressure, even during the nocturnal period.[60-63] However, other studies suggest features consistent with cardiac autonomic dysfunction are shared by HTG[64,65] and exfoliation glaucoma patients.[66] The problem of autonomic dysfunction seems inextricably linked to endothelial cell dysfunction in that affected NTG patients with low frequency heart rate variability tend to have paracentral visual defects and concomitant nail fold microvascular abnormalities.[67] Furthermore these patients also tend to have higher plasma ET-1 than age matched controls.[68] Aside from cardiovascular autonomic function, other bodily functions under the ANS have not been well studied in NTG, HTG and age matched controls and this represents a research opportunity in the field glaucoma.

CONCLUSIONS

While one cannot claim that impaired NO and endothelin signaling represents a unifying hypothesis in our understanding of POAG, it does appear to play an important role in disease pathogenesis for both HTG and NTG cases. This discussion highlights the role of genetics in contributing to this process. It is important to point out that sub-endothelial plaque formation (atherosclerosis) is not an aspect of endothelial dysfunction in POAG.[69] Furthermore, patients with POAG do not have increased risk of cardiovascular-related mortality.[70] While studies focused on NTG patients have helped to highlight mechanisms involved in optic nerve degeneration in POAG, these mechanisms are operative in NTG and HTG. More studies with novel alternative stratification of POAG (such as stratifying disease on the basis of pattern of visual field loss) are needed.

The current body of knowledge reviewed here clearly implicates systemic processes in POAG and these processes need to be addressed if we are going to more favorably impact this disease. More study in the fields of genetic epidemiology, immunology and cardiovascular medicine are likely to contribute to an improved understanding of POAG. Hopefully we may someday drop the word primary from POAG and replace it with real descriptors that speak to the multiple etiologies that exist in this condition.

CME ANSWERS

1. c
2. e
3. d

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IS NORMAL TENSION DIFFERENT FROM HIGH TENSION: GENETIC/EPIDEMIOLOGIC FACTORS

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LEARNING OBJECTIVES

1. Identify differences in prevalence of normal-tension glaucoma among glaucoma patients world-wide
2. Recognize genes responsible for early-onset forms of normal-tension glaucoma and high-tension open angle glaucoma
3. Distinguish genes/genomic regions associated with adult-onset normal-tension glaucoma from those associated with adult-onset high-tension glaucoma

CME QUESTIONS

1. What population has the highest percentage of normal-tension glaucoma patients?
2. True/False: Mutations in genes causing familial forms of glaucoma are common.
3. Trud/False: Genes/genomic regions associated with intraocular pressure in population-based studies are also associated with normal-tension glaucoma

KEYWORDS

1. Normal-tension Glaucoma
2. Primary Open-angle Glaucoma
3. Intraocular Pressure
4. CDKN2BAS
5. Choroid Plexus

INTRODUCTION

Epidemiologic and genetic studies suggest that patients with normal tension glaucoma (NTG) have a different set of pre-disposing risk factors compared with patients with primary open angle glaucoma (POAG), high-tension open angle glaucoma (HTG) or ocular hypertension. In particular, Asians (especially Japanese) are at increased risk for NTG compared to other populations. Genetic studies of NTG families as well as NTG case/control samples have identified genes that could influence optic nerve susceptibility. A different set of genetic factors appear to influence risk of high-tension open angle glaucoma. These results suggest that the disease mechanisms underlying NTG may not be the same as those contributing to high- tension glaucoma.

NTG GLOBAL PREVALENCE

NTG prevalence varies widely among different ethnic populations ranging from 92% of the open angle glaucoma patients in the Japanese Tajimi study[1] to 6% of open angle glaucoma patients in an Ethiopian clinic population[2] (Figure 1, References 1-24). Interestingly, NTG prevalence is also higher in Japanese Americans compared to other ethnic groups suggesting that the NTG risk is due to genetic, rather than environmental, factors[25, 26]. NTG prevalence is highest in Asians overall compared to Caucasians of European ancestry and African races[27].

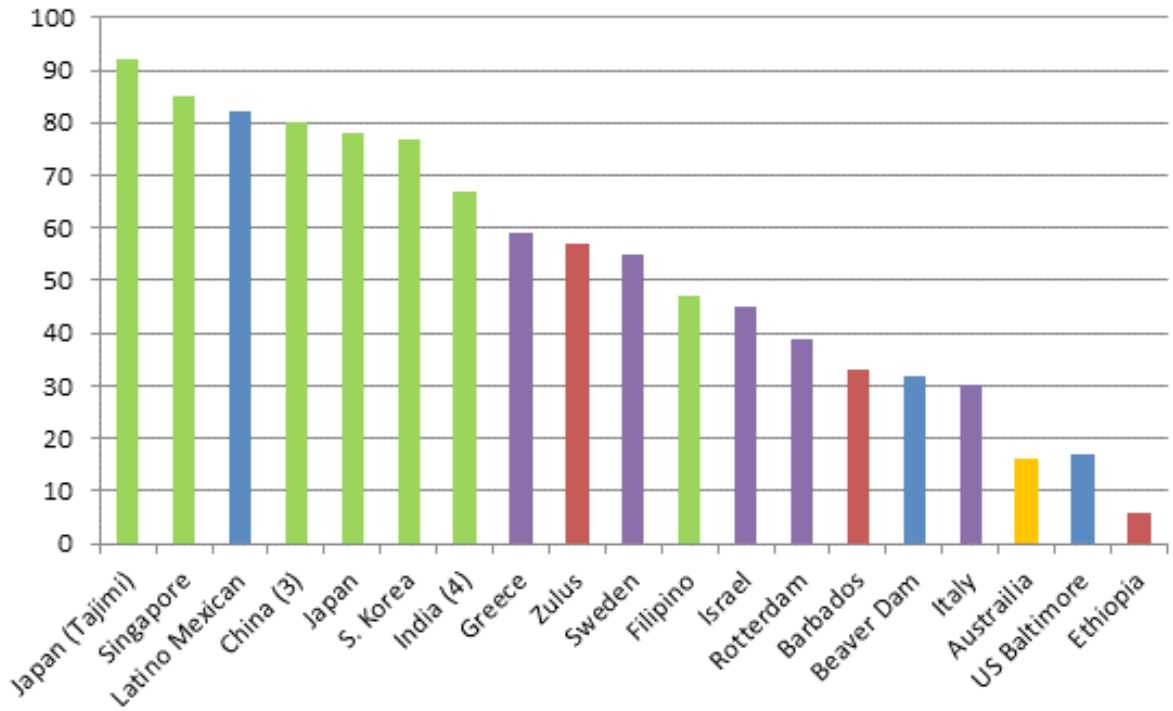

Figure 1. Prevalence of NTG in populations world-wide. The percentage of open-angle glaucoma in each population is indicated on the Y-axis. Results from the Chinese (3 studies) and India (4 studies) were averaged. Bars are colored according to geographic distributions (Green, Asia; Blue, North American; Red, Africa; Purple, Europe; Orange, Australia).

GENETICS OF NTG, HTG, POAG AND IOP

Early-onset open-angle glaucoma (familial NTG and juvenile open-angle glaucoma) is caused by rare mutations in TBK1 and OPTN (familial NTG) and MYOC (juvenile open-angle glaucoma). Although rare, these mutations have large biological effects and directly cause the disease. In contrast, late-onset open angle glaucoma (POAG and NTG) and ocular hypertension have been associated with common variants in a number of genes that individually have small biological effects. While these variants are statistically associated with disease risk they are not 'causative' (Figure 2).

FAMILIAL NTG GENES

A well characterized missense mutation in OPTN (Optineurin) (E50K, Glutamate to Lysine at protein position 50), and duplication of TBK1 (Tank Binding Kinase 1) cause familial normal tension glaucoma[28, 29]. Interestingly these proteins are binding partners and protein-protein interaction is enhanced by the OPTN E50K mutation[30]. Mutant forms of OPTN and TBK1 can influence retinal ganglion cell autophagy[31] or promote apoptosis through the TNFalpha- NFKbeta signaling pathway[32].

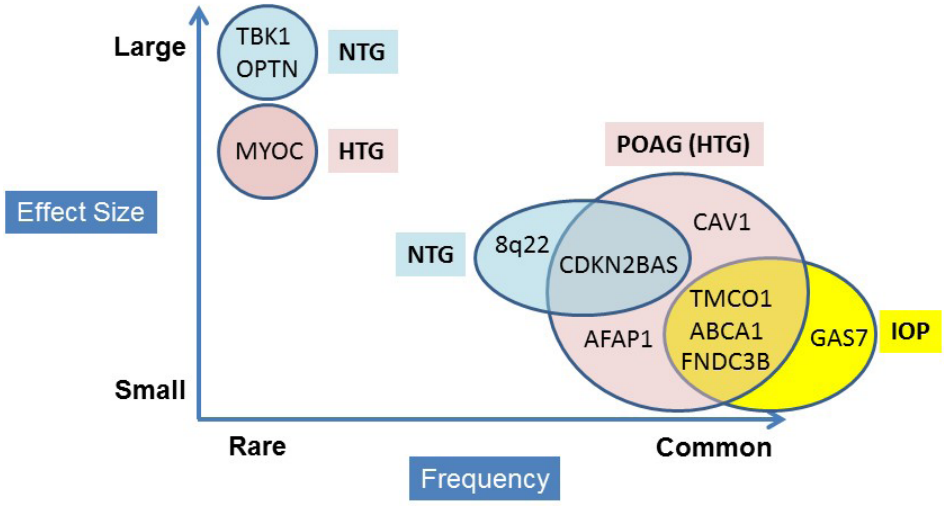

Figure 2. Genetics of Early-onset and Adult-onset primary open angle glaucoma. The relative biological impact (effect size) is shown on the Y-axis and the frequency of the mutation or variant is shown on the X-axis. OPTN and TBK1 mutations cause familial NTG, while MYOC mutations cause familial HTG. CDKN2BAS variants are associated with NTG and POAG; TMCO1, ABCA1 and FNDC3B variants are associated with POAG and IOP; CAV1 and AFAP1 variants are associated with POAG and GAS7 variants with IOP.

MUTATIONS IN MYOC CAUSE FAMILIAL HIGH-TENSION OPEN ANGLE GLAUCOMA

Missense mutations in MYOC (myocilin) cause early-onset (before age 50) autosomal dominant primary open angle glaucoma[33]. MYOC missense mutations cause misfolding of the nascent polypeptide with subsequent endoplasmic reticulum stress. The small molecular chaperone, PBA (sodium 4-phenylbutyrate) can promote secretion of the misfolded protein, relieving ER stress and lowering IOP[34,35].

ADULT ONSET NTG GENES

The NEIGHBOR and GLAUGEN case/control genome-wide associations studies have revealed two genes/ genomic regions associated with the common form of adult-onset NTG in Caucasians with European ancestry[36]. Common variants in the genomic region coding for CDKN2BAS, a long non-coding antisense RNA (also known as ANRIL) are significantly associated with NTG, as well as POAG. This finding has been replicated in a number of populations, including the Japanese[37]. CDKN2BAS regulates cell cycle division suggesting a role in retinal ganglion cell apoptosis[38]. Common variants in a regulatory region on 8q22 are also associated with NTG[36]. This regulatory region is most active in choroid plexus (producing cerebrospinal fluid) and ciliary body suggesting that it could have a role in the development of an adverse translaminar gradient that has been associated with NTG in some populations[39].

ADULT ONSET POAG (HTG) GENES

Genome-wide association studies have also identified several genes associated with high-tension open

CME ANSWERS

1. Japanese
2. False
3. False

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ROLE OF INTRACRANIAL PRESSURE IN GLAUCOMA

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ABSTRACT

Our understanding of what if any role intracranial pressure (ICP) plays in the manifestation of the optic neuropathy called glaucoma is only beginning to develop. ICP can have a profound effect on the optic nerve. Edema of the optic nerve head is of course an accepted consequence of elevations in ICP. Venous pulsations are seen in some individuals with normal or low ICP. Therefore some local alterations in the structure, blood supply or axonal transport as a consequence of changes in ICP, possibly in relation to intraocular pressure (IOP), is realistic. This talk will briefly summarize the relationship between ICP and the eye, hypothesized relationships with glaucoma and existing evidence.

CEREBROSPINAL FLUID PRODUCTION, FLOW AND RESORPTION

Cerebrospinal fluid (CSF) surrounds and fills cavities within the brain and spinal cord. Normal CSF volume is roughly 100 ml. The rate of CSF is production is surprisingly high, with the entire volume being replaced several times each day. Most lies within the subarachnoid space and basal cisterns, with approximately 25% being contained within the ventricles. Normally, the osmolality of the CSF is equal that of serum, with a similar electrolyte composition. There a small differences, for example CSF sodium concentration is usually slightly less than that of serum. There is usually less glucose in CSF. However, the CSF ionic concentration can remain relatively stable despite serum fluctuations.

CSF is produced primarily by the choroid plexus, found in all four ventricles. The ventricular choroid plexus is similar to the ciliary body of the eye, being comprised of an epithelial lined highly vascular core. The epithelium pumps ions into the CSF space, creating an osmotic gradient and the influx of water. Similar to the ciliary body of the eye, CSF production is dependent of carbonic anhydrase. Thus carbonic anhydrase inhibitors are effective in lowering both ICP and IOP.

CSF passes from the lateral ventricles to the third ventricle and onto the fourth ventricle via the *aqueduct of Sylvius*. CSF exits the fourth ventricle to the subarachnoid space, through the *middle foramen of Magendie* and two *lateral foramina of Luschka*. CSF exits the subarachnoid space through *arachnoid villi*, located in the superior sagittal sinus. Obstruction of the CSF flow can result in elevations of ICP. If the obstruction is at the aqueduct of Sylvius, the lateral and third ventricles expand. This is called obstructive hydrocephalus. Should the obstruction be at the level of the *arachnoid villi*, the term non-communicating hydrocephalus may be applied.

Under normal physiologic conditions, CSF resorption equals production. The bulk of the CSF exits through the arachnoid villi of the superior sagittal sinus. Proposed alternative routes of CSF exodus include selective resorption through the choroid plexus, interstitial efflux to lymphatics of surrounding tissue, and by following olfactory nerves through the cribiform plate. The exact contribution of these alternate routes is debated; with most agreeing that the arachnoid villi provide the primary outflow pathway. An arachnoid villi is a small out-pouching of arachnoid through the overlying dura into a venus structure, such as the superior sagittal sinus. A granulation refers to a collection of villi. Arachnoid villi function as one-way valves that open under hydrostatic pressure. Thus with increased ICP (and therefore the gradient), flow increases.

NORMAL INTRACRANIAL PRESSURE

The craniospinal compartment is relatively closed. It is filled with neural tissue, blood and CSF. Should one component increase in volume, another must decrease in volume. Should this balance be disrupted, ICP may change. ICP is most commonly and easily measured via a lumbar puncture. You can find CSF pressure measured in units of mmHg and cm H_2O, which is derived from the actual measurement of mmCSF: 1.0 mmHg is roughly equal to 1.36 cm H_2O. Normal adult ICP is considered to be between 7 and 15 mmHg. The significance of ICP measurements between 15 and 18 mmHg is often of unclear. ICP greater than 18 mmHg is elevated. Normal ICP is lower in children and even less in infants.

ICP fluctuates slightly (i.e. CSF pulsation) with respiration and the cardiac cycle. It is also thought that arterial pressure contributes directly to ICP. The balance between mean arterial pressure (MAP) and ICP is important; the difference between MAP and ICP is called the cerebral perfusion pressure (CPP). Venous pressure is important as elevations can result in a reduction in the rate to of CSF resorption, leading to increased ICP. This effect is more profound with acute changes in venous pressure, with compensatory mechanisms buffering ICP alterations with

chronic venous pressure elevation. Body position affects ICP and its measurement. When assessing ICP, measurements in sitting and supine position will be affected by the resultant change in the height of the water column.

INTRACRANIAL PRESSURE AND THE EYE

INTRAOCULAR PRESSURE

It has been theorized that ICP has a direct effect on IOP, the most plausible proposed mechanisms being via effects on venous pressure within the cavernous sinus and in turn episcleral venous pressure. Intraocular pressure is determined by the balance between aqueous production and efflux through the trabecular meshwork, which is in part dependent on episcleral venous pressure. In animal models, a close correlation between ophthalmic arterial, venous pressure and a rise in ICP has been demonstrated. Also in support of this, a highly significant correlation between central retinal vein pressure and ICP estimated by ophthalmodynamometry has also been found. When an acute large increase in ICP has been induced in animals, small changes in IOP have been recorded. One of the most convincing observations was published in 2000 by Sheeran et al. They monitored ICP and IOP in intensive care unit patients. Although there was much variability, they found a significant correlation ($p<0.0001$) with a mean change in IOP of 1 mmHg per 11 mmHg change in ICP.

However, compensatory changes would be expected to buffer the effect of alterations in episcleral venous pressure. And when looking at chronic changes in ICP and IOP this is what is found. Studies in patients with chronically elevated ICP have not found such a close correlation. Lashutka et al described a loose correlation between ICP and ICP; however, due to the substantial variability, concluded that "changes in intraocular pressure are a poor predictor of changes in intracranial pressure." Others have substantiated this finding.

PAPILLEDEMA

Alteration in ICP has many known effects on the eye. Papilledema refers to optic disk edema occurring secondary to elevated ICP. Pressure transmitted within the CSF along the subarachnoid space compresses the optic nerve, just posterior to the globe. This is thought to cause stasis of axoplasm and axonal swelling. It has also been suggested that vascular compression may contribute. Despite the presence of papilledema vision is relatively preserved. In the majority of cases, with early papilledema visual function (acuity and perimetry) is normal. Exceptions include marked edema with presumed vascular compression and infarction or adjacent retinal edema and hemorrhage. With chronic papilledema axonal loss is seen. Proposed mechanisms include a toxic effect of disrupted axonal transport and vascular compromise. As axonal swelling is not seen with glaucoma, the likelihood that pressure related axonal stasis contributes to glaucoma is negligible.

ABDUCENS NERVE

Increased intracranial pressure may also result in diplopia. This is one of the more common findings in patients with elevated ICP, and the result of unilateral or bilateral abducens nerve palsy. This is likely the result of pressure on the brainstem, with stretching the nerve(s) over the clivus.

BLOOD FLOW

Spontaneous venous pulsations (SVP) of the optic disk refer to visible pulsations of the retinal veins. Presumably SVP occurs when the pressure in the vein falls between IOP peak pressure during systole and trough pressure in diastole. The cessation of optic disk spontaneous venous pulsations (SVP) is often considered a sign of elevated intracranial pressure (ICP). This is thought to be due to ICP being transmitted to the venous outflow with elevation of central retinal vein pressure above intraocular systolic pulse pressure. Other factors may influence SVP presence. Optic disk edema occurring for reasons other than elevated ICP usually results in the loss of SVP. Presumably, disk edema causes a localized increase in venous pressure. This emphasizes the complexity in the relationship between ICP, optic disk structure and vascular pressure. Tortuosity of the retinal vasculature is also a common finding in patients with elevated ICP. Given that changes in blood flow at the optic nerve are to the degree that gross changes are visible with elevated ICP, it seems plausible that alteration in the ICP/IOP gradient might have a contributory effect to blood flow and the development of glaucoma.

ORBIT

Dynamic changes in bone are well recognized. Osteoporosis is a very familiar disease. Neoplasm can alter bone via a number of mechanisms. In the orbit, bone invasion/erosion may be indicative of malignancy. The effects of intracranial hypotension on surrounding bone are less obvious and until recently largely unrecognized. In 1996, Meyer and colleagues described three patients with congenital hydrocephalus who developed bilateral enophthalmos following ventriculoperitoneal shunting (VPS). More recent a number of reports have described adult cases with acquired enophthalmos following VPS. This has been well demonstrated to be primarily due to bone remodeling secondary to intracranial hypotension. The change in the pressure gradient between the orbital soft tissue and CSF results in upward bowing of the orbit roof with expansion of the orbit volume. The term "sagging brain, sunken eyes syndrome" has been applied to the development of enophthalmos secondary to intracranial hypotension. This change in the bony structure of the orbit illustrates the power of chronic alterations in the pressure gradient between CSF and an adjacent cavity. If bone can be moved, an affect at the lamina cribosa of the optic nerve head might be a plausible consequence of an alteration in the ICP and IOP pressure gradient.

INTRACRANIAL AND INTRAOCULAR PRESSURE GRADIENT

Of the potential mechanisms that ICP might contribute to the development of glaucoma, a pressure gradient driven mechanical alteration of the structure of lamina cribosa seems most plausible. This has been the focus of a number of recent investigations.

A number of researchers have looked at ICP in cohorts of patients with glaucoma. For example Berdahl et al compared "ICP in subjects with primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG), and ocular hypertension (OHT) with that in subjects with no glaucoma". Relative to normals they found that lower ICP in both the POAG and NTG groups and elevated ICP in the OHT group. More recently Siaudvytyte et al. assessed translaminar pressure gradient (TPG) and neuroretinal rim area (NRA) in patient with POAG and NTG. They reported that translaminar pressure gradient was higher in glaucoma patients and that in the NTG group there was a reduction of NRA in patients with higher TPG. This study was arguably flawed in that ICP was not directly measured.

The lamina cribosa (LC) is the probable site of axonal injury in glaucoma and several studies have assessed the LC in glaucoma subjects. Spectral Domain Optical Coherence Tomography (SD-OCT) has been proposed to have resolution sufficient to detect small differences in optic nerve tissue dimensions, specifically LC thickness and position. In 2008, Schuman et al imaged the LC in humans using Spectral-domain Optical Coherence Tomography (SD-OCT). Images were suboptimal due to limited contrast, vascular shadowing, and signal fade at increasing optic nerve tissue depth. Subsequent studies sought to better optimize visualization. Inoue (2009) used 3D imaging software to reconstruct the LC from standard SD-OCT images. This attempt was limited by not being able to identify the LC reliably. Newer studies employ the use of Enhanced Depth Imaging (EDI) SD-OCT first used by Lee et al (2011) to image the LC in humans.

Several studies have looked at the LC in patients with glaucoma. Changes in LC position and prelaminar tissue thickness (PTT) after surgical IOP reduction have been assessed. Images were obtained before trabeculectomy or tube shunt placement. Significant anterior laminar displacement and increased PTT were described. Weinreb et al (2012) performed a similar study with patients undergoing trabeculectomy. They looked at changes in thickness of the LC and prelaminar tissue, and displacement of the LC. They also found a significant reduction in posterior displacement of the LC as well as an increase in LC thickness and pre-laminar tissue thickness after treatment.

Although these groups have employed SD-OCT to image the lamina cribosa in patients with glaucoma, few studies if any have used it to study the lamina cribosa in patients with intracranial hypertension or hypotension. In one recent case report it was demonstrated through enhanced-depth SD-OCT that the position of the LC changed after optic nerve fenestration. The prelaminar tissues (optic cup surface) were posteriorly displaced roughly 143 microns, while the anterior surface of the LC itself was posteriorly displaced by 137 microns. This was accompanied by a significant improvement in vision in both eyes.

SUMMARY

In summary, our understanding of the relationship between ICP and glaucoma is beginning to evolve. Alterations in ICP are known to influence optic nerve structure, blood supply and function. Whether ICP plays a significant role in the development of glaucoma in all or a subset of individuals remains to be determined. The possibility is arguably plausible and worthy of further consideration.

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IS NORMAL TENSION DIFFERENT THAN HIGH TENSION GLAUCOMA: OTHER POSSIBLE FACTORS

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I. DEFINITION

A. WHAT'S IN A NAME?

Open angle glaucoma (OAG) the second leading cause of irreversible blindness in the United States[1], comprises 2 major syndromes: primary open angle glaucoma (POAG) and normal pressure glaucoma (NPG). POAG is a disease generally characterized by a clinical triad which consists of 1) elevated intraocular pressure (IOP); 2) the appearance of optic atrophy presumably resulting from elevated IOP; and 3) a progressive loss of peripheral visual sensitivity in the early stages of the disease, which may ultimately progress and impair central visual acuity[2]. Primary open angle glaucoma affects approximately 0.5% of the American population[3] and occurs in 1.3% of white and 4.7% of black Americans over the age of 40 (1.6 million persons)[4]. Studies have indicated, however, that a surprisingly high percentage of patients with open-angle glaucoma have findings identical to those of POAG but with a singular exception; namely, that the IOP has never been demonstrated to be elevated. This form of glaucoma is often called "low-tension glaucoma," but also goes by the names "normal tension" and "normal pressure" glaucoma.

While numerous arguments and custom may be used to justify either of these terms, it is prudent to state the obvious: (1) there is nothing low about the range of IOPs in these patients, and (2) the use of the word "tension" is idiosyncratic to the field of ophthalmology since it is a term used to describe tonometric readings. We prefer the word "pressure" since it is more readily understood by our medical colleagues and patients alike. Furthermore, since there is no widely acknowledged effective therapy for this disorder, the use of the term "tension" is, unfortunately, most decriptive of the interactions that commonly occur between the physician and the patient with this disorder, and it is often anything but low! The remainder of this chapter will therefore refer to this syndrome as "normal pressure glaucoma."

B. NATURAL HISTORY OF NORMAL PRESSURE GLAUCOMA

Several large population-based studies have documented the high prevalence of normal pressure glaucoma[5]. Although a few of these studies suggest that as high 50% of open-angle glaucoma patients may indeed have normal pressure glaucoma, more conservative estimations prevail in numerous population studies. It is reasonable, therefore, to consider that approximately 25% of cases with open-angle glaucoma occur in the presence of normal IOP[6]. Little is known about the natural history of normal pressure glaucoma. Most experts, however, believe that while the hallmark of this syndrome is progression of visual field loss (as it is for POAG), there are often long periods, often years, in which stability of the visual fields occur. Unfortunately, in some patients, episodes of rapid deterioration can and do occur within in a relatively short time, typically over several months to 1 year. One long-term, population-based study found that 62% of patients with NPG showed progression of visual field loss over 5 years[7]. This was significantly worse than the 42% of patients with POAG who were tested and followed similarly during the same period of time. NPG is therefore often a disease marked by continued visual field progression, but not all patients progress even during long periods of follow-up. In many patients, episodic deterioration is interrupted by long periods of stable visual function.

Several findings make normal pressure glaucoma particularly difficult for the ophthalmologist to treat. Most apparent, however, is that IOP, the target of conventional glaucoma therapy, is no longer an attractive parameter to lower, since it is already within the normal range in these patients. Several investigators have speculated, however, that further lowering of IOP may still be beneficial, presumably by facilitating vascular perfusion in the region of the laminar cribrosa, since blood flow will occur against less resistance in the presence of lowered IOP. No data, however, are yet available from a national prospective study which will address whether the rate of visual field loss in these patients is significantly altered in patients in whom the IOP is further lowered by 30% of baseline values[8]. Ongoing studies in Britain, however, have suggested that visual field progression may indeed be minimized or limited in patients in whom IOP is lowered effectively by filtration surgery[9,10]. Furthermore, in eyes of with asymmetric IOPs

lower than 21 mm and visual field loss in one eye, the eye with the field loss almost invariably has the higher IOP[11,12]. Such studies, coupled with our inability to offer better alternatives, serve as the basis for our rationale that effective IOP lowering, either by medication, laser or surgery, may be a useful therapeutic intervention for many of our patients.

II. MAKING THE DIAGNOSIS

A. A DIAGNOSIS OF EXCLUSION

The diagnosis of normal pressure glaucoma is a diagnosis of exclusion. Normal pressure glaucoma is defined by the clinical constellation of open iridocorneal angles, normal IOP, optic nerve damage, and visual field loss which is progressive in nature and may ultimately impair central vision. The first parameter that must be evaluated as an inclusion criterion is what precisely is meant by normal IOP? Although it is well known that IOPs obey a non-Gaussian distribution in humans[13], several studies specify a value which defines an acceptable entry criterion for patients with normal pressure glaucoma. These values generally range between 20 and 24 mm Hg, and although they may have some utility for clinical studies, they should be viewed with less importance in an office setting. They certainly are *not* a criteria for defining glaucoma. The key question the practitioner must ask himself is: do I think my patient has a pressure-related glaucomatous neuropathy or not? When IOPs are elevated to greater than 2 standard deviations of the population mean (e.g. > 30 mm Hg), it is often easier to guess the right answer. When pressures are in upper teens, however, the answer to this question is not nearly so easy to ascertain.

Another well accepted inclusion criterion for normal pressure glaucoma is progressive changes in either visual fields or optic nerve cupping. In many patients, changes in both visual fields and cupping will occur. However, deterioration of either constitutes legitimate glaucomatous progression.

Most importantly, the definition of normal pressure glaucoma implies the absence of alternative causes of optic neuropathy, such as meningeal disease, infections (e.g. syphilis), inflammation, ischemic disease, or compressive lesions which may account for anterior nerve fiber bundle loss. Additional alternative causes of optic neuropathy, of course, include those in which episodic or transient elevation of IOP has been documented previously such as occurs in steroid responsiveness, or as a sequelae of some forms of trauma or intraocular pathology.

Simple ophthalmoscopic examination is often helpful in ruling out ocular conditions that may mimic glaucomatous nerve fiber layer damage such as congenital anomalies of the optic disc, choroidopathies (i.e., toxoplasmosis lesions), or retinal lesions (e.g. retinoschisis). Most often, however, such conditions are easily seen. Furthermore, they generally constitute nonprogressive lesions and are therefore not easily confused with genuine glaucoma.

B. NORMAL PRESSURE GLAUCOMA IS A DISEASE WITH SEVERAL VARIANTS

Now that we have satisfactorily ruled out numerous possible causes of intrinsic glaucomatous neuropathy, as well as other conditions which may be resemble glaucomatous damage, we are left with a clinical entity whose name, normal pressure glaucoma, unfortunately tells us little about the pathophysiology that underlies this disorder. Since the hallmark of medical therapy is based on treatment directed at preventing or ameliorating specific pathological processes, it should be no surprise that we have little to offer for this illness. Fortunately, however, the clinician can often gain useful insight into the factors underlying glaucomatous damage in certain individual patients. It is becoming increasingly clear that normal pressure glaucoma is likely comprised of numerous clinical variants, or subsets, of patients in whom there appear distinct similarities and thus clues as to the etiology of neuronal cell death in many subsets of patients. The most common subsets of normal pressure glaucoma syndrome may be characterized by patients in whom:

- no known cause has been identified (idiopathic)
- there is a history of migraine headaches and/or peripheral vasospasm
- there is evidence of aberrant systemic, serum or retinal autoimmunity (i.e. specific anti-retinal antibodies)
- there is nocturnal systemic hypotension
- there has been hypovolemic shock (blood loss from transfusions, etc.)
- patients in whom there is hyposecretion in the presence of impaired outflow (so-called “burnt-out” glaucoma)
- falsely low IOP has been recorded due to excessive corneal thinness.

While distinctions in these heterogeneous patients with NPG may often be made clinically, the advent of modern genetic techniques makes it is likely that a hereditary factor will be identified for one or more of these subgroups. For example, the chromosomal loci of genes (2cen-q13) responsible for at least one form of NPG that typically manifests in the fifth decade has recently been identified[14].

The finding that there are identifiable ‘subsets’ of patients within the NPG syndrome, is not surprising in light of our contemporary views of glaucoma pathogenesis. In addition to high intraocular pressure, evidence is rapidly accumulating that prompts us to consider that damage to the optic nerve may be initiated or sustained by any number of the factors cited above, in addition to others such as excitotoxicity, neurotrophin insufficiency, peroxynitrite damage or others yet undefined. These different injurious influences then act through common final pathways that eventually disturb ion transport and

activate the cellular proteases that accompany neuronal programmed cell death.

C. LABORATORY EVALUATION

Certainly, in order to rule out certain systemic considerations to help confirm the diagnosis of normal pressure glaucoma, it is reasonable to obtain several laboratory and/or radiologic tests. In general, there have always been two schools of thought which have tempered the clinical judgment of ophthalmologists regarding testing of these patients. There are those practitioners who will obtain almost no tests whatsoever. Conversely, there are those that will obtain every test imaginable. We would advocate that in general it is reasonable to perform limited testing to detect certain obvious disorders which are either treatable, or require further medical evaluation to assess potential treatment, and therefore should be performed on all patients with normal pressure glaucoma. The following tests should be viewed as the minimal essential testing to be performed, and their rationale are as follows:

(a) complete blood count with differential and platelets. There is no easier test to identify obvious blood dyscrasias, or common anemias, which may impair the delivery of oxygen to the high energy requirement tissues of the retina and optic nerve.

(b) antinuclear antibody panel (ANA). This test is a useful screen for collagen vascular disease, and other autoimmune abnormalities. A hospital generally offers ANA panels of varying complexity and we would advocate that the most complete panel offered, which typically tests for antibodies to extractable nuclear antigens such as Ro/SSA, La and Sm antibodies, are the most useful. Positive findings to the presence of these autoantibodies may signify the identification of the autoimmune subset of patients with normal pressure glaucoma[15].

(c) VDRL and FTA. One of the great masqueraders of glaucomatous optic neuropathy is indeed luetic disease. In our experience two out of every 100 patients with optic atrophy that have been referred to us for normal pressure glaucoma have tertiary syphilis which requires treatment.

(d) Serum immunofixation for paraproteins. In our experience in a tertiary care setting, approximately 10-15% of patients with normal pressure glaucoma have a monoclonal gammopathy (i.e. paraproteinemia), which is a clonal expansion of B cells which produces excessive serum immunoglobulin[16]. While the majority of monoclonal gammopathies in an older adult population generally represents a benign condition (called "monoclonal gammopathy of undetermined significance"), approximately one-third of these gammopathies will turn out to be caused by lymphoproliferative disorders such as multiple myeloma or other neoplastic conditions. It is recommended, therefore, that the ophthalmologist test for this condition and if a paraproteinemia is found, refer the patient to a hematologist for further workup which may include a bone marrow aspirate. Although paraproteinemias can often be determined by obtaining full serum protein electrophoresis profiles, a much easier and cheaper test is available in most laboratories in which immunofixation testing is performed in order to detect a serum monoclonal protein.

Additional laboratory testing which may be useful in selected patients include the following:

(e) SMA12. It is not unreasonable to obtain electrolytes and studies of liver and renal function in patients in whom there is a high index of suspicion of such disease. We have found, however, that routine testing for these values has been rather unproductive in virtually all patients with normal pressure glaucoma.

(f) complement studies. Testing for C3 and C4 complement has been unproductive in our hands as a assessment of potential collagen vascular disease.

(g) B12 and folate. These two have likewise been unrevealing. Although they are often obtained when there is a high degree of suspicion of an intrinsic neuropathy affecting central vision, we have not found them to be of value in assessing patients with normal pressure glaucoma.

(h) cryoglobins. These may be useful in patients in whom there is Raynaud's phenomenon or evidence of marked peripheral vasospasm, but is otherwise not very helpful.

D. RADIOLOGIC EVALUATION

There is considerable debate as to whether there is any utility in obtaining a CAT scan or MRI in patients with normal pressure glaucoma. Obviously, these tests are more useful in patients in whom there is a loss of central vision with preservation of peripheral vision, or in patients in whom chiasmal lesions are suspect. On the other hand, one might argue that it is not unreasonable to leave "no stone unturned," especially in a patient in whom central vision is threatened (i.e. a progressive paracentral scotoma very near fixation). We have never found a positive MRI or CAT result which has uncovered a lesion that accounts for glaucomatous optic neuropathy although anecdotal reports exist of such findings[17,18]. On the other hand, we would not consider it unwise to obtain radiologic brain or orbit studies to help eliminate any suspected source of optic nerve damage resembling glaucoma. This is perhaps especially true if a physician is practicing in a hostile medical legal

environment like the United States. One wonders: if Hippocrates were alive today would he amend the credo "Physician-do no harm" with "Physician- protect thyself?"

Finally, another useful clinical measurement that may be relevant in some cases is the assessment of corneal thickness. Certainly, patients who have had corneal refractive surgery, and high myopes, should have pachymetry performed since applanation tonometry underestimates IOP by 3 mm Hg for a 50 micron decrease in corneal thickness[19].

III. SIGNS AND SYMPTOMS OF NORMAL PRESSURE GLAUCOMA

A. OCULAR CLUES

1. Intraocular pressure

It is well known that IOP fluctuates throughout the day. Most humans have their highest IOPs in the mid morning. Patients who are evaluated at a single visit, however, may have IOPs within the normal range during their visit and do not necessarily manifest elevated IOP at that time. For this reason, we often prefer to obtain IOP measurements not only during multiple office visits, but at various times of the day, in order to get a truer sense of an individual's IOP range. Furthermore, we find that serial recording of diurnal pressure measurements is often useful to obtain an accurate representation of the average IOP readings in the eye. Although it sounds quite simple, in practice, it is not easy to obtain detailed recordings over a 24 hour period. Most practitioners have the capability of recording pressure measurements throughout the day when their office is open, say from 8 a.m. to 5 p.m. In general, when we receive diurnal measurements for this time period, we are usually satisfied that we have obtained a sampling that will detect an episodic increase during the day. Our own diurnal measurements, however, are made throughout the night as well, with the absence of the midnight to 6 a.m. time period. Of course, patients who have an aberrant light/dark cycle, such as those individuals who work in the evening, should have their IOPs preferably tested during the 12-16 hour period following their arousal from sleep.

2. Optic nerve atrophy

Documenting progressive optic nerve atrophy is generally straightforward. Sure, there are lots of sophisticated instruments that have the ability to define numerous optic nerve parameters in a moderately objective way. Some of the nerve fiber layer or optic nerve analyzers that are on the market are able to give fairly reproducible and reliable estimates of specific measurements such as cup to disk diameter, neuroretinal rim area, nerve fiber layer height, etc. It is important to keep in mind, however, that no computer has yet been able to answer the obvious questions we would like to ask about the key parameters of interest; namely, what, exactly, constitutes a significant change of any given parameter measured at various time points. More importantly, if we don't have access to one of these wonderful research-grade instruments, can we make such assessments at all? Fortunately, there is evidence that a good set of stereo disk photographs interpreted by an astute observer, is perhaps the most reliable way to assess meaningful changes in the optic nerve head[20]. By far the most important change that should be assessed is a loss of neural tissue which is assessed by the presence of cupping which of course represents atrophy of both neural as well as glial tissue. We would advocate that three dimensional viewing is extremely advantageous in order to perform this assessment. If this is not possible, certain clues such as the displacement of vessels, or the increased appearance of laminar pores, may assist the viewer who only has access to two dimensional analysis. In short, one does not need high technology in order to assess optic nerve progression; rather, all that is needed is a good brain.

It should be noted that patients with normal pressure glaucoma often present at a later stage of their disease than their counterparts with POAG. Therefore, it is not unusual that ophthalmologists will be faced with patients in whom cupping is quite advanced and in many cases almost complete. In these patients, the progression of optic nerve cupping will not be nearly as productive as the clinical assessment of progressive visual field loss in order to characterize the clinical course of their glaucoma.

Another parameter which has received increased attention recently is the appearance of parapapillary (also called "peripapillary") atrophy. This atrophy of the retinal pigment epithelium adjacent to the optic nerve head has been found to be active and dynamic, and accompanies the glaucomatous process[21]. Alone, an increase in peripapillary atrophy is not considered a diagnostic indicator of optic nerve progression. However, the clinicians' index of suspicion that progressive nerve damage has occurred should certainly be elevated if progressive changes in peripapillary atrophy occur with time.

3. Optic disc hemorrhages

The presence or recurrence of one or more splinter hemorrhages on the optic disc surface has long been considered an important prognostic sign indicating the development and/or progression of glaucomatous damage[22,23]. The greater incidence of these hemorrhages in patients with NPG as opposed to POAG[24] is particularly troubling. It suggests that such hemorrhages are not merely the result of structural changes that accompany glaucomatous optic neuropathy, but in the case of NPG, an ominous sign of neurovascular infarction and hence, eventual progressive optic nerve deterioration. Some observers believe that the appearance of such hemorrhages are not always followed by further field loss. In fact, such hemorrhages have been observed in nonglaucomatous populations. However, many studies report further field loss does indeed occur in the nerve fiber bundles in which such disc hemorrhages were present. Such hemorrhages usually occur at the upper and lower poles of the optic nerve

head, especially inferotemporally. They are often found in association with disc "notching" of the neuroretinal rim, and this too is strong evidence that their presence is of pathogenic importance. We are inclined to view their appearance most pessimistically. When such hemorrhages occur, they often prompt our serious reconsideration of current therapy (or lack thereof). Succinctly put, the appearance of hemorrhages in NPG patientss tell us whatever we're doing to minimize future loss isn't working.

4. Visual field loss

No assessment of glaucoma can be made without confirmation that there has been a progressive decrease in light sensitivity of the peripheral and/or paracentral visual field. Since visual field analysis is performed by several instruments among practitioners, no generalized statement can be made regarding the precise definition of what constitutes visual field progression. Utilizing the automated perimetry (Humphrey) field analyzer automated perimetry (Humphrey) Instruments, San Leandro, CA), our criteria for visual field abnormalities on the computerized parametric test include a corrected pattern standard deviation with a p value < 0.05 or a glaucoma hemifield test outside normal limits obtained with at least two reliable and reproducible visual field examinations. Visual field damage is considered to have progressed if there was a change in 5 or more points with at least 3 being contiguous compared with their baseline values based on the glaucoma change probability analysis (STATPAC). Utilizing manual perimetry (Goldmann), kinetic visual field defects typically include reproducible nasal steps of at least 10 degrees in width or paracentral scotomas over 5 degrees in width, in addition to classical Seidel and Bjerrum scotomas. The criteria for progression commonly consists of a reproducible and meaningful increase in either the depth or the extent of the scotoma.

Although it has been the subject of considerable controversy, most observers would agree that characteristic changes of the visual field often seen in patients with normal pressure glaucoma include visual field defects that are steeper, deeper, and closer to fixation than those seen in patients with POAG. If paracentral defects are present, it is often helpful to utilize the 10-2 program of the Humphrey instrument, and if visual acuity is poor, the use of a size V stimulus as opposed to a III stimulus is often preferred[25]. There are many patients on whom we alternate 30-2 and the 10-2 programs on sequential visits.

B. SYSTEMIC CLUES

1. Vasospasm

Patients with vasospasm constitute one of the earlest and best-characterized subsets of patients with NPG[26]. The literature is replete with studies which measure the vascular diameter of fingernail bed capillaries in response to temperature changes in order to assess peripheral vasospasm in these patients[27]. Should the clinician feel inadequate if they do not have access to such nifty technology? The answer of course is a resounding no!

The eminent Dr. Stephen Drance has taught us that the easiest way to assess the presence of vasospasm is simply to shake your patients' hands. Naturally, some patients may have cold hands if they are nervous, as may merely by a visit to the doctor, but your perception of cold hands should prompt directed questions to ascertain whether or not the patient is vasospastic. Are their feet cold? Do they sleep with socks on, particularly in the summertime? There is a high yield of positive responses to these questions in patients who have cold hands detected with a simple hand shake.

An additional history that is often given by vasospastic individuals with NPG is that of migraine headaches[28]. In attempting to elicit this history, it is important to keep in mind that the presentation of migraine headaches spans the gamut from classical migraine to acephalgic migraine, in which the headaches are not nearly as prominent as visual disturbances associated with spasm of either retinal or cerebral vessels.

Not only is one of the largest subset of normal pressure glaucoma patients those that are vasospastic, but it is a group for which some rational, however unproven therapy, may be considered. Recently, the use of calcium channel antagonists has been popularized for the treatment of normal pressure glaucoma. We consider the evidence that this family of compounds is efficacious in this disorder to be anecdotal and not utterly convincing[29,30]. In addition, there are many studies which have shown that these compounds in fact do not favorably alter visual field progression in either normal pressure or high pressure glaucoma[31,32]. Complicating this issue even further have been a number of interesting reports which suggest that patients who use these drugs chronically may experience an increased risk of cancer[33]. Before offering patients calcium channel blockers, consider this: If the practitioner does not experience enough "tension" already in dealing with patients with this disease, one can only imagine what happens when informing patients of these studies? We nevertheless do advocate the use of these drugs in select individuals, particularly the ones with frank and overt manifestations of peripheral vasospasm and/or migraine headaches, in which visual field worsening has occurred despite other efforts such as maximum reduction of IOP.

Calcium channel antagonists vary in their selectivity of cardiac as opposed to vascular receptors. Although ideally one would expect that the most vasoselective calcium channel antagonist is the one which should be used, the reality is that initiating therapy with these compounds will often result in untoward side effects such as headache, and lethargy. Therefore we generally initiate therapy with nonselective agents such as verapamil (Calan SR) prior to escalating our therapy with more selective compounds such as nifedipine (Procardia). (Nimodopine, the most vaso-selective compound, is prohibitively expensive and therefore not a practical choice.) The use of calcium

channel antagonists is a two-edged sword in more than one way. Effective concentrations may ameliorate vasospasm to a significant degree. However, excessive doses of this compound may cause decreased cardiac ionotropy and chronotropy, which would decrease cardiac output, and thus result in decreased ocular perfusion and be counterproductive. Patients should be explicitly told to monitor their pulse rate and blood pressure when using this family of compounds.

2. Systemic hypotension

Here lies one of the most treatable of conditions that affect a subset of patients with normal pressure glaucoma. Many factors affect blood flow to the optic nerve, including systemic blood pressure, vascular resistance, and intraocular pressure. A meaningful way to integrate the relationship between IOP and blood pressure is to refer to "perfusion pressure", which is the systemic diastolic blood pressure minus IOP. Studies suggest that the risk of glaucomatous damage increases markedly when diastolic perfusion pressure decreases below 50 mm Hg[34]. Several studies have been performed which demonstrate that patients with both the high and low pressure form of glaucoma (in fact all individuals), may experience nocturnal hypotension in which their blood pressure drops precipitously during the evening hours of sleep[35,36]. This of course, decreases perfusion pressure and likely increases the risk of optic neuropathy. In our experience this syndrome occurs most typically in thin, older individuals, particularly women.

We have been impressed that self monitoring of blood pressure with automated sphygmomanometry devices readily available at the local pharmacy have detected profound decreases in diastolic pressures which routinely fall to lower than 60 mm Hg. In these individuals we take a common sense approach and prescribe the use of a salt tablet after dinner as a dietary supplement. Salt tablets are generally available in any health food store and usually consist of 450 mg of sodium chloride and 50 mg of potassium chloride. In these patients, we are often successful in preventing nocturnal hypotension by increasing salt and fluid intact prior to retiring. Of course, the long-term effects on their optic neuropathy is unknown. However, we believe it is reasonable to advocate such an approach to facilitate ocular circulation and minimize the potential harm of lowered systemic blood pressure.

3. Is there a role for aberrant autoimmunity?

Many patients in whom we suspect that there is an autoimmune component to their optic neuropathy can be identified easily by history taking. Questions relating to the presence of musculoskeletal and joint involvement, skin rashes, and sicca complex are all useful in order to identify these potential patients. However, we should recognize the fact that the presence of such symptoms are generally nonspecific. In fact, in the case of sicca complex and/or dry eyes we all know that this condition is quite common in elderly individuals, not just those with glaucoma. The most useful hallmark, therefore, of potential autoimmune involvement in glaucomatous optic neuropathy is eliciting a history in patients in whom there is another autoimmune disease. We have identified several patients who belong to this subset of normal pressure glaucoma based on the clues that they have other autoimmune diseases such as Paget's disease, Addison's disease, multiple myeloma, chronic inflammatory peripheral neuropathy, hypothyroidism, etc. In fact, the epidemiologic association of patients with autoimmune disorders obtained from their history was the first clue which identified the subset of patients in whom autoimmunity may mediate the optic neuropathy that occurs in this disease[37]. Of course, it is beyond the scope of the ophthalmologist to treat these other disorders. Also discouraging is that the treatment of autoimmune diseases is in its infancy. The use of global suppressants such as steroids are often successful in ameliorating certain symptoms of several diseases, but the price is often high, and furthermore there is no evidence to suggest that the relief of symptoms due the use of steroids or other immunosuppressants will have any favorable bearing on the glaucomatous process, if indeed a similar autoimmune mechanism underlies both diseases. Nevertheless, it is the responsibility of the ophthalmologist to be alerted by the presence of accompanying autoimmune diseases, and to work closely with a patient's internist throughout the course of the patient's care. Certainly, any use of steroids in these patients must be monitored closely in order to detect steroid responsiveness, which, if it occurs, can certainly compromise an already glaucomatous nerve.

IV. TREATMENT

A. WHEN AND WHY TO TREAT CONSERVATIVELY

Much as it may seem like an anathema to the practicing glaucoma specialist, we would nevertheless state that not all patients with progressive visual field loss require treatment. Let us take for example a 90 year old woman with documented normal pressure glaucoma for 30 years. During that period of time she has had excellent visual acuity in both eyes, but with perhaps a paracentral scotoma in one eye and an arcuate defect in the other eye which has been noted to undergo episodic worsening over a 30 year period. We do not believe it would be unreasonable to consider that minimal, if any, impairment in functional vision would occur in this patient's expected lifespan if left untreated. Thus, the ophthalmologist's decision to treat should be tempered by several considerations such as the age of the patient, the level of visual function, and the level of visual needs. On the other hand, there are certainly patients in whom we would advocate aggressive treatment is worth pursuing, although again it must be emphasized that the efficacy of any treatment is unclear. Certainly, the

younger the patient the more inclined we are to consider treatment since there is an increased span of years during which further deterioration may occur.

The decision to treat based on the usual hallmarks of progression, namely, changes in the visual field or the optic nerve, garner the most attention. However, we believe that in many patients, the occurrence of repetitive optic nerve hemorrhages are the harbinger of future field loss, and their appearance often prompts us to treat aggressively. This is certainly true in younger patients.

Assuming one has made the decision that treatment should be initiated to minimize future damage, the basic tenets for treatment vary little from those of other glaucomas. The risks and benefits of any individual therapy, whether it be medical, laser or surgical, must be ascertained on an individualized basis. Patients with multiple allergies to the use of topical drops would certainly make the further use of that modality unattractive. Similarly, patients who are tremulous or uncooperative may not be able to successfully undergo argon laser trabeculoplasty. Finally, older patients who have had multiple ocular surgeries or who have undergone multiple filtering procedures that have been unsuccessful may not be the best candidates for further filtering surgery due to the risk of intraoperative complications such as expulsive hemorrhage.

In general, we do not advocate surgery for patients in whom the IOP is controlled in the low teens. We are much more likely to recommend pressure lowering by whatever means necessary for patients whose IOP > 15 mm Hg. The reason for this is twofold and is rather obvious. First, it is difficult to guarantee successful filtering surgery that yields pressure in single digits or the low teens. Obviously, the desired potential benefit following filtering is limited in an eye whose initial pressures are not that different that obtained post-operatively. Secondly, although it appears that there is a continuum of visual field loss with IOP in glaucoma (with low pressures generally having the least loss), it is again by no means clear that a pressure of 9 mm Hg is necessarily better than a pressure of 12 mm Hg in a disease in which the contributing role of any level of IOP is poorly understood. We would also add that we would have no quarrel for those that feel differently and for whom the reduction of IOP in the single digits is a sought after goal in all patients.

Regarding filtering surgery, we generally prefer the use of a guarded trabeculectomy procedure employing the use of releasable sutures to obtain low pressures early in the postoperative course while avoiding the frequent complications of full-thickness procedures such as choroidal effusions and flat chambers. We routinely employ antimetabolites in all filtering surgery although the dose and duration are varied based on individual patient characteristics. We use low doses of mitomycin C (0.2 mg/ml for 2 minutes) in individuals with thin sclera such as myopes, particularly in young myopic males since this group is one in whom hypotonous maculopathy antimetabolite therapy has been reported.

B. FUTURE OUTLOOK

The best opportunities for treatment will obviously be based on evidence that a specific pathologic mechanism mediates neuronal cell death in any or all of the variants of normal pressure glaucoma. Unfortunately, at the present time there is little evidence that any presumed mechanism of glaucomatous neuropathy is specific to normal pressure glaucoma as opposed to POAG. Although it is likely that many normal pressure and high pressure glaucoma patients may share a common mechanism for their neuropathy, the identification of these mechanisms need to occur prior to rationalizing optimum strategies for treatment. Unfortunately, it is entirely too premature to expect that neuroprotectants, immunosuppressive agents or gene therapy will be available to us in the immediate future. At present, common sense which tempers sound medical judgment offers the best opportunity for decreased morbidity resulting from the diminished optic nerve function that may accompany this most perplexing optic neuropathy.

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DEBATE: THAT WE SHOULD ELIMINATE THE TERM 'NORMAL TENSION GLAUCOMA' POSITION: CON

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HISTORICAL

- First mentioned by von Graefe in 1857 – rejected out of hand
- Before 1950, glaucoma divided into congestive and non-congestive, acute or chronic
- 1950s – population studies to define mean IOP in population
- 2 standard deviations from mean, ≤21 mmHg, accepted as normal IOP

DEVELOPING CONCEPTS OF GLAUCOMA

- IOP ≥22 mmHg became equated with glaucoma in the late 1950s and early 1960s
- Patients were treated irrespective of optic nerve head or visual field damage on the basis of IOP alone
- Other factors, such as central corneal thickness, were unknown
- 1960s – concepts of cup/disc ratio, ocular hypertension
- Early reports of non-IOP risk factors largely ignored – nocturnal hypotension, central corneal thickness, low cerebrospinal fluid pressure – rediscovered after 20-30 years

NORMAL-TENSION GLAUCOMA

- Until the last 2 decades, thought to be rare.
- Despite publications, many ophthalmologists, including academicians, found any excuse to rationalize why a patient could not have glaucoma at normal IOPs
- Diagnosis was often markedly delayed, patients being referred with severe visual field loss because discs and fields were often not examined in patients with IOPs in the mid-teens
- It was not incongruous for a patient with IOP 21 mmHg to be diagnosed differently from a patient with IOP 22 mmHg
- Collaborative Normal-Tension Glaucoma Study showed lowering IOP could be beneficial
- Also marked the beginning of differentiation into subgroups according to progression rate – vasospasm, disc hemorrhage, migraine, cardiovascular disease
- People with elevated IOP can also have other risk factors for damage

TERMINOLOGY

Until this point, I have avoided the question as to whether the term "normal-tension glaucoma" should be considered valid or retained in usage.

Part of this is because I don't think I could fill 7 minutes simply presenting an argument to retain it. You have heard my colleague, Bob Weinreb, argue why we should eliminate the term. I will present reasons for continuing to use it, with the caveat that we are all on the same page when we do so.

POAG WAS LONG DIVIDED INTO OCULAR HYPERTENSION, GLAUCOMA (HTG, NTG)

It took years of arguing before getting people to drop glaucoma from every other entity. People never said "neovascular ocular hypertension" or "chronic angle-closure ocular hypertension".

We know very well now that IOP exists on a continuum, and there is no dividing line between one mmHg and another. We define glaucoma without using the term IOP. We know that IOP is not the disease itself, as once thought, but a risk factor, albeit the most important known risk factor and to date, the only one inarguably proven to modify outcomes when treated.

What term could we use to replace NTG? When we speak of other risk factors, we speak not of IOP-independent risk factors, but risk factors other than IOP that contribute to a propensity for glaucomatous damage.

But we don't say this when speaking – it takes too long to say. Nor when we speak of other risk factors, do we say "glaucoma associated with low nocturnal blood pressure"

or “obstructive sleep-apnea associated glaucoma”. The terms are unwieldy and perhaps overly inclusive or insufficiently precise. Thus, knowing what we are speaking about when we use the term NTG, we can retain using it, at least for the time being.

It is also useful, but not necessary terminologically, for separating groups in clinical trials. If all the patients in one arm of a trial have IOP consistently <21 mmHg and those in the other arm have IOP consistently ≥24 mmHg, we can use NTG and HTG to describe these groups in looking for differences between them, whatever those may be.

Since the literature is replete with this terminology, changing it at this point without a specific and widely understood replacement would lead more to confusion than to consolidation.

THE MORPHOLOGICAL DIFFERENCE BETWEEN GLAUCOMA AND OTHER OPTIC NEUROPATHIES

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LEARNING OBJECTIVES

1. Recognize that "cupping" is a clinical term that is non-specific
2. Recognize the clinical features of a "glaucomatous" form of "deep" "cupping"
3. Describe how intraocular pressure, cerebrospinal fluid pressure lamina cribrosa and peripapillary scleral connective tissue material properties and ocular perfusion pressure influence optic nerve head biomechanics at all levels of intraocular pressure and determine the form of cupping present in all forms of optic neuropathy
4. Recognize that optic nerve head connective tissue deformation and remodeling are the defining causes of what clinicians comfortably call "deep" or "glaucomatous" cupping. While we necessarily focus on how retinal ganglion cell axons are insulted within the optic nerve head in glaucoma – optic nerve head biomechanics likely determines the level of pressure and the location at which that damage will occur in a given eye
5. Describe why we should expect to find IOP-related optic neuropathies at all levels of IOP that demonstrate shallow forms of "cupping"
6. Recognize that the continuum between age related axon loss—glaucoma at "normal levels of IOP"—and glaucoma at elevated levels of IOP—is governed by optic nerve head susceptibility

KEYWORDS

1. Glaucoma
2. Optic Nerve Head
3. Biomechanics
4. Cupping
5. Optic
6. Neuropathy
7. Aging

The defining features of a "glaucomatous" optic neuropathy include "glaucomatous" "cupping" which is difficult to describe and therefore phenotype except when "deep" cupping is present and is accompanied by some degree of excavation of the rim tissues beneath Bruch's Membrane Opening (BMO) and/or the anterior scleral canal opening. Discussion of what constitutes "glaucomatous" cupping are made difficult by the fact that "cupping" is a clinical term which is used to describe optic nerve head (ONH) structural change in all forms of optic neuropathy, however "cupping" is also used as a synonym for the pathophysiology of glaucomatous damage to the ONH. Because the clinical and pathophysiologic contexts for "cupping" are seldom clarified there is a confusing literature regarding the presence, importance and meaning of "cupping" in a variety of disorders. We have previously proposed that only "laminar" or "deep" forms of "cupping" (those that include a connective tissue component) are pathognomonic for glaucoma. We have further clarified that even a glaucomatous form of "cupping" is only one manifestation of the underlying pathophysiologic processes which drive the optic neuropathy of glaucoma. Cupping is therefore a manifestation of the neuropathy of glaucoma, not the optic neuropathy itself. Damage to the retinal ganglion cell axon within the ONH is a second component of the optic neuropathy of glaucoma, but it also is not the optic neuropathy itself. The clinical phenomenon of cupping has two principal pathophysiologic components in all optic neuropathies: prelaminar thinning and laminar deformation (Figure 2). We define prelaminar thinning to be the portion of cup enlargement that results from thinning of the prelaminar tissues due to physical compression and/or loss of RGC axons. We define laminar deformation or laminar cupping to be the portion of cup enlargement that results from permanent, IOP-induced deformation of the lamina cribrosa and peripapillary scleral connective tissues following damage and/or remodeling. We propose that the defining phenomenon of glaucomatous cupping is deformation and/or remodeling of the neural and connective tissues of the ONH, which is governed by the distribution of IOP-related connective tissue stress and strain, regardless of the mechanism of insult or the level of IOP at which that deformation and/or remodeling occurs. Said in another way, *"glaucomatous*

cupping" is the term clinicians use to describe the clinical appearance and behavior the ONH assumes as its neural and connective tissues are deformed and/or remodeled: 1) in a pattern and 2) by the several pathophysiologic processes governed by IOP- related connective tissue stress and strain. ONH Biomechanics can help us understand why a given optic nerve head will demonstrate a certain form of "cupping" and at what level of IOP that might happen. Animal models are allowing us to tease apart the important components of cupping in IOP-related and non-IOP related forms of optic neuropathy. A paradigm change in SDOCT ONH, RNFL and Macular imaging should improve our ability to phenotype all forms of damage to the visual system including glaucoma.

THE OPTIC NERVE HEAD (ONH) IN GLAUCOMA

While glaucomatous damage to the visual system likely includes important pathophysiologies within the retinal ganglion cell (RGC) body[1-3] photoreceptors,[4-10] peripheral RGC axon and its synapse,[11, 12] lateral geniculate body[13-15] and visual cortex[15] strong evidence suggests that damage to the RGC axons within the lamina cribrosa of the ONH[16-22] is a central pathophysiology. Recent studies in the monkey,[17, 18, 23-26] rat, [27,28] and mouse,[29-33] support the importance of the ONH, by describing profound alterations and axonal transport disruption within the prelaminar, laminar and retrolaminar tissues of the ONH at the earliest detectable stage of experimental glaucoma (EG).

The ONH tissues make up a dynamic environment wherein 1.2 to 2.0 million RGC axons converge, turn, and exit the eye through the inner (Bruch's Membrane opening) and outer (scleral) portions of the neural canal (Figure 1, see next page). Within the scleral portion of the canal, the bundled axons pass, through a 3- dimensional (3D) meshwork of astrocyte-covered, capillary containing, connective tissue beams known as the lamina cribrosa (Figure 1, see next page). Within the lamina, axonal nutrition is thought to depend upon the movement of oxygen and nutrients from the laminar capillaries, through the laminar beam extracellular matrix, across the astrocyte basement membrane into the astrocyte, finally reaching the peripheral and central axons of each bundle, via cell processes.[35]

WHAT, REALLY, IS GLAUCOMATOUS "CUPPING"?

"Cupping" is a clinical term which is used to describe ONH structural change in all forms of optic neuropathy. However, "cupping" is also used as a synonym for the pathophysiology of glaucomatous damage to the ONH. Because the clinical and pathophysiologic contexts for "cupping" are seldom clarified there is a confusing literature regarding the presence, importance and meaning of "cupping" in a variety of disorders. Cupping in glaucoma is highly variable.[40, 41] We have previously proposed that only "laminar" or "deep" forms of "cupping" (those that include a connective tissue component) are pathognomonic for glaucoma.[26, 42, 43]

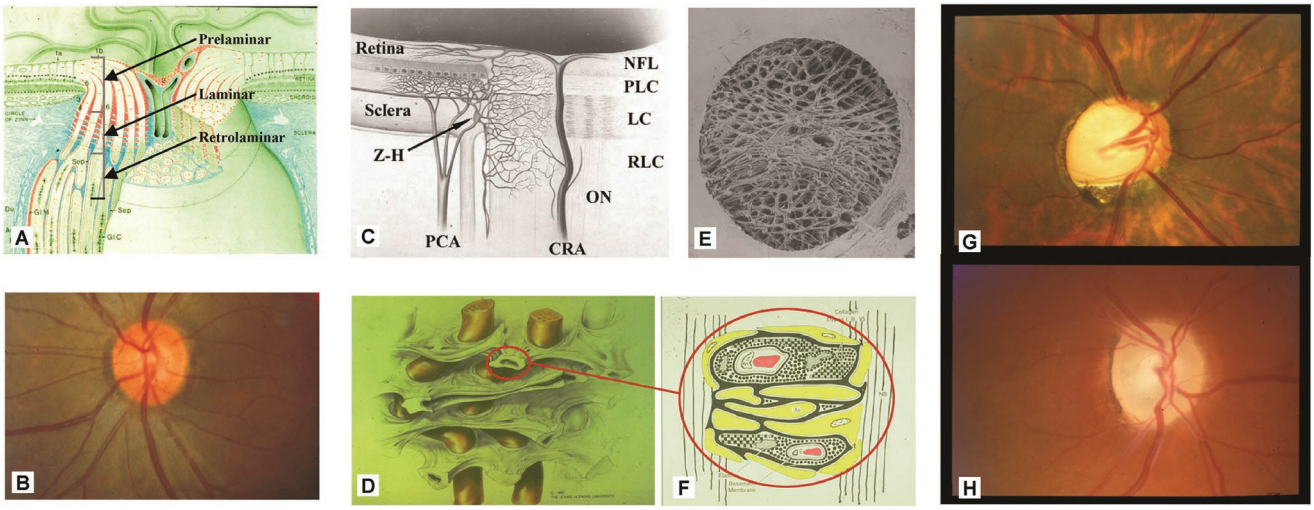

Figure 1. Glaucoma, cupping and axonal insult within the optic nerve head (ONH). The ONH is made up of prelaminar, laminar and retrolaminar regions (A). Within the clinically visible surface of the Normal ONH (referred to as the optic disc) (B), central retinal vessels enter the eye and RGC axons appear pink due to their capillaries (which are principally supplied by branches from the posterior ciliary arteries (PCA) in (C). The primary site of RGC axon insult in glaucoma is within the lamina cribrosa (schematically depicted with axon bundles in (D), isolated by trypsin digest in a scanning electron micrograph in (E) and drawn with stippled extracellular matrix (ECM), central capillary (red) and surrounding astrocytes (yellow with basement membranes in black) (F). Blood flow within the ONH, while controlled by autoregulation, can be affected by non IOP-related effects such as systemic blood pressure fluctuation and vasospasm within the retrobulbar portion of the PCAs. Additional IOP-induced effects may include compression of PCA branches within the peripapillary sclera (due to scleral stress and strain) and compression of laminar beam capillaries reducing laminar capillary volume flow (C and F).[34] There is no direct blood supply to the axons within the laminar region. Axonal nutrition within the lamina (F) requires diffusion of nutrients from the laminar capillaries, across the endothelial and pericyte basement membranes, through the ECM of the laminar beam, across the basement membranes of the astrocytes, into the astrocytes, and across their processes to the adjacent axons (vertical lines). Chronic age-related changes in the endothelial cell and astrocyte basement membranes, as well as IOP-induced changes in the laminar ECM and astrocyte basement membranes may diminish nutrient diffusion to the axons in the presence of a stable level of laminar capillary volume flow. The clinical manifestation of IOP-induced ONH structural change is most commonly "deep cupping" (G) but in some eyes cupping can be shallower accompanied by pallor (H). Z-H = circle of Zinn-Haller; PCA= posterior ciliary arteries; NFL = nerve fiber layer; PLC = prelaminar region; LC = lamina cribrosa; RLC = retrolaminar region; ON = optic nerve; CRA = central retinal artery. *(A) Reprinted with permission from Arch Ophthalmol;[35] (C) reprinted with permission from The Glaucomas. St. Louis: Mosby; 1996:177–97;[36] (D) reprinted with permission from Optic Nerve in Glaucoma. Amsterdam: Kugler Publications; 1995:15–36;[37] (E) reprinted with permission from Arch Ophthalmol;[38] (F) reprinted with permission from Arch Ophthalmol.[39]*

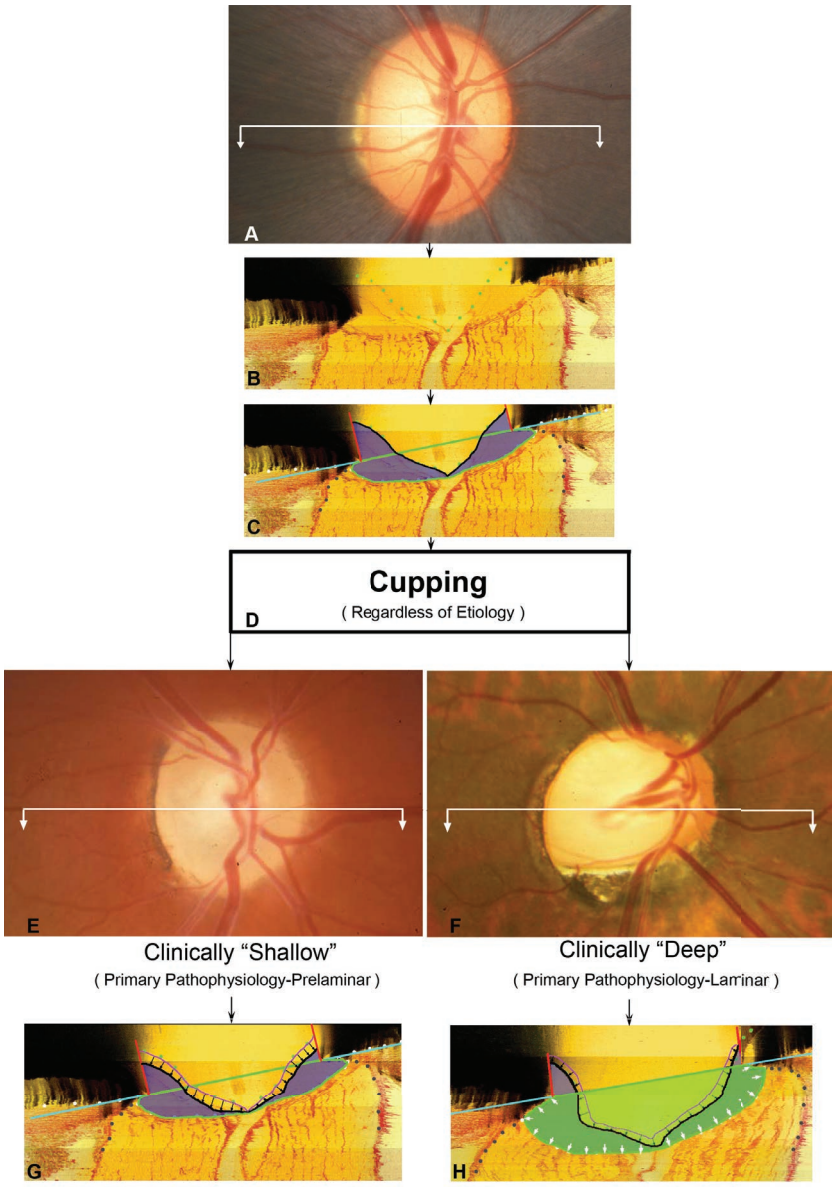

Figure 2. All Clinical Cupping, Regardless of Etiology, is a Manifestation of Underlying "Prelaminar" and "Laminar" Pathophysiologic Components. A. Normal ONH. To understand the two pathophysiologic components of clinical cupping, start with **(B)** a representative digital central horizontal section image from a post-mortem 3D reconstruction of this same eye (white section line in (A)) - vitreous top, orbital optic nerve bottom, lamina cribrosa between the sclera and internal limiting membrane (ILM) delineated with green dots. (**C**) The same section is delineated into principle surfaces and volumes (Black – ILM**;** purple - prelaminar neural and vascular tissue; cyan blue line – Bruch's Membrane Opening (BMO)-zero reference plane cut in section; green outline – Post-BMO Total Prelaminar area or a measure of the space below BMO and the anterior laminar surface). **(D)** Regardless of the etiology, clinical cupping can be "shallow" **(E)** or "deep" **(F)** (these clinical photos are representative and are not of the eye in (A)). A prelaminar or "shallow" form of cupping (**G**, black arrows) is primarily due to loss (thinning) of prelaminar neural tissues without important laminar or ONH connective tissue involvement. Laminar or "deep" cupping (**H**, small white arrows depict expansion of the green shaded space) follows ONH connective tissue damage and deformation that manifests as expansion of the total area beneath BMO, but above the lamina. Notice in (H) that while a laminar component of cupping predominates (white arrows) there is a prelaminar component as well (black arrows). While prelaminar thinning is a manifestation of neural tissue damage alone, we propose that laminar deformation can only occur in the setting of ONH connective tissue deformation and remodeling. *Reprinted with permission*[26]

We now further clarify that even a glaucomatous form of "cupping" is only one manifestation of the underlying pathophysiologic processes which drive the optic neuropathy of glaucoma. Cupping is therefore a manifestation of the neuropathy of glaucoma, not the optic neuropathy itself.

Damage to the retinal ganglion cell axon within the ONH is a second component of the optic neuropathy of glaucoma, but it also is not the optic neuropathy itself. While the pathophysiology of RGC axon damage is of fundamental importance in preserving vision, it may be only one component of, (or secondary to) the larger pathophysiologic events that drive the neuropathy.

The clinical phenomenon of cupping has two principal pathophysiologic components in all optic neuropathies: prelaminar thinning and laminar deformation (Figure 2, see left). We define prelaminar thinning to be the portion of cup enlargement that results from thinning of the prelaminar tissues due to physical compression and/or loss of RGC axons. We define laminar deformation or laminar cupping to be the portion of cup enlargement that results from permanent, IOP-induced deformation[26] of the lamina cribrosa and peripapillary scleral connective tissues following damage and/or remodeling.[26, 44-46]

The clinical hallmarks of a glaucomatous optic neuropathy are *"glaucomatous cupping"* of the tissues of the optic nerve head (ONH) (Figure 3, see below) — a progressive posterior displacement of the surface of the ONH and progressive excavation of the prelaminar tissues beneath the anterior-most aspect of the scleral canal, the anterior scleral ring (Figure 1, see p. 529) — and glaucomatous visual field loss, which most commonly starts as a nasal step and progresses through an arcuate scotoma to full hemifield loss. These clinical hallmarks distinguish a glaucomatous optic neuropathy from the many other optic neuropathies in which damage to the RGC axons, either at the nerve head or within the orbital optic nerve and chiasm, leads to RGC death. Although exceptions exist, ischemic, inflammatory, and compressive damage to the nerve head, orbital optic nerve, or optic chiasm usually results in pallor and atrophy of the nerve head but little or no excavation of the remaining rim tissue (Figure 1, right). In addition, in these entities the pattern of axon damage within the optic nerve, and as detected by visual field testing, is usually different from that of glaucomatous optic neuropathy.

Thus, while the ONH is the primary site of damage for a group of optic neuropathies, only a subset of these disorders assume the clinical appearance and behavior commonly associated with the term glaucomatous. What then constitutes a *"glaucomatous"* cupping? We propose that the defining phenomenon that underlies the glaucomatous optic neuropathies is deformation and/or remodeling of the neural and connective tissues of the ONH, which is governed by the distribution of IOP-related connective tissue stress and strain, regardless of the mechanism of insult or the level of IOP at which that insult occurs. Said in another way, *"glaucomatous cupping"* is the term clinicians use to describe the clinical appearance and behavior the ONH assumes as its neural and connective tissues are deformed and/or remodeled: 1) in a pattern and 2) by the several pathophysiologic processes governed by IOP-related connective tissue stress and strain.

OPTIC NERVE HEAD BIOMECHANICS

The biomechanical paradigm of glaucomatous ONH damage does not argue that the ONH is the earliest or only site of damage. ONH biomechanics provides a framework for explaining how IOP-related stress (force/cross-sectional area of the tissue experiencing that force) and strain (a measure of local deformation of a tissue induced by applied stress) within the load-bearing tissues of the ONH influence the physiology and pathophysiology of all three ONH tissue types at all levels of IOP. These include: 1) the connective tissues (load-bearing connective tissues of the peripapillary sclera, scleral canal wall, and lamina cribrosa), 2) the neural tissues (RGC axons), and 3) the cells which exist alone or in contact with both 1 and 2 (astrocytes, glial cells, endothelial cells, and pericytes and their basement membranes).[42-44, 47-51]

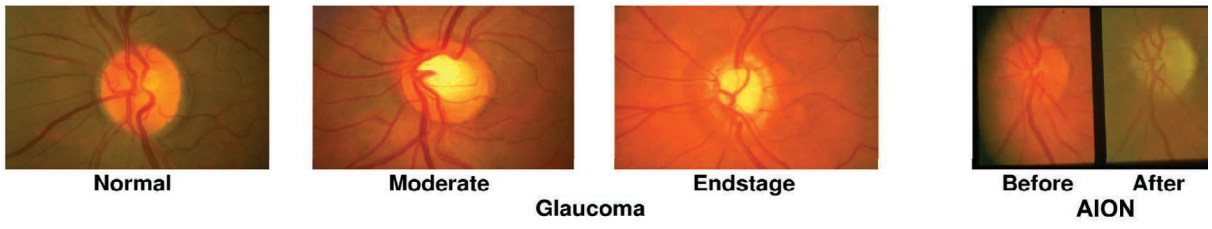

Figure 3. Progressive deformation and excavation of the tissues of the optic nerve head (ONH) beneath Bruch's Membrane Opening (BMO) and/or the anterior rim of the scleral canal is the clinical hallmark of a glaucomatous optic neuropathy (middle). Axonal damage resulting from an episode of anterior ischemic optic neuropathy (AION), right, usually results only in ONH pallor. *AION images reprinted from the Transactions of the American Academy of Ophthalmology and Otolaryngology, Volume 83: Quigley, H.A., Anderson, D.R., 1977. Cupping of the optic disc in ischemic optic neuropathy. pp. 755–762, Copyright (1977), with permission from American Academy of Ophthalmology.*

ONH biomechanics provides a logic by which non IOP-related risk factors such as ischemia, inflammation, auto-immunity, astrocyte and glial molecular biology are influenced by or interact with the effects of IOP.[43, 44] ONH biomechanics attempts to combine these *"non-IOP-related"* factors with laminar and peripapillary scleral connective tissue geometry and material properties (strength, stiffness, structural rigidity, compliance and nutrient diffusion properties) to explain the physiology of normal ONH aging, ONH susceptibility to IOP, and the clinical manifestation of all forms of optic neuropathy (Figure 4, see below).

To understand when, why and how the lamina deforms at a given level of IOP in a given eye, and perhaps also to understand some portion of the contributing mechanisms of axonal insult in glaucoma, the biomechanical determinants of the translaminar pressure gradient or the transition from intraocular pressure to retrolaminar tissue pressure experienced by the ONH tissues are illustrated and explained in Figure 5, see right. The importance of this gradient to axonal physiology is separately discussed below. The key messages of this and the following sections are five-fold. First, energy is required for axon transport and the translaminar pressure gradient may increase the energy requirements of the RGC axons within the lamina cribrosa. Second, IOP-related stresses and strains within the ONH connective tissues are complicated and do not necessarily lead to deformation of the lamina out of the plane of the sclera. Third, scleral canal expansion that tightens the lamina within the canal and lessens posterior laminar deformation, still increases strain within the lamina. Fourth, posterior deformation of the lamina is likely not required for axon transport compromise. Fifth, IOP-related stress and strain within the ONH connective tissues may independently affect the delivery of nutrients to the RGC axons (and therefore affect axon transport) in the presence or absence of frank laminar deformation.

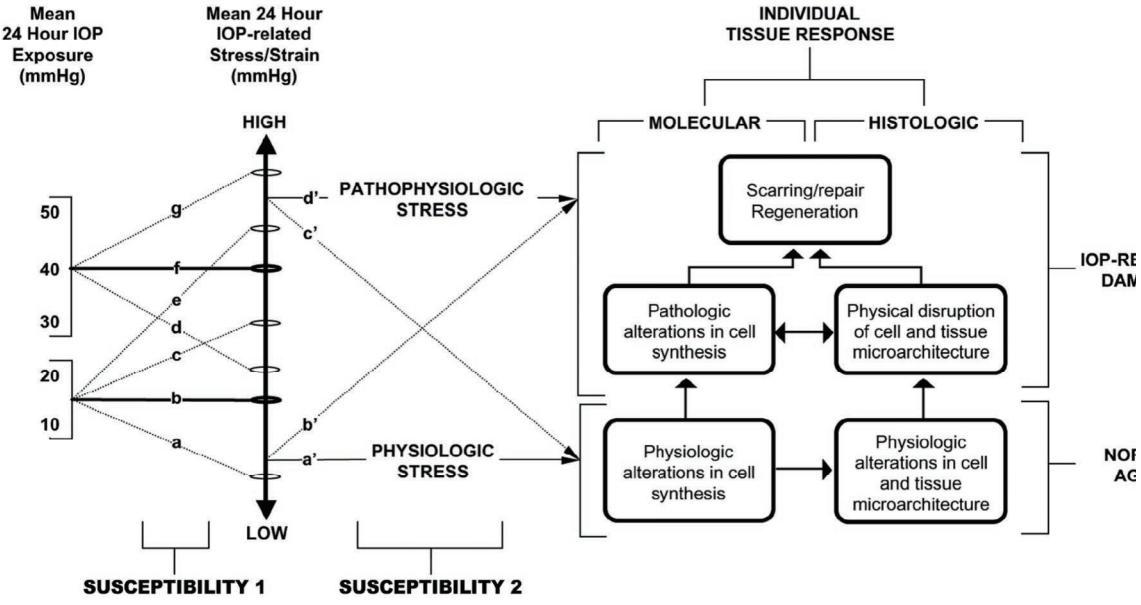

Figure 4. Whether, Over the Course of a Lifetime, an Eye Demonstrates the "Neuropathy of Aging" or the Neuropathy of Glaucoma Lies in ONH Susceptibility. For a given ONH, IOP generates low or high levels of stress depending upon the 3D architecture (geometry) of the ONH connective tissues (size and shape of the canal, thickness of the lamina and sclera) - **(Susceptibility 1).** Some ONHs will have relatively low stress at high IOP (d). Others will have high stress at low IOP (e). Whether a given level of IOP-related stress is physiologic or patho-physiologic depends upon the ONH's microenvironment **(Susceptibility 2).** Strong connective tissues, a robust blood supply and stable astrocytes and glia increase the chance of Normal ONH Aging (right – bottom). While the existence of a neuropathy of aging is controversial, the difference between "normal" age-related axon loss (if it is shown to exist) and the development of glaucomatous damage is a matter of ONH susceptibility. *Reprinted with permission*[42]

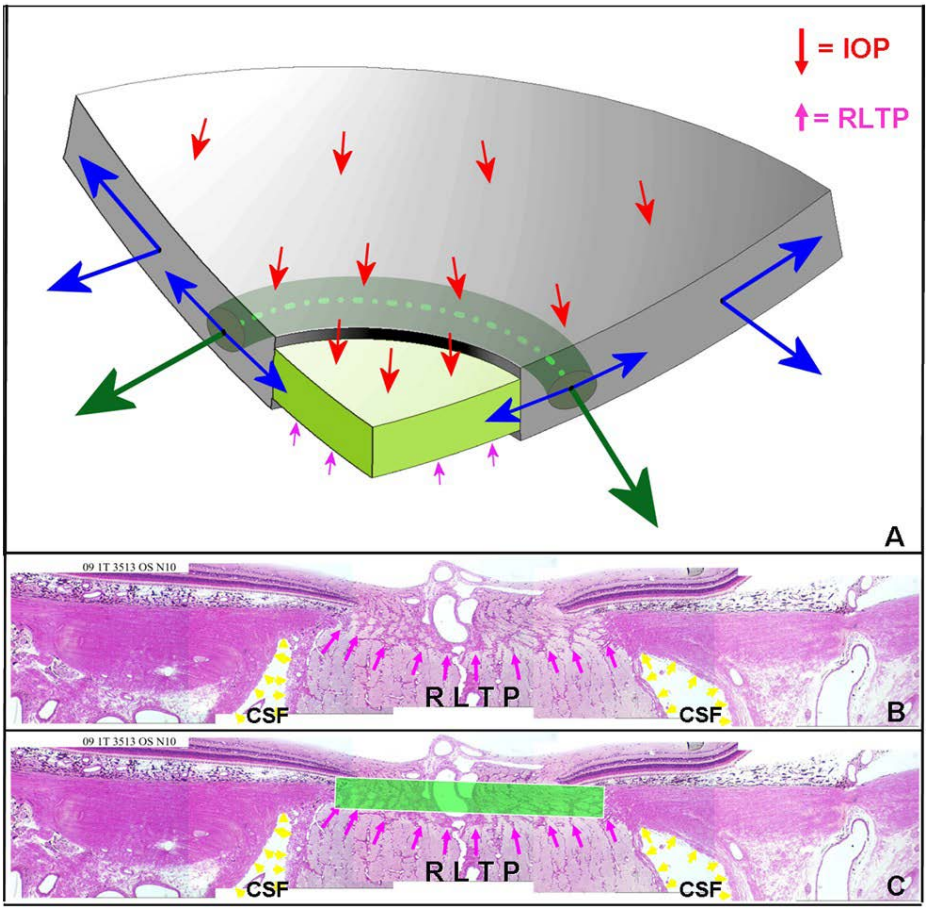

Figure 5. Principle distribution of forces, pressures and the translaminar pressure gradient within the optic nerve head (ONH), A. Cut-away diagram of IOP-induced mechanical stress in an idealized spherical scleral shell with a circular scleral canal spanned by a more compliant lamina cribrosa. In this case, the majority of the stress generated by IOP/orbital pressure difference (red arrows on the inner surface of the sclera) is transferred into a hoop stress borne within the thickness of the sclera and lamina (blue arrows) that is concentrated circumferentially around the scleral canal (green arrows). **B.** Note that the pressure behind the lamina is not simply cerebral spinal fluid (CSF) pressure but is retrolaminar tissue pressure (**RLTP**) which has been demonstrated to be approximately 0.82 x CSF + 2.9 mm Hg by Morgan, et al in dogs.[52] **C.** The difference between IOP and the retrolaminar tissue pressure is the translaminar pressure difference which generates both a net posterior (outward) force on the surface of the lamina (the red arrows over the lamina) and a hydrostatic pressure gradient (the translaminar pressure gradient - schematically shown in green) within the neural and connective tissues of the pre-laminar and laminar regions. **Note that the in-plane hoop stress transferred to the lamina from the sclera is much larger than the stresses induced by the translaminar pressure difference.** CSF directly influences laminar position through its effect on the translaminar pressure difference. CSF may also effect scleral flange position within the region it projects to the sclera (Figure 2), but in most eyes, because the projection of the CSF space is minimal this is not likely important (the CSF space within Panels B and C in this figure is greatly expanded due to perfusion fixation). IOP has a similar direct effect on laminar position, but has an additional (and potentially more important) effect on laminar position through the peripapillary sclera. However, while the magnitude of the translaminar pressure difference may be small relative to the stresses within the sclera and lamina, the axons experience it as the translaminar pressure gradient the steepness of which is influenced by the thickness of the tissues over which it is experienced. The translaminar pressure gradient, as such, may serve as a primary barrier to axon transport and flow within this region and an important physiologic determinant for the ONH axons and cells. *Reprinted with permission.*[44]

The difference between intraocular and orbital pressure establishes "engineering" or "mechanical" *stresses* (force/cross-sectional area of the tissue bearing the load) within the ONH neural and connective tissues, the magnitude of which are determined by the level of IOP and the 3D geometry or architecture of the tissues that carry them.[43, 48, 53] These *mechanical stresses* are separate from *physiologic stress* which we define as physical and metabolic changes within a cell in response to alterations in its environment. The direct (outward) effect of intraocular pressure on the internal limiting membrane of the ONH prelaminar tissues is resisted by the pressure within the retrolaminar optic nerve tissues (retrolaminar tissue pressure) and the outward expansion of the scleral canal which pulls the lamina cribrosa "tight" within the canal, effectively increasing its resistance to outward deformation.[53, 54]

The important concept for this discussion is that engineering models suggest that the stresses generated by the IOP/orbital pressure difference within the scleral connective tissues are far higher than the direct (outward) stresses on the neural and connective tissues of the lamina (Figure 2, see page 530).[51, 53, 55] How the ONH connective tissues respond to a given distribution of mechanical stress is determined by their material properties. A growing body of experimental[54] and theoretical work [49-51, 55] supports the concept of a laminar- scleral dynamic in which the net compliance or rigidity of the sclera exerts a large influence over the magnitude of lamina cribrosa deformation at all levels of IOP. While a previous study of ONH surface deformation in dogs suggested substantial ONH surface movement with acute IOP elevation,[56] recent studies in which laminar deformation was measured directly, suggest variable magnitudes of posterior laminar deformation follows acute IOP elevation in normal monkey[17, 57, 58] and human eyes.[59]

How the axons respond to laminar deformation, (when present) cannot be separated from other axonal effects of the constituent neural and connective tissue stresses and strains. Said in another way, the components of IOP-related stress and strain that drive ONH connective tissue deformation may not be the components that influence axon transport. Glaucomatous damage to the RGC axons within the ONH may not simply occur at locations with the highest levels of IOP-related connective tissue strain or stress. Rather as neural and connective tissue stress and strain increase, axon physiology may become compromised at those locations where the translaminar tissue pressure gradient is steepest (Figure 5, see previous page) and/or where the axon's energy supply is or otherwise becomes most vulnerable.

In these regards, it is important to clarify the separate concepts of the translaminar pressure difference (the difference between IOP and the retrolaminar tissue pressure) - which generates a net posterior (outward) force on the surface of the lamina and the translaminar pressure gradient (schematically shown in green in Figure 2) which is the hydrostatic pressure gradient within the neural and connective tissues of the pre-laminar and laminar regions created by the translaminar pressure difference. Note that the in-plane hoop stress transferred to the lamina from the sclera is much larger than the stresses induced by the translaminar pressure difference (Figure 5, see previous page). CSF directly influences laminar position through its effect on the translaminar pressure difference. CSF may also effect scleral flange position within the region it projects to the sclera (Figure 2, see page 530), but in most eyes, because the projection of the CSF space is minimal this is not likely important (Figure 2, see page 530).

IOP has a similar direct effect on laminar position, but has an additional (and potentially more important) effect through the peripapillary sclera (Figure 2, see page 530). However, while the magnitude of the translaminar pressure difference may be small relative to the stresses within the connective tissues of the sclera and lamina, the axons separately experience it as the translaminar pressure gradient, the steepness of which is influenced by the thickness of the tissues over which it is experienced. In eyes with thin laminas or in which the lamina becomes thin through the course of the neuropathy,[52, 60-63] the translaminar pressure gradient may serve as a primary barrier to axon transport and flow within this region and an important physiologic determinant for the ONH axons and cells.

To understand if and how the lamina cribrosa will deform and remodel at a given level of CSF- and IOP-induced load requires engineering finite element models that take into account the geometry of the ONH connective tissues and their constituent material properties. Taken together these components determine the net "structural stiffness" of the lamina cribrosa and peripapillary sclera. It is this net structural stiffness combined with the inherent propensity of the astrocytes to remodel the laminar extracellular matrix of the lamina at a given level of strain, that will determine whether a given eye demonstrates a shallow or deep form of cupping at a given translaminar pressure difference (Figure 6, see next page).

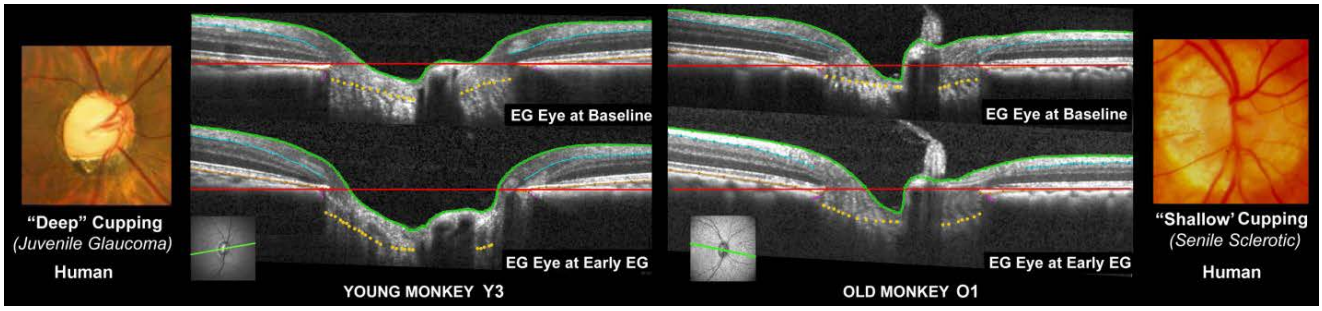

Figure 6. Differences in ONH connective tissue structural stiffness and/or remodeling may underlie "shallow" and "deep" forms of glaucomatous cupping in monkeys and humans. Deep (far left) and shallow (far right) forms of human glaucomatous cupping occur at all ages and IOP levels but are classically seen in youthful and elderly eyes, respectively. We have proposed that the ONH connective tissues "harden" with age and that on average aged eyes should demonstrate a shallower form of cupping (i.e. a shallower "phenotype") as a result.[42] Spectral domain optical coherence tomography (SDOCT) ONH B-scans (green, lower left) from the EG eye of a young (left) and old (right) monkey, when the eye was normal (upper) and at the second confirmation of confocal scanning laser tomography (CSLT) detection of ONH surface change in the young eye (lower left) and at the (later) pre- sacrifice data set in the old eye (lower right). All images were obtained after 30 minutes of manometer controlled IOP (10 mm Hg). In both eyes, while prelaminar neural tissue thickness alterations are present, laminar deformation is also apparent as an increase in the magnitude of space between the Bruch's membrane opening reference plane (red line) and the anterior lamina cribrosa surface (gold dots). Laminar deformation in the old eye is far less than in the young eye and this profound difference in laminar deformation occurred in the setting of a cumulative IOP insult that was approximately 5 times greater in the old eye. *Reprinted with permission[64]*

"CUPPING" IN FOUR MONKEY OPTIC NEUROPATHY MODELS

We have characterized glaucomatous damage to the ONH tissues within the monkey model of chronic unilateral experimental IOP elevation using 3D histomorphometric and more recently SDOCT imaging techniques.[17, 18, 24-26, 45, 57, 64-66] Our studies together suggest that early "cupping" (0-30% optic nerve axon loss) in the monkey ONH includes profound deformation and remodeling of lamina cribrosa that includes "posterior" (outward migration) of both the anterior and posterior laminar insertions, laminar thickening, that may involve recruitment of the retrolaminar orbital septa into more transversely oriented laminar beams. These laminar alterations occur in the setting of variable scleral canal expansion and myelin remodeling[67, 68] within the immediate retrolaminar orbital optic nerve (Figures 7, 8 and 9).

As the neuropathy progresses, there is eventual thinning of the lamina, further expansion of the scleral canal and splitting of the peripapillary sclera above the anterior most projection of the sub-arachnoid space (Figure 10). While our findings in advanced glaucoma, support classic descriptions of advanced monkey and human disease, our findings of profound laminar remodeling early in the neuropathy are important because they depict "deep" glaucomatous cupping to be an active process of deformation and cellular remodeling – rather than the passive response of deformation alone. Our findings in monkeys need to be confirmed in human disease. New SDOCT-based approaches to deep optic nerve head imaging, (Figures 11 and 12 and covered briefly in the final section) should not only make this possible (targeting human ocular hypertensive patients) but will eventually allow for the characterization of the laminar component of cupping in all forms of clinical optic neuropathy.

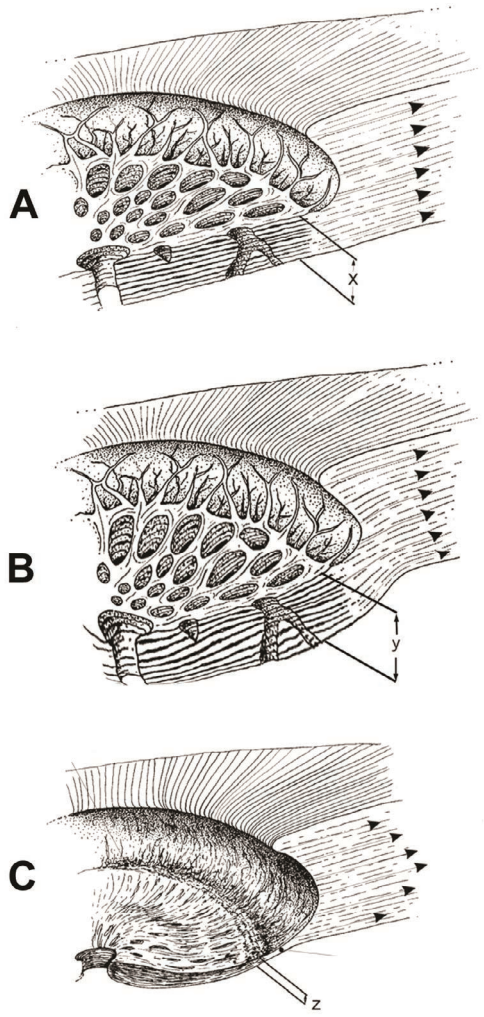

Figure 7. Our Central Hypothesis Regarding ONH Connective Tissue Damage In "Laminar" Cupping. **"**Deep", "laminar" or "glaucomatous" cupping is a manifestation of ONH connective tissue deformation, remodeling and/or damage which can be caused by either IOP-related or non-IOP-related insults. (See Figure 5). However, regardless of the primary insult to the ONH connective tissues, their deformation (if present) is driven by IOP-related connective tissue stress and strain. Thus the presence of ONH connective tissue deformation in any optic neuropathy is evidence that the level of IOP at which it occurred, (whether normal or elevated) is too high for the connective tissues in their present condition. **(A)** Schematic of normal laminar thickness (x) within the scleral canal with scleral tensile forces acting on the scleral canal wall. **(B)** Early IOP-related damage in the monkey eye (Figure 6)[17, 18, 23-26] includes posterior bowing of the lamina and peripapillary sclera accompanied by neural canal expansion (mostly within the posterior (outer) scleral portion) and thickening (not thinning) of the lamina (y). In our studies to date this appears to represent mechanical yield (permanent stretching) and or remodeling of the lamina rather than mechanical failure (physical disruption) of the laminar beams. **(C)** Progression to end-stage damage includes profound scleral canal wall expansion (clinical excavation) and posterior deformation and thinning of the lamina (z) by mechanisms that are as yet uncharacterized. If all other aspects of the neuropathy are identical, the stiffer the lamina, the more resistant it will be to deformation. Whether this is better or worse for the adjacent axons is a separate question that remains to be determined. *Reprinted with Permission*[42]

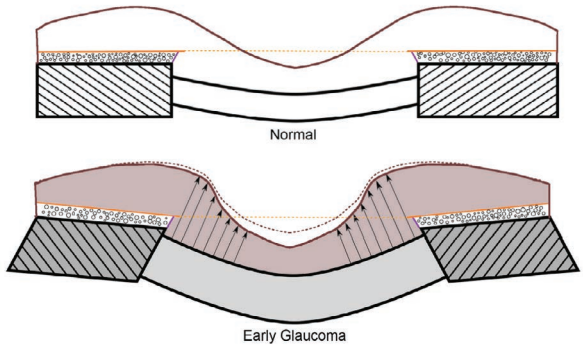

Figure 8. Profound Subsurface Structural Change Accompanies the Onset of CSLT-Detected Clinical Cupping in the Young Adult Monkey Eye but this May be Different in the Old Monkey Eye. Upper: Normal lamina cribrosa (unhatched), scleral flange (hatched), prelaminar tissue (beneath the internal limiting membrane - brown line), Bruch's membrane (solid orange line), Bruch's Membrane Opening (BMO) zero reference plane (dotted orange line), Border tissue of Elschnig (purple line), choroid (black circles) are schematically represented in the upper illustration. **Lower:** Overall changes in the ONH surface and subsurface architecture at the onset of CSLT-detected ONH surface change in experimental ocular hypertension in young adult monkey eyes are depicted below. Posterior bowing of the lamina and peripapillary scleral flange, thickening of the lamina and thickening (arrows) not thinning of the prelaminar neural tissues (brown shading) underlie posterior deformation of the ONH and peripapillary retinal surface (dotted brown to solid brown ILM). Thus, while expansion of the clinical cup and deformation of the surface are clinically detectable at this early stage of the neuropathy, because they occur in the setting of prelaminar tissue thickening, (not thinning), clinical cupping in experimental ocular hypertension in these young adult eyes is "laminar" in origin, without a significant "prelaminar" component (Figure 3). Because aged eyes will have (on average) stiffer connective tissues, we predict they will demonstrate less laminar and more prelaminar cupping at the onset of clinically detectable ONH surface change – a prediction that has been confirmed in a recent study (Figure 6, above). *Adapted from Yang, et al*[26]

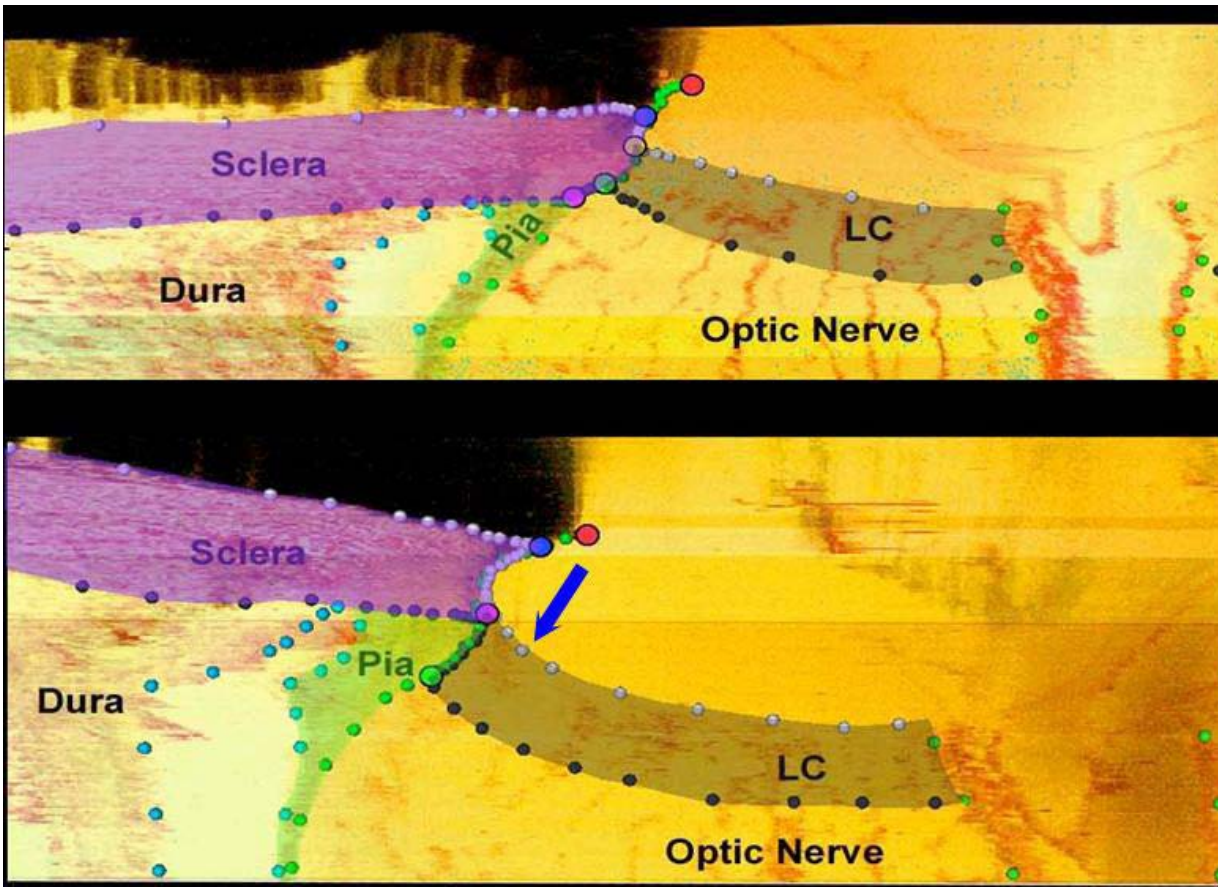

Figure 9. The pathophysiology of early experimental glaucomatous damage to the monkey ONH includes not only "thickening" but regional "migration" of the laminar insertion away from the sclera to the point that "complete pialization" of the laminar insertion is achieved in a subset of eyes.[44] Neural canal landmarks (**Red** – Neural Canal Opening (end of Bruch's Membrane); **Blue** – Anterior Scleral Canal Opening; **Yellow** – Anterior Laminar Insertion; **Green** – Posterior Laminar Insertion; **Purple** – Posterior Scleral Canal Opening) and segmented connective tissue (*dark grey* - lamina cribrosa; *purple* - peripapillary sclera; *light green* - pial sheath) within digital section images from the inferior region of the normal (**top**) and the contralateral early experimental glaucoma (**bottom**) ONH of a representative monkey. Note that in most normal monkey eyes, the lamina inserts into the sclera as is demonstrated in this monkey's normal eye (top). However at an identical location in the early experimental glaucoma eye of this animal (bottom) in addition to the lamina being thickened and posteriorly deformed, the laminar insertion has migrated outward such that both the anterior and posterior lamina effectively insert into the pial sheath. While regions of laminar insertion into the pia have been reported in normal human eyes[69], these findings are the first to suggest that active remodeling of the laminar insertion from the sclera into the pia is part of the pathophysiology of "glaucomatous" ONH damage. This phenomenon when present has important implications for the mechanism of axonal insult within these regions. *Adapted from Burgoyne, et al*[44]

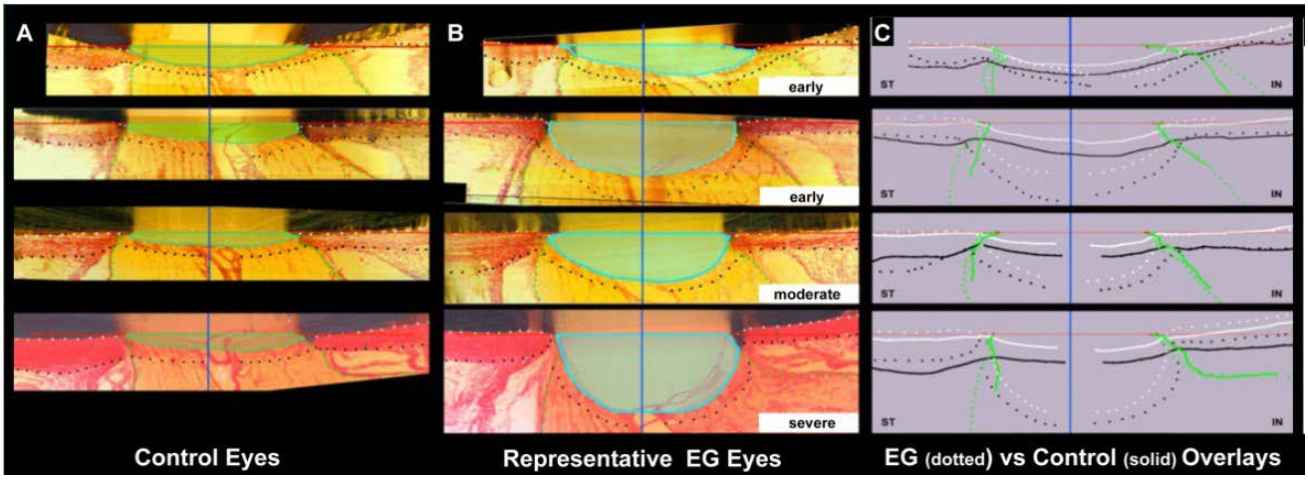

Figure 10. 3D Histomorphometric characterizations of early, moderate and severe monkey EG provide our targets for SDOCT phenotyping of the optic neuropathy of chronic IOP elevation in the monkey and human eye. We have previously proposed that regardless of its contribution to the mechanisms of RGC axonal insult, it is the presence of ONH connective tissue deformation and/or remodeling that underlies and defines a "glaucomatous" form of cupping, and that its character and magnitude determine the cupping "type" (i.e. its glaucoma phenotype) in a given eye. The schematic depiction of central horizontal 3D histomorphometric section images from the Control **(A)** and EG **(B)** eyes of 4 representative animals with *"early"*, "*moderate"* and *"severe"* axon loss are depicted in **(C)**. Eye-specific, EG eye deformation of the ONH connective tissues can be quantified by the (EG – Control eye) difference in our 3D volumetric parameter post-BMO total prelaminar volume[26] (shaded in light green in A and B). ONH connective tissue remodeling includes laminar thickening (also see Figure 5) and thinning and insertion migration (note that the lamina inserts into the pia in the bottom panel of (B).[45] We predict that laminar deformation/remodeling in optic nerve transection will be minimal, making it "*non-glaucomatous"* in character – a prediction which is in the process of being confirmed in 5 unilateral optic nerve transection (ONT) animals.[70]

Characteristics of three monkey experimental models of non-glaucomatous optic neuropathy have recently been reported.[70-73] Not surprisingly, optic nerve head features of pallor without excavation were described in unilateral experimental anterior ischemic optic neuropathy (AION),[71, 72] and pallor accompanied by diffuse retinal nerve fiber layer thickness (RNFLT) loss without evidence of laminar deformation was demonstrated by SDOCT in a subset of animals that underwent chronic experimental CSF lowering.[73] In a paper during the AGS portion of this joint meeting[70], our group will additionally describe the lack of SDOCT-detected lamina cribrosa deformation in the setting of profound ONH rim and RNFLT loss in 5 animals followed longitudinally after unilateral surgical optic nerve transection. These findings are in prominent contrast to SDOCT detection of profound laminar deformation in the setting early chronic IOP elevation.[66]

The lack of laminar deformation in the AION, CSF-lowering and ONT models, while not surprising, is important because it distinguishes them from chronic unilateral IOP elevation. The findings of no laminar deformation in the setting of RNFL loss in a subset of eyes following chronic CSF lowering are important for two reasons. First it suggests that the magnitude of translaminar pressure increase induced by CSF lowering from 12 to 4 mmHg is not enough to overcome the scleral tensile forces (at normal levels of IOP) holding the lamina taut within the canal. Second, it suggests that while the translaminar pressure increase that resulted from primary CSF lowering did not induce laminar deformation, the translaminar pressure gradient increase likely contributed to axonal compromise at normal levels of intraocular pressure in a subset of eyes. This finding suggests the translaminar pressure gradient may be a risk factor for RGC axon loss at all levels of IOP. Finally, the presence of laminar deformation and remodeling in chronic IOP elevation is important because it confirms those phenomena to be defining features of the optic neuropathy of chronic IOP elevation that are detectible at its earliest clinically detectable stage.

The search for a model of low tension glaucoma is important to identify non-IOP-related insults that are capable of not just damaging axons in a glaucomatous pattern but weakening the ONH connective tissues such that they deform and remodel at previously tolerated levels of "normal" IOP. We do not have an experimental model of glaucoma that does not require IOP elevation. Using SDOCT to detect early deformation of the lamina should be considered a target until proven otherwise. New SDOCT imaging paradigms for phenotyping the ONH/RNFLT/Macular tissues should enhance this kind of characterization (Figures 11 and 12).

OCT PARADIGM CHANGE IN PHENOTYPING THE ONH/RNFL/MACULA OF MONKEYS AND HUMANS

Whether the desire is to detect laminar deformation in a human patient in which the role of IOP and its lowering is uncertain, or to detect laminar deformation in experimental models of normal pressure glaucoma, a new paradigm for SDOCT image acquisition and regionalization relative to the anatomic axis between the SDOCT detects fovea and the centroid of Bruch's Membrane opening[74-78] should enhance our ability to phenotype all forms of damage to the visual system in diseases that are dear to both of our sub- specialties. A growing literature is using SDOCT and adaptive optics imaging to characterize the ONH cupping in all stages and manifestations of monkey and human glaucoma.

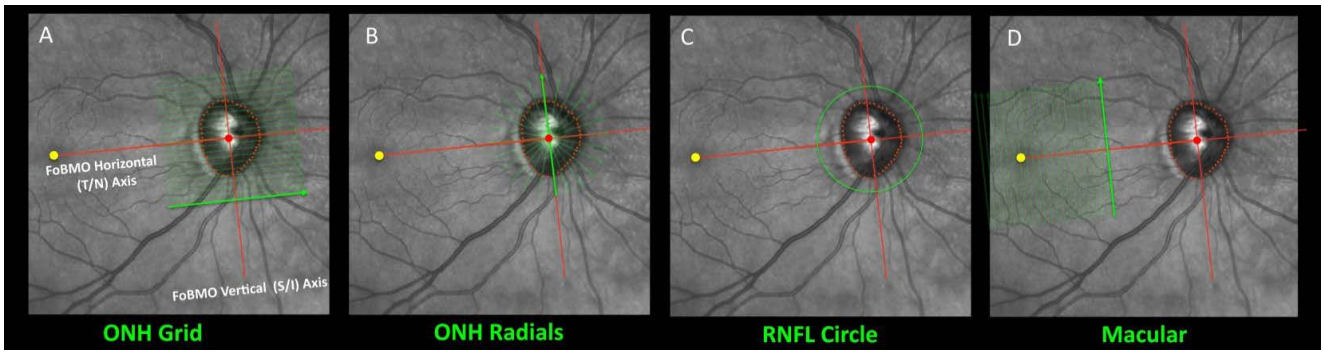

Figure 11. SDOCT ONH, RNFL and Macular data sets acquired relative to the SDOCT determined Foveal to BMO (FoBMO) axis. FoBMO ONH 768 x 256 grid, 48 radial, RNFL Circle and macula Grid scans identically acquired using eye tracking[79] each time the eye is imaged after BMO, its center and the fovea are anatomically identified during the first imaging session.

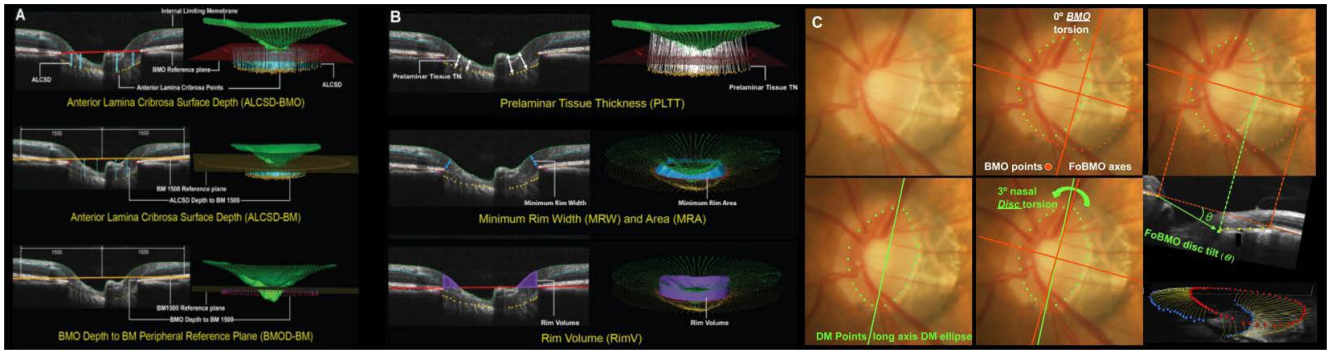

Figure 12. FoBMO ONH phenotyping will include quantification of ONH *tilt*, *torsion* and the *neural canal minimum*. We have published extensively on the ONH parameters **ALCSD-BMO**, **ALCSD-BM**, **BMOD-BM**, **PLTT**, **MRW**, **MRA** and **Rim Volume** (**(A)** and **(B)**).[66, 78, 80-82] The SDOCT definitions of ONH torsion and tilt are evolving.[83, 84] *ONH torsion* will be defined as the angle of the long axis of the disc margin ellipse relative to the vertical FoBMO axis (**(C) -** lower center). *BMO torsion* will be defined as the angle of the long axis of the BMO ellipse relative to the FoBMO vertical axis (shown as zero in (C - upper middle) because BMO is a circle). *ONH tilt* will be defined as the angle between a line connecting the nasal BMO point and the temporal SDOCT projection of the Disc Margin within the FoBMO B-scan (C – lower right). The *neural canal minimum* defines the smallest cross-sectional area through which the RGC axons pass using all BMO (red) and anterior scleral canal opening (blue) points (lower right).[78, 85]

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Author Conflicts of Interest: Dr. Burgoyne is NIH funded to study the effects of aging in the monkey experimental glaucoma model using 3D histomorphometric techniques. He is also NIH funded to use SDOCT imaging to translate techniques developed in monkeys to human patient care. In this regard, he is a consultant to Heidelberg Engineering from which he receives unrestricted research support and occasional travel funds but no honorarium or personal income. He has received no travel support or honorarium to attend this meeting.

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GLAUCOMA AS A NEUROLOGICAL DISEASE

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INTRODUCTION

The retinal ganglion cells (RGC) and their axons that form the optic nerve are anatomically and developmentally an extension of the central nervous system (CNS). In fact, the optic nerve should not be considered a "nerve" but rather a CNS white matter "tract" containing glia of the white matter of the brain and spinal cord namely oligodendrocytes, astrocytes, and microglia, rather than Schwann cells. The optic nerve is also surrounded by meninges like other white matter tracts. It is not surprising that pathological processes that affect the optic nerve, therefore, demonstrate changes in the brain. However, many ophthalmologists and members of the lay public have focused on glaucoma as exclusively a disease of the eye and have been surprised when pathological abnormalities have been identified in the part of the afferent visual pathway that extends into the brain. This view has been pervasive because the recognized risk factors associated with glaucoma have been ocular: intraocular pressure, corneal thickness, abnormalities of the trabecular meshwork and the angle. Many investigators have highlighted that this perception has resulted in lost opportunities.

Consideration of glaucoma in the context of the CNS reveals that it has significant similarities with other neurodegenerative disorders. This is an exciting paradigm shift in thinking and has played a critical role in the recent advances in understanding glaucoma pathophysiology. This paper will review the changes in the brain that occur in glaucoma as well as focus on the similarities glaucoma displays with other neurodegenerative disorders.

CHANGES IN THE BRAIN THAT OCCUR IN GLAUCOMA

In glaucoma the RGC is the principal cell type injured. The components that are located within the eye are the RGC dendrites, cell body and unmyelinated axons. However, the majority of the RGC lies within the brain forming the intraorbital, intracanalicular, and intracranial components of the optic nerve, optic chiasm, and optic tract. The axons relay information to several nuclei, but the majority of the axons synapse in the lateral geniculate nucleus (LGN). Other areas of the brain that receive input from axons are the pretectal nucleus, superior colliculus, and suprachiasmatic nucleus.

Axonal degeneration after optic nerve injury, including glaucoma, occurs both in retrograde direction (towards the proximal cell body) and towards the distal axon terminal (orthograde or Wallerian degeneration) at the LGN. In addition, transynaptic degeneration, the process whereby damage is transmitted through synaptic connections along anatomic and functional neuronal pathways, occurs in glaucoma as well as other CNS diseases. Therefore, secondary changes in the brain are well-recognized to occur following various types of optic nerve injury including glaucoma. Research suggests that in glaucoma the entire visual pathway is involved extending from the retina to the visual cortex. Studies on glaucoma-associated changes in the human brain have included postmortem investigations, assessed biochemical changes (e.g., cytochrome oxidase) in primates or more recently, neuroimaging.[1–7] These changes include atrophy of the LGN laminae corresponding to the injured optic nerve and a reduction in visual cortex thickness corresponding to the termination of the LGN relay neurons.

Neuroimaging studies have expanded our understanding of brain involvement in glaucoma providing evidence that these changes in the brain correlate with the clinical severity of glaucoma. Diffusion tensor imaging reveals that the white matter of the visual pathway (optic tract and radiations) shows proportional damage to that seen in the structural and functional changes in the optic nerve[8] while 3T MRI also correlate LGN atrophy with stage of glaucoma.[9] An intriguing finding revealed by 3T MRI studies is that there are widespread abnormalities in the brain beyond the afferent visual pathway including the reduction in bilateral gray-matter volume in the lingual gyrus, calcarine gyrus, postcentral gyrus as well as in the right cuneus, right inferior occipital gyrus, left paracentral lobule, and right supramarginal gyrus.[10]

One emerging concept in neurodegeneration that requires further exploration in glaucoma but potentially could explain these widespread findings is that of spread of disease through pathological proteins.[11]

Other lines of investigation have also suggested that the changes in the brain in glaucoma extend beyond the afferent visual pathway. Blood flow abnormalities

have been shown to occur in the brain of patients with both primary open angle glaucoma and 'normal tension glaucoma'. These include abnormal regional cerebral blood flow patterns, vasoreactivity to hyperoxia, diffuse white matter lesions, and lacunar infarcts.[12–15] These findings suggested widespread change in cerebral perfusion and a partial cerebrovascular insufficiency in glaucoma. Recently, numerous studies have further delineated these vascular abnormalities using functional MRI. [16–19]

The changes that have been described in the afferent visual pathway are consistent with our understanding of the processes of transynaptic degeneration. However, the widespread changes in the brain identified in glaucoma patients is intriguing and requires further investigation.

FEATURES OF GLAUCOMA THAT ARE CONSISTENT WITH NEURODEGENERATIVE DISORDERS

Although the etiologies of neurodegenerative disorders are diverse, they share many common elements. Glaucoma is increasingly recognized to share these features to varying extent with neurodegenerative processes such as Alzheimers Disease (AD), Parkinsons Disease (PD), Huntingtons Disease (HD), and amyotrophic lateral sclerosis (ALS) amongst others.

1. Age- related
2. Genetic predisposition
3. Predilection for sub-population of neurons
4. Mechanism of Cell Injury
5. Early functional deficits that precede loss of neuronal substrates

FEATURES COMMON WITH OTHER CNS DISORDERS

AGE

Age is the greatest recognized risk factor for glaucoma with the likelihood of developing glaucoma increasing nearly 7-fold after 55 years. Although neurodegenerative disorders can occur at any age, they tend to become more common with aging with a geometrically increasing prevalence. Although the exact reasons for this are unclear, several possible explanations have been postulated. These include mitochondrial changes with age, change in susceptibility of the affected tissues to injury, and deposition or increased levels of one or more substances that increases toxicity or loss of protective substances. Investigators have suggested that this may suggest shared pathophysiological mechanisms between glaucomatous optic neuropathy and other neurodegenerative disorders. [20, 21]

GENETIC PREDILECTION

Most neurodegenerative disorders have a less common variant that occurs at a younger age that has a strong genetic origin, and a sporadic form that manifests later in life which has not been associated with a specific gene mutations although still may be associated with a genetic predisposition. For example, early onset forms PD, AD and HD comprise less than 10% of cases. The more prevalent form of neurodegenerative disorders are late-onset and are thought to be a combination of genetic susceptibility with other risk factors although the pathophysiological mechanisms overlap the early onset forms. Similarly, primary open angle glaucoma in children and young adults often follows simple Mendelian genetics whereas primary adult-onset open angle glaucoma rarely does.[22, 23]

PREDILECTION FOR CERTAIN POPULATION OF CELLS

A common feature of neurodegenerative disorders is a predilection for specific cell populations although there is extension to involvement of other cell types especially in advanced stages. For glaucoma the RGC are selectively involved, AD tends to have a predilection for hippocampal cells, PD for the nigrostriatal dopaminergic neurons, and ALS for upper and lower motor neurons. [24] However, there is a strong body of evidence that suggests that photoreceptors and other retinal neurons are involved in glaucoma.[25]

MECHANISM OF CELL INJURY

Neurodegenerative diseases share common pathways in the process of cell death which ultimately occurs largely by apoptosis. The pathophysiology is a complex process with many of the areas still to be elucidated. However, there are some important emerging concepts.

MISFOLDING PROTEINS

The vast majority of neurodegenerative disorders have been shown to involve aberrant processing, misfolding and aggregation of proteins. Several types of abnormal aggregated proteins have been identified. In AD, extracellular β -amyloid (Aβ) senile plaques and intracellular neurofibrillary tangles composed of abnormally phosphorylated tau protein have been identified. The fibrillation of tau proteins occurs in frontotemporal dementia (FTD). Alpha-synuclein in the Lewy bodies of Parkinson disease (PD) and in Lewy body disease are also recognized features.[26]

In glaucoma misfolding of proteins has become increasingly studied. Tau proteins have been detected in horizontal cells in human glaucoma retina.[27] However, in mouse models of ocular hypertension there is a loss of tau proteins in the retina. [28] This absence of tau is thought to be secondary to proteolysis and has been suggested to contribute to the pathogenesis of RGC death. The mechanism is thought to be an increase in calcium, which in turn activates calpain, a calcium-dependent protease. One possible explanation for the failure to detect phosphorylated tau is that tau protein is cleaved by calpain before detection is possible. [29] However, investigators have have shown that amyloid

precurson protein (APP) is abnormally processed and neurotoxic amyloid- species is upregulated in retina of rodents exposed to chronically elevated eye pressure.

ACTIVATION OF GLIA

Activation of glia occurs in all neurodegenerative disorders and is thought to be closely linked with the pathogenesis of these conditions. Astrocytes maintain neuronal homeostasis by mediating extracellular ion and neurotransmitter balance, regulating vascular flow and blood–brain barrier integrity, and secreting a host of growth factors and neurotrophic factors.[30] [31] In neurodegenerative disorders astrocytes become reactive, hypertrophic and migratory .[32] In glaucoma activated astrocytes at the optic nerve head have been proposed to secrete matrix metalloproteases and signal a variety of cytokines and growth factors that may result in optic nerve head excavation. Activation of Muller glia has also been described following chronic ocular hypertension. [33]Furthermore, retinal astrocytes and connex 43 protein , the main astrocytic gap junction protein, have been shown to be upregulated in human post-mortem glaucomatous eyes. [34] Once activated, glia may provide some supportive function such as degradation and elimination of amyloid precursor protein peptides, but can also release damaging cytokines and chemokines that contribute to the pathogenesis.[35]

NEUROINFLAMMATION

Neuroinflammation has become recognized to be a contributor to a wide range of chronic neurodegenerative disorders such as AD and PD. Receently, there has been a growing body of research that has revealed that neuroinflammation also has a role in glaucoma. Complement proteins, tumor necrosis factor (TNF-alpha), and serum amyloid A (an acute marker for inflammation and infection) have been shown to be upregulated in glaucoma as well as AD. [36]

CONCLUSIONS

The focus on the brain changes in glaucoma provides opportunities as well as challenges. On the one hand, it should not detract from exciting developments that are emerging from the study of ocular risk factors such as scleral changes and advances in trabecular meshwork pathology. Therefore, the findings that there are brain changes in the CNS should not be viewed as mutually exclusive or independent from the ocular processes, but rather intricately connected. Furthermore, the relative sequence of brain and RGC damage needs to be clarified. However, further understanding of the CNS involvement in glaucoma should provide intriguing insights into the progression of the disease as well as opportunities for new therapies.

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THE BRAIN IN GLAUCOMATOUS OPTIC NEUROPATHY: EVIDENCE FOR TROPHIC-FACTOR MEDIATED SELF-REPAIR

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LEARNING OBJECTIVES

1. Describe that pathogenesis in glaucoma involves the entire optic projection to the brain, especially retinal recipient areas in important hypothalamic, thalamic, and midbrain nuclei
2. Describe that axonal dysfunction including deficits in active transport is an early event in most age-related neurodegenerative disorders including glaucoma. When axon dysfunction is prevented, outright degeneration of the optic nerve is also abated
3. Describe that in models of glaucoma, central brain targets respond to early loss of transport from retinal ganglion cell axons with increased brain-derived neurotrophic factor. This increase is concurrent with an interval of persistence of synapses and post-synaptic neurons

CME QUESTIONS

1. Explain how glaucoma involves early events in the brain but should not be considered a "brain disease" *per se.*
2. Explain how preservation of anterograde axonal transport from the retina to the brain is a useful outcome measure for testing experimental neuroprotective therapies.
3. Describe evidence that central brain structures in the optic projection do not quickly degenerate even after depletion of axonal transport from the retina and that mechanisms of self-repair could be relevant.

KEYWORDS

1. Neurodegeneration
2. Axon Transport
3. Superior Colliculus
4. Brain-derived Neurotrophic Factor
5. Astrocyte

ABSTRACT

As in other age-related neurodegenerative diseases, progression of neurodegeneration in glaucoma involves early axonopathy. In glaucoma, this is marked by degradation of active transport along retinal ganglion cell (RGC) axons stretching from the retina to the brain. In experimental systems, transport degradation fails first in the most distal site in the optic projection, the superior colliculus of the midbrain. Even as degradation progresses from one retinotopic sector to the next, important structures in the affected sectors persist, including RGC synapses to SC neurons. This structural persistence defines a therapeutic window of opportunity and is accompanied by focally increased brain-derived neurotrophic factor (BDNF) in hypertrophic SC astrocyte glia. Thus, central brain structures in glaucoma may respond to disease-relevant stress by induction of mechanisms useful for maintaining retinal signals.

A NEUROBIOLOGICAL PERSPECTIVE OF GLAUCOMA

Increasingly the focus in glaucoma research from a neuroscience approach is shifting away from the elimination of retinal ganglion cell (RGC) bodies, which is late in progression, and towards degeneration of the optic projection to the brain, which includes many early events in pathogenesis (Calkins, 2012). As this shift occurs, the involvement of a broader neuroscience community brings with it the realization that experimental studies of vision loss and its mechanisms in glaucoma are useful tools for understanding neurodegeneration more broadly and potential therapeutic targets in other diseases of the central nervous system (CNS). This is especially so for age-related diseases (Trovato Salinaro et al., 2104; Namekata et al., 2014).

Linking glaucoma to CNS disease, however accurate, bears with it the danger of a prominent misunderstanding – that glaucoma is at its etiological roots a brain disease; something that begins in the brain and affects the eye. It is not, nor should it be construed as one, even though certain early events in pathogenesis are observed in the brain before the retina or optic nerve (Crish et al., 2010). In its most general terms, and with some noteworthy exceptions (Wax et al., 2008), glaucoma is a family of diseases in which sensitivity to intraocular pressure (IOP) causes degeneration of the optic projection through stress most likely conveyed at the nerve head through complex

interactions with the RGC axon. Many of these interactions involve biomechanical stressors that affect axon function (Burgoyne, 2011; Chidlow et al., 2011). That this stress can be read early in the brain, where RGC axon terminals form connections with post-synaptic neurons, is not tantamount to the disease originating in the brain. To state otherwise, as popular media have done in recent years, is a misinterpretation of empirical data that tends towards sensationalism.

This caveat does not in any way diminish the importance of considering glaucoma from a neuroscience viewpoint that focuses on the brain. We are beginning to understand that the optic projection and visual brain are not passive during progression. Quite the contrary; the retina (Ward et al., 2014), optic nerve head (Fu and Stretevan, 2012), and higher visual structures (Sponsel et al., 2014) all demonstrate compensatory mechanisms to counter loss of function. Mechanisms of plasticity, remodeling and adaptability ultimately are just as relevant for glaucoma – and by extension other CNS diseases – as they are for complex synaptic functions in the healthy brain. Thus, translational research targeting new therapies must evolve from an exclusive focus on how glaucoma progresses from IOP-related stress at the nerve head to a new spotlight on intrinsic mechanisms that counter loss of function.

EARLY PATHOGENESIS INVOLVES THE OPTIC PROJECTION

The optic projection is defined by the path of RGC axons out of the retina and through the optic nerve to their termination targets in the brain (Figure 1). RGC axons from each eye cross at the optic chiasm to form the ipsilateral and contralateral projection to the brain. From there, axonal terminals provide synapses to neurons in several important nuclei. In primates, the primary target for RGC axons is the lateral geniculate nucleus (LGN) of the thalamus, which relays visual information directly to the primary visual cortex. In rodents, nearly every RGC projects primarily to the superior colliculus (SC) of the midbrain, with axon collaterals extending to other nuclei including the LGN. In all mammals, the SC is the most distal pre-cortical site, and therefore the most susceptible to bioenergetic stressors affecting the unmyelinated RGC axon segment in the retina and nerve head (reviewed in Calkins, 2012).

Early in pathogenesis, age-related neurodegenerative disorders like glaucoma involve axonal dysfunction, including diminished active transport to and from major projection targets in the brain (Adalbert et al., 2009; Morfini et al., 2009). One of the earliest pathogenic events in both chronic and inducible experimental models of glaucoma is degradation of active anterograde axon transport from the retina to the brain (Crish et al., 2010; Dapper et al., 2013; Ward et al., 2014). Anterograde transport in rodent models fails first at the most distal site in the projection, the SC, and degrades over time in a distal-to-proximal progression before failing completely in the retina (Crish et al., 2010; Figure 2). There are intriguing metabolic possibilities to explain why failure occurs first at the most distal site. These are reviewed elsewhere (Baltan et al., 2010; Rintoul and Reynolds, 2010; Calkins, 2012). Anterograde transport is more metabolically demanding than retrograde axonal transport, due to differences in the molecular machinery involved (Mallik et al., 2004). Thus, in models of glaucoma, transport from RGC axon terminals in the brain to the cell body in the retina persists long after anterograde transport is depleted, probably as long as the axon itself survives structurally (Calkins, 2012). The relative sustainability of retrograde transport is likely to have implications for therapeutic interactions between RGC axon terminals and the post-synaptic brain structures with which they interact.

Several important points arise from rodent studies utilizing degradation of active anterograde transport in the SC as a functional outcome measure. Age is the critical determinant of transport failure, with elevated IOP serving as an additional stressor that increases the likelihood of failure (Crish et al., 2010; Calkins, 2012; Calkins and Horner, 2012; Calkins, 2013). In multiple experimental models, both chronic and inducible, deficits in anterograde transport are detected earlier than a variety of other pathogenic outcomes – including axon degeneration in the optic nerve and RGC body loss in the retina. This chronology renders transport read-out in the SC a convenient outcome measure for experimental interventions (Lambert et al., 2011; Bosco et al., 2012; Dapper et al., 2013; Ward et al., 2014). Finally, degradation of axon transport in the SC is spatially progressive, filling in from one retinotopic sector to the next. In early progression, a given SC is very likely to contain both affected and unaffected regions. This provides a convenient internal control for investigations directed at how post-synaptic structures in the optic projection respond to glaucomatous challenges (Crish et al., 2013), a topic we take up below.

A THERAPEUTIC WINDOW IN PROGRESSION

Across different experiment models, both chronic (e.g., DBA2J mouse) and inducible, degradation of anterograde axonal transport to the brain marks the beginning of an important window of opportunity for intervention. This window is defined by the interval during progression between the onset of deficits in axon function and actual degeneration of RGC axons in the optic projection, which occurs later. These functional deficits can be detected quite early, either through axonal or retinal physiology (Quigley and Addicks, 1980; Baltan et al., 2010; Saleh et al., 2007). A similar interval likely exists in human glaucoma, with reversal of physiological deficits with timely IOP-lowering interventions (Sehi et al., 2010). Experimental interventions that target this period of functional quiescence in the projection and are successful in restoring axon transport also abate subsequent steps in pathogenesis. For example, daily topical application of a potent and highly selective inhibitor of retinal p38 MAPK activity was effective at stopping progression entirely in the microbead-occlusion

FIGURES AND LEGENDS

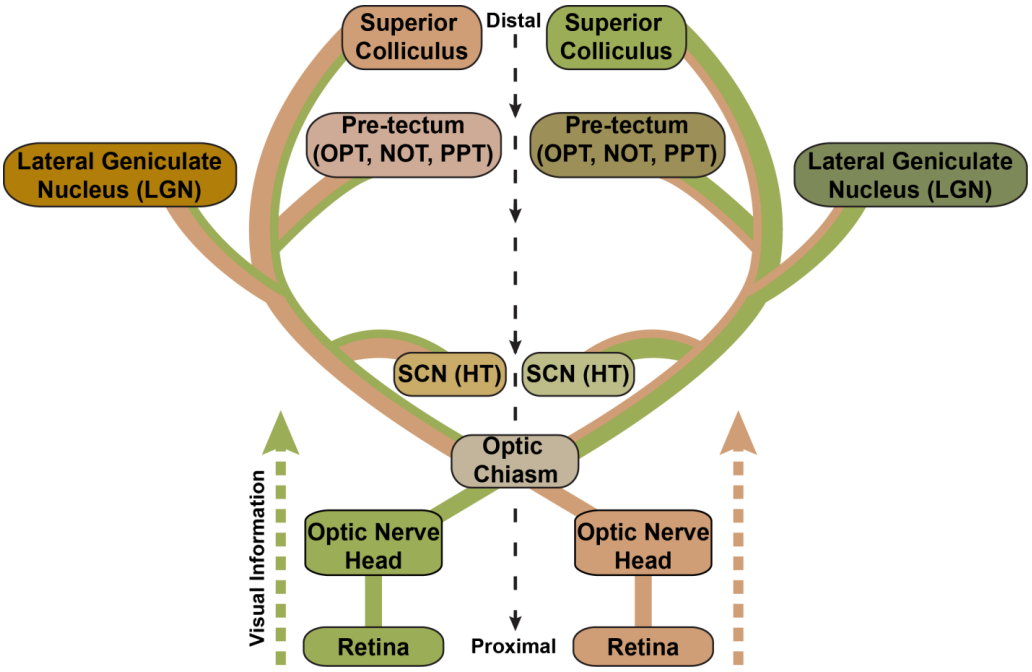

Figure 1. Retinal Projection in the Rodent Brain. Schematic diagram illustrates the dominant contralateral projection of the retina in the rodent visual system. RGC axons exiting the retina through the optic nerve head cross at the optic chiasm to join either the ipsilateral or contralateral optic tract in the brain. Central targets for RGC axons are highly conserved across mammals and include the suprachiasmatic nucleus (SCN) of the hypothalamus (HT) and the olivary pretectal nucleus (OPT), nucleus of the optic tract (NOT), and posterior pretectal (PPT) nucleus of the pre-tectum in the subcortical midbrain. In primates, the lateral geniculate nucleus (LGN) of the thalamus is the primary RGC recipient. Across mammals, the superior colliculus of the midbrain is the most distal direct target for ascending RGC axons. In rodents, all or nearly all RGCs project to the colliculus, while extending axon collaterals to nuclei lying more proximal to the retina (e.g., anterior to the colliculus; Linden and Perry, 1983). There are numerous inter-species differences in the strength of specific RGC projections.

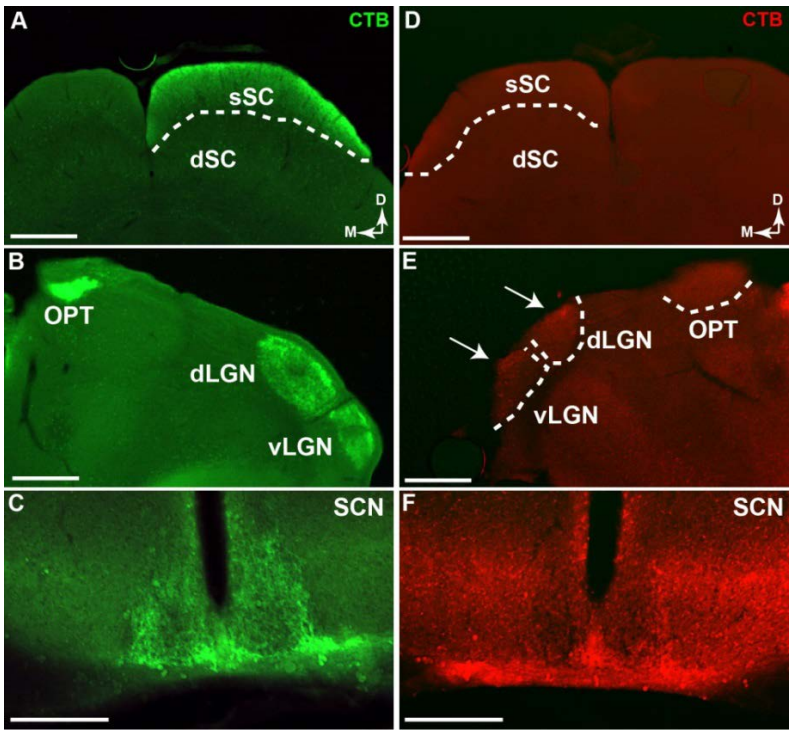

Figure 2. Deficits in Axon Transport Progress Distal to Proximal. (A) Cross-section (coronal plane) through the superior colliculus (SC) from an 8 month DBA2J mouse following intravitreal injection of cholera toxin β (CTB). Dashed line demarcates fully intact anterograde transport of CTB in retinal recipient region in superficial SC (sSC), just dorsal to deep (dSC). **(B)** In same brain, anterograde transport of CTB is also intact in structures more proximal to the retina, including the olivary pretectal nucleus (OPT) and dorsal and ventral lateral geniculate nucleus (dLGN and vLGN), as well as the suprachiasmatic nucleus (SCN), as shown in **(C)**. The contralateral SC from the same brain **(D)** demonstrates a complete depletion of CTB transport from the retina. In distal to proximal progression, transport has also failed in the OPT, but persists at a residual level in the LGN **(E)**. More proximally, in the SCN **(F)**, axonal transport remains intact. Scale = 500 µm (A,B, D,E) or 100 µm (C,F).

inducible rat model (Dapper et al., 2013), as was systemic delivery of the alpha-2 adrenergic receptor agonist brimonidine in another inducible model (Lambert et al., 2011). In these cases, for control/vehicle cohorts, deficits in anterograde transport exceeded axon degeneration in the optic nerve which, in turn, exceeded RGC body loss in the retina (see Figure 4 of Calkins, 2012). Correspondingly, with treatment, rescue of transport was a surrogate marker for survival of RGC axons and bodies.

A key avenue of investigation addresses how RGC post-synaptic targets in the brain respond to glaucomatous stressors and whether this response includes mechanisms that promote RGC axon survival. At one end of the spectrum, post-mortem samples of LGN from human patients with significant field loss show significant loss of tissue (Gupta et al., 2006). With prolonged exposure to elevated IOP, non-human primate LGN demonstrates significant depletion of neurons post-synaptic to RGC axon terminals (Harwerth et al., 2002; Weber et al., 2000; Yucel et al., 2003). Even so, loss of LGN neurons generally lags by 20-30% RGC axon degeneration in the optic nerve (Yucel et al., 2003). Our studies show similar persistence of post-synaptic neurons and of RGC synaptic terminals in the SC well after axonal transport from the retina is depleted completely (Crish et al., 2010). This is so for both the DBA2J mouse model of hereditary pigmentary glaucoma as well as the microbead model. Thus, just as RGC axons in the optic nerve persist for a period of time following loss of anterograde transport, so too do their axon terminals and synapses with relay neurons in the brain.

POSSIBLE MECHANISMS OF SELF-REPAIR IN GLAUCOMA

Structural persistence in the optic projection is testimony to the resilience of the CNS and offers clues to possible intrinsic pro-survival mechanisms in glaucoma. Post-synaptic structures in the brain respond to disease-relevant stressors including degraded axon transport in ways thought to promote recovery of axon activity. This response may include a certain degree of synaptic remodeling to compensate for loss (Kimura et al., 2006, Hennigan et al., 2007 and Song et al., 2008). In retinotopic sectors of depleted transport in the SC, astrocyte glia become hypertrophic compared to SC regions with intact transport (Figure 3). These same astrocytes demonstrate increased levels of brain-derived neurotrophic factor (BDNF) that is likely sequestered after release from SC neurons (Crish et al., 2013). These changes occur prior to elimination of important structures in the SC, including synapses from RGC axons and dendrites of SC post-synaptic neurons, visualized with antibodies against MAP2 (Figure 4). Increases in BDNF occur with other injury models, including NMDA-induced excitotoxicity and acute elevations in IOP (Tanaka et al., 2009; Sasaoka et al., 2008; Zhang et al., 2009).

Why would retinorecipient targets in the brain respond this way to disease-relevant stressors? One possibility lies in the fact mentioned earlier that retrograde axonal transport in the optic projection persists in glaucoma as long as RGC axons themselves. BDNF is implicated in axonal guidance and RGC dendritic arborization during development (He et al., 2003). Whereas retinal-derived BDNF inhibits dendritic arborization, BDNF shuttled in retrograde fashion along RGC axons promotes outgrowth (Cohen-Cory and Lom, 2004). In the adult visual system, when IOP is elevated acutely, retrograde transport of exogenously applied BDNF from the SC to the retina is greatly diminished (Pease et al., 2000). Thus, SC-derived BDNF might be uploaded to RGC neurons in retinotopic sectors challenged by degradation of anterograde axon transport for the purpose of protecting RGC dendritic arbors in the retina. Supporting this hypothesis, combined application of exogenous BDNF to the eye and brain is far more effective in protecting RGCs than application to the eye alone (Chen and Weber, 2004; Weber et al., 2010).

In our studies, however, the greatest fraction of BDNF was found to be in stored membrane vesicles and not observed directly in RGC axon terminals (Crish et al., 2013). We argued that perhaps vesicle-stored BDNF in SC neurons is released and sequestered by astrocytes in response to diminished RGC axonal transport to promote synaptic activity and survival. In the CNS, BDNF contributes broadly to maintenance of synaptic function and plasticity of neural circuits (Huang and Reichert, 2001; Lessmann et al., 2003). Astrocytes are likely to play an important role. In the hippocampus, astrocytes expressing the TrkB.t1 receptor isoform bind extracellular BDNF for storage prior to re-release into the extracellular space (Alderson et al., 2000). This pathway could explain the high levels of BDNF in both SC neurons and astrocytes as a mechanism to conserve local excitatory interactions from RGC axon terminals (Crish et al., 2013). In support of this, in experimental Huntington's disease, over-expression of BDNF in astrocytes conserves striatal synapses (Giralt et al., 2011). Such a mechanism could also contribute to the highly plastic coordination of residual retinal input to the brain to optimize binocular visual field coverage observed recently in human patients (Sponsel et al., 2014).

CME ANSWERS

1. Functional outcomes involving the retinal ganglion cell axon reflect the physiology and state of the entire ganglion cell. Pathogenic outcomes in the brain, such as degradation of anterograde transport, likely reflect stress originating within the optic nerve head or retina. To call glaucoma a "brain disease" implies there is strong evidence for causal or etiologically events originating in the brain in most types of glaucoma.

2. Deficits in axon transport from retina to brain occur early in relevant animal models, with outright degeneration of the optic nerve and retina later. Experimental interventions that are successful in preserving axon transport also preserve optic nerve and retinal structure.

3. Careful studies of progression indicate that axon degeneration in the optic nerve and loss of neurons in the SC in particular lag considerably behind depletion of axon transport. As well, RGC synapses to SC neurons remain, as do SC dendritic processes. One possible mechanism in the SC is the focal elevation in BDNF in retinotopic regions of transport deficit – which could work to preserve synapses and associated structures.

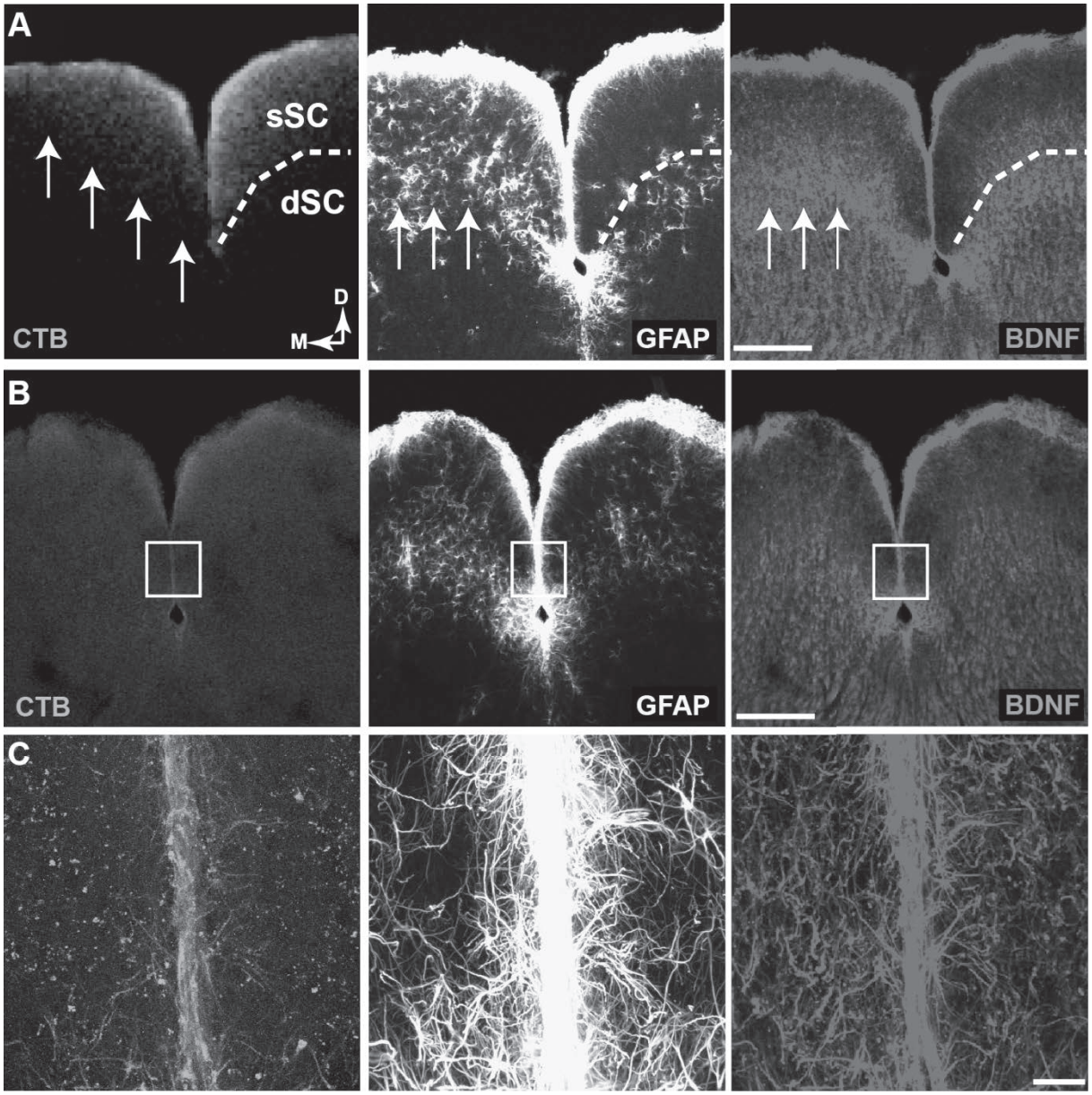

Figure 3. Deficits in Axon Transport Increase BDNF Focally. (A) Coronal section through the SC of an 10 month DBA2J mouse following bilateral intravitreal injection CTB shows fully intact anterograde transport in sSC from one eye (dashed line) with degradation of signal in the opposing SC (arrows). Staining for glial acidic fibrillary protein (GFAP) shows increased astrocyte hypertrophy in same SC, while brain-derived neurotrophic factor (BDNF) also increases. **(B)** SC from a 10 month DBA2J mouse shows bilateral deficit in anterograde transport of CTB, corresponding to a more uniform distribution of hypertrophic GFAP-labeled astrocytes and BDNF. Higher magnification images of the midline (boxed region) between the two SC (**C**) shows depleted CTB signal corresponding to increased BDNF in hypertrophic astrocytes. Scale = 200 µm (A,B) or 20 µm (C).

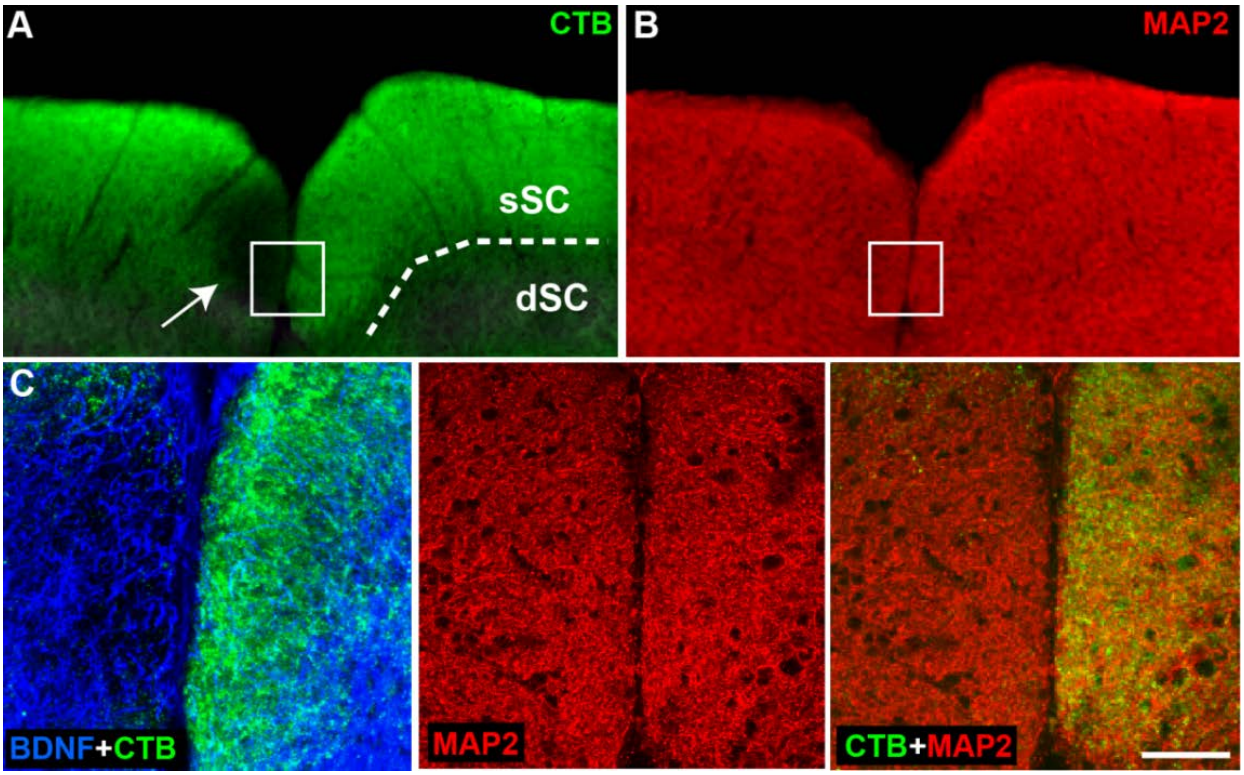

Figure 4. Persistence of Neuronal Structure. (A) SC from an 3 month DBA2J mouse shows a focal deficit in CTB transport from the retina (arrow) near the midline to the fellow SC, which has intact transport (dashed line). **(B)** Label for microtubule-associated protein 2 (MAP2) in the dendritic arbors of SC neurons remains unchanged despite the transport deficit. **(C)**. Higher magnification images of the midline between the two SC (boxed region in A,B) shows increased BDNF where CTB transport is depleted and consistent MAP2 staining. Scale = 20 µm for C.

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THE CELL AND MOLECULAR BIOLOGY OF GLAUCOMA: COMMON NEURODEGENERATIVE PATHWAYS AND RELEVANCE TO GLAUCOMA

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Glaucoma is an age-related, chronic neurodegeneration of the optic nerve. The molecular and cellular pathologies that characterize glaucoma are shared by other chronic neurodegenerations such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Therapies directed at treating chronic neurodegenerations could potentially be used to treat glaucoma, and conversely therapies that are successful in treating glaucoma could be used to treat other chronic neurodegenerations.

OUTLINE

1. Classification of chronic neurodegenerations
    a. Early-onset forms (autosomal dominant, "familial")
        i. Alzheimer's disease
        ii. Huntington's disease
        iii. Parkinson's disease
    b. Late-onset forms (multi-factorial)
        i. Alzheimer's disease
        ii. Huntington's disease
        iii. Parkinson's disease
        iv. Amyotrophic Lateral Sclerosis
2. Affected pathways
    a. Cellular aging (senescence):
        i. Protein folding/chaperones
        ii. Ubiquitination/proteasome function
        iii. Autophagy/lysosomes
        iv. Programmed cell death (apoptosis)
    b. Cellular components:
        i. Axonal transport/integrity
        ii. Synaptic function
        iii. Mitochondrial function
    c. Gene regulation
        i. Excitotoxicity/oxidative stress
        ii. DNA damage/repair
        iii. micro RNA
    d. Neuroinflammation
        i. Complement activation
        ii. Tumor necrosis factor
        iii. Astrocyte activation

INTRODUCTION

Recent work in our laboratory has shown that glaucoma and Alzheimer's disease (AD) share similar molecular and cellular pathways that may contribute to neuronal loss in glaucoma.[1] Investigating these shared pathways will yield valuable clues to aid in rational drug design for the treatment of glaucoma.

CLASSIFICATION OF CHRONIC NEURODEGENERATIONS

Most neurodegenerations can be classified into one of two categories: Specific genetic mutations cause autosomal dominant ("familial"), early-onset forms of AD, Huntington's disease (HD), and Parkinson's disease (PD). Fortunately, the incidence of these familial types of neurodegeneration is low, comprising less than 10% of total cases of AD, HD, and PD. These mutations have been exploited to create transgenic mouse models that have greatly aided in the understanding of the pathobiology of these diseases. The more prevalent category of neurodegenerations includes AD, PD, and amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). These sporadic diseases manifest in the later decades of life and are not associated with specific gene mutations, as are the familial forms of the diseases—facts that closely parallel those in open-angle glaucoma. Mounting evidence shows that late-onset neurodegenerations are characterized by a combination of genetic susceptibility and environmental exposure with mechanisms that overlap those in the familial or early- onset forms of the disease.

ALZHEIMER'S DISEASE

AD is a progressive, debilitating neurodegeneration and is the most common form of dementia. It causes loss of neurons in the hippocampus and cerebral cortex, leading to short-term memory loss.

It is characterized by the formation of aggregated proteins composed of amyloid,-β known as amyloid plaques, and neurofibrillary tangles, composed of hyperphosphorylated tau protein.[2] Amyloid-β is cleaved from the membrane-bound protein amyloid precursor protein (APP) by enzymes termed secretases. The pathologic forms of amyloid-β are cleaved by-β and γ-secretases; these are currently target components of drugs under development for the treatment of AD. A third secretase, the α subtype, cleaves APP to form a soluble form that is important in neuronal survival and synaptic maintenance.

APP is the most abundant protein in the optic nerve. It is rapidly transported in the optic nerve in small vesicles and is transferred to the axon plasma membrane and synapses.[3] The incidence of glaucoma is significantly higher in AD patients than in age-matched controls: 26% versus 5% in a German population[4] and 24% versus 9% in a Japanese population.[5] Furthermore, progression of visual field defects is accelerated in patients with open-angle glaucoma and AD versus patients with open-angle glaucoma without AD.[6] We have shown that APP is abnormally processed, and neurotoxic amyloid-β species are upregulated in the retina of rats[7] and mice[8] exposed to chronically elevated eye pressure. Hyperphosphorylated tau protein has also been detected in the retinas of glaucoma patients.[9] Glaucoma and AD are characterized by synaptic degeneration in the brain, which implies that it is not just a disease of the eye, but of the brain as well.[10]

Memantine, a treatment approved by the U.S. Food and Drug Administration for AD, has been used in a clinical study for the treatment of human glaucoma. Unfortunately, the clinical endpoints (preservation of visual fields) for the study were not reached, probably due to an ineffective mechanism of action.[11] However, directly targeting the formation of amyloid-β has shown promise in preserving retinal ganglion cells (RGCs) in a rat glaucoma model.[12]

PARKINSON'S DISASE

PD is the most common neurodegenerative movement disorder, caused by loss of dopaminergic neurons in the substantia nigra of the brain.[2] It is characterized by slowness of movement, difficulty in walking, rigidity, and shaking. As with AD, cognitive and behavioral problems and dementia occur in advanced stages of PD. Hereditary forms of PD show mutations in α synuclein and phosphatase and tensin homolog (PTEN), and pathology shows eosinophilic cytoplasmic inclusions of fibrillar, misfolded proteins termed Lewy bodies.

The synucleins are a family of proteins with unknown function, but a link between γ-synuclein and PD and other synucleinopathies has been established. γ-Synuclein has been noted to be deposited in a specific area of the optic nerve head where myelin begins to be expressed. A recent study has shown that optic nerve astrocytes digest and process RGC axonal processes, suggesting that optic nerve head astrocytes are important for normal maintenance of RGCs. Axonal material found inside these astrocytes contained a protease-resistant form of γ-synuclein, possibly contributing to the loss of RGCs in glaucoma.[13]

PTEN is a negative regulator of the mammalian target of rapamycin (mTOR) pathway,[2] and in wild-type adult mice, mTOR activity is suppressed and protein synthesis is impaired in axotomized RGCs.[14] Of note, deletion of PTEN promotes axon regeneration after optic nerve crush in mice, and the manipulation of PTEN and mTOR pathways is an exciting new therapeutic approach to promoting axon regeneration after central nervous system injury, both in the eye and in the brain and spinal cord.

AMYOTROPHIC LATERAL SCLEROSIS

ALS is a progressive, fatal motor neuron disease caused by the degeneration of neurons located in the ventral horn of the spinal cord and the cortical neurons that provide their afferent input. It is characterized by rapidly progressive weakness, muscle atrophy, fasciculations, spasticity, dysarthria, dysphagia, and respiratory compromise.[2] Mutations in Cu/Zn superoxide dismutase (SOD), a potent antioxidant enzyme, cause 2% to 3% of ALS cases. Oxidative stress and the expression of reactive oxygen species have been linked to the pathogenesis of glaucoma,[15] and the use of antioxidants such as SOD analogues represents a promising therapeutic approach to the treatment of glaucoma.

NEUROINFLAMMATION

Neuroinflammation is rapidly emerging as a major contributor to the development of chronic neurodegenerations such as AD and PD, as well as glaucoma. Complement proteins are part of the immune system that aid antibodies and phagocytic cells in clearing pathogens. C1q is the first element in the classic complement activation pathway, and it activates several proteases (C1r, C1s, C2, C3, and C4) that initiate opsonization and anaphylactic reactions that attract phagocytic cells. Increased neuronal

C1q expression occurs in AD,[16] and C1q has been shown to be upregulated in mouse and monkey glaucoma models.[17] In a recent study involving a model of inherited mouse glaucoma, the normal developmental mechanism of complement-mediated synapse elimination was aberrantly reactivated in retinal astrocytes.[18] The authors conjectured that C1q tags retinal synapses for early elimination and drives dendritic atrophy and axon degeneration that occur in glaucoma.

Tumor necrosis factor (TNF)-α is an inflammatory cytokine, and its receptors TNFR1a and TNFR1b have been noted to be upregulated in the retinas of glaucoma patients.[19] In a study of a mouse glaucoma model of elevated IOP, the absence (knockout) of the TNFR1b gene afforded robust neuroprotection of RGCs and their axons. Serum amyloid A is an acute-phase marker of inflammation and infection, and gene-profiling studies of glaucoma have shown upregulation of serum amyloid A in the trabecular meshwork and retina of glaucoma patients.[20,21]

MICRO-RNA REGULATION OF GENE EXPRESSION IN CHRONIC NEURODEGENERATIONS

Because glaucoma and other chronic neurodegenerations share common genetic mechanisms, it is critical to understand how the expression of genes are regulated in the retina and optic nerve in glaucoma, as this knowledge may enable rational drug design for therapeutic intervention. Recent investigations into the regulation of gene expression have focused on micro (mi)RNAs, which are short, endogenously expressed, noncoding RNAs that bind to the 3' untranslated region of messenger RNA, targeting it for downregulation or degradation.[22]

Several laboratories have shown significant changes in expression of some miRNAs in the brains of AD patients. Down regulation of these miRNAs is believed to contribute to increased production and accumulation of amyloid-β in these brains. Other miRNAs dysregulated in AD, such as miR-27b, -34a, and -146a, have been hypothesized to contribute to AD pathogenesis by increasing oxidative stress and inducing inflammation.[23] In a recent report, human astrocytes from normal individuals were cultured in vitro and treated with interleukin-6 to induce astrogliosis, a detrimental cellular process that occurs in AD brains. Levels of miRNAs were assayed, and miRNA-125b was noted to be upregulated. When miRNA-125b activity was repressed with antisense miRNA-125b, glial cell proliferation and increased expression of CDKN2A (cyclin dependent kinase inhibitor 2A) were found. CDKN2A is a miRNA-125b target and negative regulator of cell growth. CDKN2A downregulation has been noted in advanced AD and Down's syndrome brains, disorders associated with astrogliosis. The authors reasoned that miRNA-125b upregulation contributes to cell cycle defects and the astrogliosis that is characteristic of neurodegeneration.[24] This finding may be of major importance, given recent reports of a significant association between polymorphisms in CDKN2BAS and open-angle glaucoma.[25,26]

Given the relationship between AD and glaucoma, we hypothesize that in glaucoma, the retina and optic nerve experience changes in miRNA expression similar to those reported in the brains of AD patients. The observation of changes in expression of specific miRNAs associated with glaucoma should be useful in elucidating the pathogenic mechanisms involved in the loss of RGCs and could identify novel therapeutic targets.

SUMMARY

Glaucoma is an age-related, chronic neurodegeneration of the optic nerve. The molecular and cellular pathologies that characterize the disease are shared by other chronic neurodegenerations such as AD, PD, and ALS. Therapies directed at treating chronic neurodegenerations have potential for use in treating glaucoma; conversely, therapies that are successful in treating glaucoma could be used in treating other chronic neurodegenerations. The following are targets for therapeutic intervention in chronic neurodegenerations and glaucoma:

- Axonal transport and integrity
- Autophagy and lysosomes DNA damage and repair
- Excitotoxicity and oxidative stress
- Gene regulation and miRNA
- Mitochondrial function
- Neuroinflammation
- Programmed cell death (apoptosis)
- Protein folding and chaperones
- Synaptic function
- Ubiquitination and proteasome function

Finally, many of the molecular and cellular pathologies that characterize chronic neurodegenerations could be detected first in the eye, leading to earlier diagnosis and more effective treatments.

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NEURO-PROTECTION IN GLAUCOMA: WHERE ARE WE GOING?

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LEARNING OBJECTIVES

1. Describe new developments in designing clinical trials for neuroprotection
2. Recognize the importance of power calculations in the development of neuroprotective therapies
3. Describe how drug delivery impacts neuroprotective efficacy in the clinical setting

CME QUESTIONS

1. Which of the following is <u>not</u> relevant to calculating the n needed in a clinical trial of neuroprotection?

    a. Significance level sought
    b. False negative rate
    c. Critical value for difference sought between groups
    d. Standard deviation of the outcome measure
    e. None of the above (all are relevant)

2. Proof-of-concept studies are valuable because:

    a. They make Phase 3 studies unnecessary
    b. They are the main source of toxicity/safety data
    c. They are typically powered to have an 80% or 90% chance of detecting an effect
    d. They use a mixture of non-human primates and humans

3. Drug delivery for neuroprotection should meet the following criteria:

    a. Allow sufficient drug to reach the target
    b. Lead to preservation of the RGC axon
    c. Lead to preservation of the RGC soma
    d. Lead to preservation of the RGC dendrites
    e. All of the above

KEYWORDS

1. Neuroprotection
2. Power Calculations
3. Clinical Trial Design
4. Proof-of-concept Studies
5. Drug Delivery

INTRODUCTION

As any user of Google Maps or Mapquest knows, to get to where one is going, it helps to know where is the starting point. For neuroprotection, there have been numerous excellent reviews on the topic of the current status of neuroprotection in glaucoma. These include cell culture studies, animal models testing therapies, clinical trials, the two largest of which are still unpublished, and even systematic reviews. Yet all of this work can be summarized in a very simple "FROM" box: there is no convincing clinical evidence that neuroprotection works in glaucoma. The subject of this syllabus is a discussion of some future possibilities for a Rd. map that takes us "TO" evidence for neuroprotection in glaucoma.

TRANSLATIONAL BREAKDOWN AND ANIMAL MODELS

There are many neuroprotective drugs and other strategies that have been developed and work in laboratory animals, but this has not translated into clinically available compounds in glaucoma and other optic neuropathies. The reasons for this are manifold, and reflect mostly a general problem of translational research that is common to many other areas of medicine[1]. One of the issues is that the preclinical models used for testing neuroprotective drugs and other interventions may not reflect the human disease as accurately as desired[2]. For example, there are animal models that have significant intraocular inflammation or that require reactive tissue processes for the model to take place. Inflammatory or other injury processes may confound the study of neuroprotective drugs because inflammation or injury itself can have pro- or anti-neuroprotective effects. Another reason for translational breakdown is when models that are based on acute injuries or rapid progression are used to model a chronic disease such as human glaucoma, which takes place over decades. Finally, there is increasing realization that biomechanical processes at and around the optic nerve head may help explain features of glaucomatous progression. Rodent optic nerve heads, which are frequently used in glaucoma models, differ substantially from primate optic heads. It therefore is not be surprising if translational issues arise from using mouse and rat models to assess neuroprotection in glaucoma.

We can expect that better models will arise over the next decade. Nonhuman primates have ocular and optic nerve architecture very similar to humans, but their routine use in neuroprotection studies is difficult because of the

complexity and expense of carrying out studies in large numbers of animals. In the past, a study of a small number of rhesus or cynomologous macaque monkeys has been considered less helpful in preclinical research because of the high likelihood that there will be a false negative result because of the small n associated with the study. The marmoset is a much smaller nonhuman primate that has a fovea, retina, and optic nerve architecture very similar to other primates[3]. Marmosets may thus be good candidates for the final stage of preclinical research before initiating clinical trials because of the ability to perform nonhuman primate studies in larger numbers. This would increase the likelihood of translation to the human.

BETTER CLINICAL TRIALS

Based on the failure of two large clinical neuroprotection trials to meet their primary endpoints, based on press releases[4,5], there has been great interest in better ways to perform clinical trials. Some issues are discussed in a recent review[6]. One of the suggestions has been to use proof-of-concept trials as a first step in the neuroprotection development process, with continuation to pivotal Phase 3 studies if the treatment shows an obviously good result. If proceeding would be futile, development stops, i.e. a *futility trial* [6,7].

The issues of decision-making with respect to proof-of-concept trials are complex, and are highly dependent on power calculations. In general, the number of patients required to do a clinical trial in neuroprotection (or any other test) depends on four factors. The first is the *alpha* level for signficance, which is typically less than 0.05. This means that a positive outcome is expected to be seen by chance less than one out of twenty times. The second factor is the *power*, i.e. the likelihood that if there really is an effect of the intervention, the trial will be able to detect it. This is usually chosen as 80% or 90%, implying that 20% or 10% (respectively) of the time, even an inherently effective intervention will show up as being ineffective in the trial, i.e. a false negative result.

The third factor is the *difference* that is being sought between the two groups being studied, e.g. placebo and active drug. For neuroprotection, this could be something like how much the mean deviation progression rate should decrease for an intervention to be neuroprotective, e.g. a decrease of 50% or more. The fourth factor is the *variability* of the population values for the endpoint, e.g. the standard deviation of the mean deviation progression rate in the population that is likely to be studied.

The classic methods for powering clinical trials may not be applicable to the development process for risk-associated development pathways such as neuroprotection. For example, most clinical trials that are submitted to the FDA have historically used power values of 80% or 90%, as mentioned above.

A new approach that our group has been studying is to reconsider how the power calculations interact with the financial analysis, in the case where a pharmaceutical company is deciding whether or not to perform a clinical trial and how it will be performed. This is based on the financial aspects of drug development. In general, companies develop drugs to make profits. There is a high risk associated with the development of any new drug, and this has historically been true for the development of neuroprotection strategies, for which there are almost no examples besides memantine in Alzheimer disease, tirilazad mesylate in subarachnoid hemorrhage in Australia, and riluzole in amyotrophic lateral sclerosis.

The basis of the mixed-model decision analysis is that the expected value in present-day dollars (or euros or pounds) represents the long-term revenue stream corrected for the development or other costs associated with the drug approval. For the sake of argument, this can be assumed to be in the billions of dollars.

This means that if a Phase 2 clinical trial is used as a proof of concept for drug development in neuroprotection, and the trial is powered at 80%, then 20% of the time false negative results will be seen. This means that the possibility of a multibillion dollar revenue stream has the potential of being abandoned, while if the trial had been powered at a more stringent level, then this false-negative rate would be lower. In other words, there is an opportunity cost by under-powering a study. Although historically, powers of 80% and 90% have been used, this analysis would suggest that much higher powers should be used, given the balance between the cost of actually performing the trial and the expected value in the long term. There is also value to performing more than one Phase 2 studies, with different approaches, and letting a positive value in any trial advance further development[8].

Similar analyses can be done for Phase 3 clinical trials, with the understanding that they are usually two independent trials, one of which may yield a significant result and one which may not. There are situations where the power should be even higher than would otherwise be for a single trial.

There are several strategies that are being studied to decrease the number of patients required and/or the length of time that they need to be followed for a trial of neuroprotection to take place. One approach is to take patients with high progression rates, so that the effect size will be greater compared to the variability in the measurements of the progression rate. A closely related approach is to improve the homogeneity of the groups, so that the variability is less and the signal-to-noise ratio is greater.

Calculations based on modeling and on real data suggest that in many cases, a trend-based analysis of visual field data may have more sensitivity and specificity for assessing the effects of an intervention such as neuroprotection than event-based analyses. The literature on this has been developed over the last few years, and reflects the fact

that several visual fields can be used to calculate the slope with fairly good confidence intervals, and therefore an intervention which changes the slope over time of visual field progression can be detected with a higher ratio of effect size divided by standard deviation than within event-based analysis. The caveat is that the number of fields and the stage of the disease matters, meaning that the design of the clinical trial is critical to any perceived advantage. An excellent discussion relating to issues in comparing methods for field progression analysis has been recently performed[9]. Although it is impossible to predict, in the future, this and related information might be used to design optimal neuroprotection studies that would require fewer patients than with past trial designs.

DRUG DELIVERY OF NEUROPROTECTIVE AGENTS

Glaucoma and almost all other optic neuropathies begin with damage to the axon of the retinal ganglion cell. The study of neuroprotective drugs (or non-drug therapies) requires that the intervention address the injured part of the retinal ganglion cell, either directly or indirectly. For example, if a drug were to protect only the cell body (soma) of the retinal ganglion cell without protecting the axon, then an injury to the axon at the optic nerve head from glaucoma may result in a "zombie" RGC that cannot transmit information to the rest of the brain because its axon was lost or nonfunctional. This concept of the importance of the site of injury for neuroprotection[10] is critical for development of future therapies. Recent research has focused not only on protecting the soma but also the axon. The study of the Wld^S mouse and rat, where the axons do not undergo Wallerian degeneration after injury, has been helpful in understanding the importance of preserving the axon[11,12]. More recently, the importance of the involvement of the dendritic tree as a response to injury has come about, as well as the response of target neurons of retinal ganglion cells within the lateral geniculate nucleus and elsewhere[13,14].

Along these lines, it will be important to deliver drug or other interventions to the locations involved in the injury. Under the best of circumstances, a topically delivered drug could reach the retinal ganglion cell bodies, their dendrites, their axons within the retinal nerve fiber layer, and even their axons within the optic disk. However, the drug would not reach the retrobulbar optic nerve, and therefore for a disease such as indirect traumatic optic neuropathy, where the damage occurs at the optic nerve canal, a topical drug would not be helpful. On the other hand, such an approach may be feasible in glaucoma if there is enough penetration in and around the disk and laminar tissues, where the damage likely occurs. A variety of drug delivery methods have been developed and it is expected that these will continue to improve over subsequent years. Both sustained-release formulations within the eye and in other depot spaces will continue to be optimized. Systemic delivery is always an option, but may be less helpful when there are adverse effects associated with this approach.

There is a recognition that transcleral penetration of drugs after topical delivery may be more important than transcorneal penetration when the goal is to deliver drug to the retina and anterior optic nerve head. Overall, advances in drug delivery are likely to be part of the critical path that will eventually enable clinical neuroprotection in glaucoma.

CME ANSWERS

1. e
2. c
3. e

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NEURO-REGENERATION FOR GLAUCOMA AND OTHER OPTIC NEUROPATHIES

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LEARNING OBJECTIVES

1. Describe that failure of retinal ganglion cell survival and axon regeneration underlies the permanent loss of vision in glaucoma and other optic neuropathies
2. Describe that loss of survival and growth signals, including neurotrophic factors and electrical activity, contribute to retinal ganglion cell dysfunction in these diseases
3. Describe the potential efficacy measures that could be used to study neuro-regenerative therapies in optic neuropathies

CME QUESTIONS

1. Electrical activity is _____ for retinal ganglion cells after injury
   a. Good
   b. Bad
2. Regenerative failure is attributable to problems in _____.
   a. Retinal ganglion cells
   b. The optic nerve environment
   c. Both
3. In a chronic disease such as glaucoma, is it easier to measure _____.
   a. Neuroprotection
   b. Axon Regeneration
   c. Neuroenhancement

KEYWORDS

1. Neurotrophic Factors
2. Electrical Activity
3. Axon Regeneration
4. Neuroprotection
5. Neuroenhancement

INTRODUCTION

Retinal ganglion cells degenerate in glaucoma and other optic neuropathies, and regenerative failure leads to permanent loss of vision in these diseases. RGC axons injured in the optic nerve fail to regrow back to their targets in the brain, and the cell bodies die a short time afterwards. Here we will discuss recent data revealing new signalling pathways regulating RGC survival and regeneration, and approaches to reversing regenerative failure in the visual pathway.

The search for treatments that promote the survival and regeneration of retinal ganglion cells (RGCs) in optic neuropathies including glaucoma and ischemic optic neuropathy remains a major goal for basic and clinical research.[1] Neurotrophic factors impact the survival, proliferation, differentiation and function of neuronal cells, and one such neurotrophic factor, ciliary neurotrophic factor (CNTF), has begun to bridge from laboratory to human studies.

CNTF is a well-studied neurotrophic factor shown to act as an injury-activated signal to protect neural tissues, including the retina. CNTF is expressed in the retina under stressful conditions, such as experimental ocular hypertension[2] and optic nerve trauma,[3] where it directly stimulates intracellular signaling called the Jak-STAT cascade in retinal Muller glial cells, retinal ganglion cells (RGCs) and astrocytes. It is thought that the activation of the STAT3 signaling pathway directly mediates the neuroprotective effect of CNTF on neuronal cells. Also, glial cells activated by STAT signaling are associated with protection of neurons from neuronal degeneration.[4]

Animal models of retinal degeneration have shown good evidence to suggest that CNTF has a neuroprotective effect on photoreceptors. CNTF protein injection into the vitreous cavity[5] and intraocular adenovirus-mediated gene transfer of CNTF[6,7] prevent the photoreceptor cell death in rodent retinal degeneration models.

Similarly, in pre-clinical models CNTF provides a neuroprotective effect in RGCs against severe stress such as optic nerve trauma.[8] Long-term delivery using adeno-associated virus serotype 2 (AAV2) vectors that express a secretable form of CNTF make long term delivery to RGCs possible. AAV2-CNTF intravitreal injection 1 week before optic nerve trauma enhanced RGC survival almost fourfold compared with control retinas at 7 weeks.[8,9] Similarly,

AAV2-CNTF intravitreal administration in laser-induced glaucoma can exert a significantly protective effect against axon loss in the optic nerve.[10]

Interestingly, CNTF has an additional positive effect, promoting axon regeneration after optic nerve damage in pre-clinical models. Purified RGCs extensively elongate their neurites in the presence of CNTF in culture.[11 12] In vivo, CNTF enhances RGC axon regeneration in the optic nerve. Intravitreal application of CNTF[13] and AAV2-CNTF injection[8] substantially enhanced the regeneration of damaged axons into a sciatic nerve graft after optic nerve axon transection.

Thus, numerous preclinical studies support the idea that CNTF may be both neuroprotective against RGC loss, and also promote regeneration in the optic nerve. The key question is, can CNTF slow the progression of visual field loss, or even bring vision back, in human patients with glaucoma or other optic neuropathies? Recently, another method of long-term CNTF delivery to the retina, using an intravitreal implant, has been developed (Neurotech, RI). A small capsule of human cells engineered to secrete CNTF are enclosed in a semi-permeable membrane that allows CNTF secretion into the vitreous. Human testing in retinitis pigmentosa and age-related macular degeneration completed phase II trials, and the implants were generally found to be safe.[14] The data also showed that CNTF secretion was maintained at similar levels even after 2 years,[14] suggesting that long-term drug delivery is feasible in the human eye.

Would CNTF work in humans to support RGC survival or encourage optic nerve regeneration? A pair of phase I trials in glaucoma and in non-arteritic ischemic optic neuropathy recently completed 18 months of follow-up. Although phase I trials are designed to evaluate safety in the patient population being studied, suggestion of biological activity will be expected to drive further investigation in later-phase trials.

Although much work will have to be done to cycle back and forth between human testing and pre-clinical development, the premise of moving promising candidate therapies from the laboratory to the clinic raises the hope of identifying new treatments for patients.

(Adapted from ref 15)

CME ANSWERS

1. (a) Although electrical activity in excess is thought to lead to "excitotoxicity" and cell death of retinal ganglion cells, after optic nerve injury providing extra electrical activity appears to promote retinal ganglion cell survival and growth, both in animal models and in early data from human testing.
2. (c) Deficits both in the glial environment of the optic nerve, and in the retinal ganglion cells themselves, contribute to regenerative failure in optic neuropathies. Newer data increasingly support the premise that manipulating retinal ganglion cells directly can promote survival and regeneration.
3. (c) We have no current methods to measure axon regeneration in humans, and in chronic diseases like glaucoma it may take longer to measure neuroprotection than to measure acute increases in visual function, termed neuroenhancement.

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MITOCHONDRIAL DISEASE AND GLAUCOMA

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LEARNING OBJECTIVES

1. Describe the clinical characteristics of mitochondrial optic neuropathies (MON)
2. Explain the risk factors of the optic disc size and shape for MON
3. Describe reasons why some glaucomas have mitochondrial impairments as a pathophysiological mechanism

CME QUESTIONS

1. What are the two hereditary MONs?
2. Which hereditary MON may masquerade as glaucoma?
3. What protein helps regulate optic nerve size and is the pathophysiological basis of DOA?

KEYWORDS

1. Mitochondrial Optic Neuropathies
2. Glaucoma
3. Dominant Optic Atrophy

There are several mitochondrial optic neuropathies (MON). There are probably many glaucomas. So perhaps it is not surprising that there exist overlaps in these two conditions. More importantly, however, the pathogenic mechanisms recently elucidated in MON may provide insights and opportunities in the management of at least some glaucomas. Furthermore, there is a growing body of evidence that mitochondrial disease may affect tissues of the eye other than retinal ganglion cells (eg. trabecular meshwork and the optic nerve) and may even directly alter some of the dynamics that determine intraocular pressure[1]. The purpose of this talk and manuscript is to delve into the relationship between mitochondria and glaucoma. In particular, we will address these considerations:

1. There are many similarities between some glaucomas and mitochondrial optic neuropathies (MON).
2. These similarities are greatest for low tension glaucoma that often present with paracentral scotomas that remind us of MON.
3. Dominant Optic Atrophy (DOA) is a hereditary MON with particular connection to glaucoma including the optic disc appearance.
4. Leber's Hereditary Optic Neuropathy (LHON), another MON, has disc size as a risk factor for visual loss and the severity of this loss (large discs do better).
5. We are exploring the role of OPA-1 on development of the optic nerve as well as the degeneration of DOA.
6. Mitochondrial metabolism and dynamics may play a role in the pathology of glaucoma and provide clues to new therapeutic approaches.

MON represent a group of optic neuropathies that can be genetic, nutritional or toxic in basis[2-4]. For example, hereditary mitochondrial optic neuropathy may be in the autosomal form as DOA or maternally inherited through mtDNA mutations as LHON. In the former case, over 212 mutations have been described[2]. There are 3 major mtDNA mutations that produce LHON[2].

The clinical presentation of MON is characterized by bilateral loss of central vision, dyschromatopsia, central or cecocentral scotomas[5, 6]. Ophthalmoscopic features during the acute/subacute stage often reveal a hyperemic optic disc and peripapillary retinal nerve fiber layer swelling[7]. With time, temporal pallor of the optic disc develops. There is no relative afferent pupillary defect due in part to symmetric optic nerve involvement. The fibers of the papillo-macular bundle (PMB) are most susceptible due to their long unmyelinated segment in the retina and their small caliber. Preferential involvement of the PMB is a feature common to a wide range of acquired and genetic mitochondrial optic neuropathies[3, 7, 8].

Nutritional optic neuropathies are often (but not always) mitochondrial as well[5]. Deficiencies, especially of B-12 and folic acid can impair mitochondrial metabolic pathways and produce diseases that mimic LHON or DOA. An ever larger body of toxins, especially antibiotics, have been shown to impair mitochondrial function and also mimic or produce a similar clinical profile. Drugs proven to cause MON by blocking oxidative phosphorylation include ethambutol, chloramphenicol, linezolid, erythromycin, streptomycin,

and antiretroviral drugs[5]. Once again, the small fibers of the PMB are the main site of injury.

Leber's hereditary optic neuropathy is characterized by severe visual loss, which may manifest acutely or subacutely in young adulthood[2]. In 1988, the genetic basis was determined to be due to a mitochondrial DNA (mtDNA) point mutation[9]. This Wallace mutation, at nucleotide 11778/ND4, was discovered first and later 14484/ND6 and 3460/ND1 were established as other common mtDNA mutations[2]. These three mutations affected components of respiratory complex I, and account for about 95% of LHON cases.

The typical story would be that of a young adult male who first notices abrupt and profound loss of vision in one eye, and then, weeks to months later, suffers a similar loss of vision in the other eye. Less commonly, LHON occurs later in life and may occur in women at menopause. There is evidence that estrogen, by controlling mtDNA copy number, is protective, explaining the menopausal association as well as the gender bias for conversion[10]. Environmental factors such as smoke and excessive alcohol, may act as triggers for visual loss in LHON[2, 3, 11-15].

The size of the optic disc can play a role in the pathogenesis of LHON[16]. The optic disc was found to be larger in LHON carriers than in LHON-affected, suggesting that a small optic disc may be a risk factor for LHON carriers to convert to affected. In fact, amongst LHON-affected, larger optic discs were also associated with a better visual outcome and the propensity for some recovery of vision[16]. It is intriguing to consider that mechanical factors, such as those that may play a role in the pathogenesis of glaucoma or anterior ischemic optic neuropathy, may also influence the outcome in LHON.

Dominant optic atrophy is autosomal in genetics and in most cases due to a mutation in the OPA1 gene[17, 18]. It affects both genders equally and usually presents as a slow and insidious progressive visual loss starting in prepubescence. The central scotoma is smaller and grows more slowly than in LHON and the optic disc atrophy usually confined to the temporal side[18]. The temporal disc may also become excavated or cupped in appearance[19]. It is not surprising, then, that the main differential diagnosis in DOA is for low tension glaucoma. Furthermore, the optic disc in DOA is smaller than in controls, suggesting a role for OPA1 in regulating apoptosis and thereby controlling the size and shape of the optic nerve head[20].

The optic disc area may also correlate with the rapidity and severity of visual field progression in patients with low tension glaucoma[21]. And, indeed, OPA1 polymorphisms have been found to correlate with both normal tension and primary angle glaucoma[22]. Hence, DOA has certain clinical similarities with glaucoma, and especially, in the absence of high intraocular tension, with low tension glaucoma. More intriguing, OPA1 probably plays an important role in both diseases.

On the flip side, there is substantial evidence that patients with primary open angle glaucoma may have mitochondrial impairment. In particular, Lee and colleagues found that lymphoblasts from glaucoma patients had complex-I impairments leading to decreased ATP production in many ways analogous to that seen in LHON that leads to RGC death[23]. Furthermore, mitochondrial DNA polymorphisms are not uncommon in low tension glaucoma[24]. Hence, it is likely that at least some glaucomas have mtDNA mutations or polymorphisms as a risk factor. Mitochondrial dysfunction probably predisposes RGCs to glaucoma damage[25]. Furthermore, elevations of intraocular pressure may damage mitochondria through oxidative stress[26].

This overlap in glaucoma and mitochondrial impairment that leads to retinal ganglion cell (RGC) death should not be surprising. We are reminded that RGCs are probably exquisitely sensitive to mitochondrial dysfunction due to their having a very long unmyelinated segment and that the PMB fibers, by virtue of their small caliber, have a particularly poor "mitochondrial stress index" imposed because of the exposed membrane-to-mitochondrial volume ratio[3, 8]. Superimposed, of course, may be stressors at the lamina cribrosa that relate to pressure gradients.

The role of mitochondria in apoptosis makes it a major "final common pathway". Glaucoma is now sometimes viewed as a neurodegenerative disease of the optic nerve. The accelerated death of RGCs and their axons may be due to primary mitochondrial impairment and the role of mitochondria in apoptosis. Neuro-ophthalmologists and glaucoma specialists interested in the optic nerve head, have much to talk about.

CME ANSWERS

1. LHON and DOA
2. DOA
3. OPA-1

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DEBATE:
NON-IOP LOWERING THERAPIES WILL BE THE FUTURE OF GLAUCOMA MANAGEMENT
PRO:

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INTRODUCTION

While IOP-lowering eyedrop treatment is effective at decreasing glaucoma's visual function loss, its disadvantages require renewed effort to improve the future of glaucoma treatment. This will involve a change to sustained delivery of medications directly to the eye, and, agents whose mechanism of action is to block retinal ganglion cell death by pathways other than and in addition to pressure lowering.

The treatment of the glaucomas evolved relatively slowly over the last 50 years, as the use of gonioscopy separated open angle from angle closure and secondary glaucomas. The role of the level of intraocular pressure (IOP) in all forms of glaucoma was established by scientifically valid methods of tonometry (Goldmann) applied in population-based studies. Open angle glaucoma (OAG) is now understood to be an optic neuropathy in which IOP is an important risk factor, regardless of whether its level in the individual patient is above or within the range found in the population (so-called normal). In every population around the world yet studied, one-half or more of those with OAG undergo retinal ganglion cell (RGC) death at "normal" levels of IOP (Tielsch). For those with angle closure and secondary glaucoma, it is predominately higher than normal IOP levels that produce RGC loss.

Lowering of IOP has been shown to reduce the incidence and progression of glaucoma in large controlled clinical trials, including those evaluating pre-injury OAG suspects (OHTS), those with early OAG (EMGT), and those with OAG whose damaging IOP level was in the normal range (CNTGS). We do not yet have definitive information on what the most desirable level to which IOP should be lowered in the typical person with OAG. Target IOP in various controlled trials varied from 20% to 40% below baseline. While some have advocated dramatic lowering of IOP in all glaucoma eyes, suggesting that 12 mm Hg is a form of magic potion (Palmberg), the risk/benefit ratio for treatment to achieve such levels is not acceptable. One recent evaluation of a cohort of treated persons from Canada showed that standard treatment achieved very slow worsening of measured function in the vast majority of eyes (Chauhan).

In fact, the proportion of those with OAG who will become blind or seriously impaired represents a minority of those with the disease, even if one includes those who remain undiagnosed. This is not to ignore the fact that the glaucomas are the second-leading cause of world blindness (Quigley). But, the large number of blind glaucoma persons derives from the substantial prevalence of disease, not from a high rate of morbidity. Yet, the 10-15% of OAG glaucoma patients who progressively worsen at a substantially greater rate than the majority (Broman) represent a challenge for improvement. There could be several approaches to further decrease vision loss from glaucoma.

Some would argue that we simply need to do a better job with IOP-lowering. IOP therapy has several drawbacks that are only partially amenable to change. Eyedrop treatment has at least 3 major problems. First, patients adhere to drop treatment poorly in many cases. Even under ideal monitored conditions, patients take only 70% of doses of drugs that are well-tolerated and provided free in studies (Friedman). Interventions to increase adherence are moderately successful when they use reminder systems (Boland). Yet, some groups are not amenable to any presently tested intervention, and no study has generated close to ideal adherence in any population. Second, the side-effects of all drops on the eye are well-known, including pain, redness, overt allergic reaction, and chronic scarring/shrinkage of the subconjunctival connective tissues (Schwab). Each class of IOP-lowering drugs has, in addition, its own panoply of undesirable effects on the eye and systemically. Third, some persons are refractory to successful IOP-lowering, producing no effect despite actually documented delivery to the eye.

Laser and surgical treatment to lower IOP have further problems. Despite development and aggressive marketing of SLT laser angle treatment in the last decade, no improvement in efficacy or safety has been demonstrated over the ALT laser method used since 1978. Nearly one-third of laser-treated eyes have no IOP lowering, while among the remainder, it is the exception, not the rule, to achieve a target range of IOP without additional eyedrops (GLT). As to trabeculectomy surgery, it has been shown under controlled trial conditions to equal the benefit of eyedrops in vision preservation (CIGTS study). But, its use is

limited by the rate at which it is associated with more rapid cataract development, hypotony, and late infection (Solus).

IOP lowering therapy could be improved by any one of several approaches, though none of these appears ready to be applied to large groups in replacement of eyedrops. First, sustained delivery of drugs (Hanes) could improve adherence and reduce side effects of frequent chronic eyedrops use, especially if delivered subconjunctivally (Wong). Second, a variety of "new" glaucoma surgical procedures, often involving innovative micro-devices are being tested. While their promise is to decrease detrimental effects while achieving safe IOP levels, none of these has been tested in a controlled clinical trial against standard IOP lowering medical or surgical treatment. Thus far, the IOP lowering by new surgeries has been less impressive than even prostaglandin eyedrop treatment alone (Samuelson).

For the short-term, then, clinicians will continue to use the present quiver of IOP-lowering approaches, since they generally are effective enough. But, this discussion was intended to point out what the future will bring to glaucoma therapy. Our vision should be multiple approaches that go beyond the blinders imposed by IOP-lowering alone. Death of RGC is the nature of glaucoma's detrimental effects and, thus, RGC preservation by any means possible should be our goal—an approach generally referred to as neuroprotection.

The fundamental feature of glaucomatous optic neuropathy is disruption of normal structure and function of the RGC axon within the optic nerve head, leading to dual parallel processes of RGC cell body and RGC axon death (Levkovitch-Verbin). In human glaucoma, including in eyes with normal IOP, the differentiation of glaucoma from other optic neuropathies that share the same injury site quite clear. Despite past anecdotes of "cupping" in non-glaucoma eyes that putatively blurred the differences among these disorders, the phenotype of OAG is different from conditions such as ischemic optic neuropathy, optic neuritis, Leber's optic neuropathy, and optic disc drusen. In general, the major difference is that glaucoma is associated with connective tissue stretching and rearrangement along with RGC loss, while the others involve RGC loss alone. The disorder closest to glaucoma in its pattern of RGC loss/field loss, ischemic neuropathy, has now been repeatedly shown not to develop deepening and widening of the nerve head (Danesh-Meyer).

There are several insults that may begin the glaucoma process at the nerve head and each of these may be amenable to therapeutic intervention, including:

- altering ganglion cell body injury response
- altering ganglion cell axon injury response
- scleral and lamina connective tissue treatment
- improved autoregulation of nutritional blood flow
- mitigation of glial cell cytokine release

The RGC death process uses similar pathways to that of programmed cell death for poorly targeted RGCs in embryological life, known as apoptosis. Interventions that directly block this process have been shown to delay RGC death in animal models (McKinnon).

To show in more detail some of these potential mechanisms, we can begin with approaches that alter the response of the RGC body to injury. Among these are neurotropin overexpression (Pease), calcineurin inhibition (Grosskreutz), β secretase inhibition (Cordeiro), blockade of glutamate excitoxicity (Sharma), and inhibition of tumor necrosis factor α (Nakazawa), among others. Each of these has proven to extend RGC life in rodent models of elevated IOP. These approaches would be most effective if they aim at restoring equilibrium to the RGC soma soon after the first injury signal arrives from the axon at the nerve head ("upstream" therapy). Recent research by Welsbie and colleagues at Wilmer illustrates such an approach, which was identified in a large library screening of potential drugs to extend the life of RGC. Activation of c-Jun N-terminal kinase and subsequent activation of phosphorylated c-Jun has been shown to be a "death pathway" for RGC, including in models of glaucoma (Levkovitch-Verbin). Welsbie identified preceding activation in dual leucine zipper kinase (DLK) as a key event in this pathway and found what is now a series of inhibitors, which were delivered in a sustained delivery formulation to the vitreous cavity of rats with experimental glaucoma, protecting RGCs from death). Inhibition of apoptosis by genetic knockout of the bax gene in mice produced animals with remaining RGC long after loss of their axons (John). While this would not lead to any functional vision, it is proof that the adult RGC soma can remain alive, despite loss the axon—a potentially useful state if regrowth of the axon can be encouraged (Goldberg).

The inhibition of RGC axon loss has been suggested by specific mechanisms. Rats with the slow Wallerian degeneration (Wld^{s}) mutation can undergo RGC somal loss with retention of apparently intact axons to the brain (Martin), showing that the axonal death process can also be mitigated, and is separable from somal loss. It may be that combination therapy that protects both the RGC soma and axon will be more effective than either alone, though this has not been tested experimentally.

Epidemiological evidence for glaucoma risk factors suggests approaches to altering RGC injury and death by one of several means. The strength and response to IOP-generated stress is transmitted to RGC axons by the sclera and lamina cribrosa. Myopes, whose sclera and optic nerve heads are known to differ in thickness and configuration, are more susceptible to OAG (Boland). The protection of RGC by alteration of the scleral response and that of the lamina

cribrosa connective tissue is suggested by several lines of evidence, notably the demonstration that the Aca23 mutant mouse is significantly resistant to experimental glaucoma damage. This mouse has a mutant in collagen 8α and at baseline has larger eyes than the corresponding wild type C57Bl/6 mouse. Detailed study of the resistance conferred by this mutation is underway. Another initial experiment tested the hypothesis that increased cross-linking of scleral connective tissue would alter susceptibility to glaucoma injury. Indeed, mice with glyceraldehyde-induced stiffer sclera were more susceptible to losing RGC than controls. These experiments suggest that beneficial alteration of the sclera will more likely involve increasing its elasticity, rather its stiffness.

There is considerable evidence that poor nutritional blood flow to the nerve head, exemplified most consistently by low perfusion pressure, increases both incidence (Tielsch) and progression of OAG (Leske EMGT). While much has been written on the role of poor blood supply for glaucoma, there is minimal evidence for an approach that would beneficially increase nutrition. Acute experiments show it is the perfusion pressure that determines acute autoregulatory failure in animals, but chronic experiments have not been published that show benefit from vascularly active agents. Small clinical trials with calcium channel inhibitors have suggested some improvement in the rate of decline, though confirmation of these findings has not been provided (Araie). This may be a particularly difficult area to duplicate in animals, as the age-related changes in vessels that may be present in the (subset) of those with glaucoma and poor nutritional flow may not be present, even in aged animals. Furthermore, the susceptibility to experimental RGC glaucoma damage is different among strains of mice (Steinhart). The application of a systemic drug for neuroprotection, as in the calcium channel inhibitors, has the disadvantage of serious side effects that limit continuation, as well as detrimental off-target effects. Glaucoma patients have, most often, no symptoms of their disease. Any new medication that has serious or modestly frequent side effects is a non-starter for the glaucoma market. For agents that might have difficulty with oral delivery side effects, or, that would have blood—retinal barrier issues, the delivery through the sclera by depot injection would be a better approach.

While not detectable from clinical features, the contribution of astrocytes of the nerve head was potentially suspected and confirmed by studies showing abnormal cytokine release (TNFα). There is substantial information that TNFα is released in the glaucomatous optic nerve head and that its inhibition or elimination of its receptors is beneficial to RGC survival (Nakazawa). The presumed source of the cytokine is/are glia, including astrocytes of the optic nerve. Several approaches to TNFα inhibition are presently being implemented in treatment of systemic diseases. However, these are delivered either orally or intravenously, and have considerable side effects (Ma). For glaucoma, a more acceptable delivery system and side effect profile would be needed.

It is worth mentioning that glutamate toxicity was considered one of the potential mechanisms by which RGCs die in glaucoma, based on work that was done by a now-discredited investigator. Perhaps stimulated by this body of work, a controlled clinical trial of oral memantine was conducted, but announced some years later as having failed to achieve its end point—without providing any data on what really happened. This study has acted to "poison the well" for any subsequent research into glaucoma neuroprotection—the attitude being that it is too difficult and too expensive to develop a new glaucoma drug. On the contrary, the deficiencies in study design and implementation, as well as the poor choice of the drug, were known prior to its apparent failure in the trial. An objective analysis shows that neuroprotection trials, carried out in an efficient manner, using visual fields as the end point, can be conducted effectively in time frames typical for the testing of drugs in other chronic diseases (Quigley).

The future of glaucoma therapy will be to terminate the use of daily eyedrops and to move to methods of sustained delivery of drugs to the eye by systems that are now available for packaging agents efficiently. It is likely that these methods will involve the use of both IOP-lowering and non-IOP drugs to maximize the chance that visual impairment can be kept as low as possible. In some patients, the IOP-dependent part of their glaucomatous pathology may be so low or so difficult to achieve that only neuroprotective therapy will be used. In others, the ease and safety of IOP-lowering may have been demonstrated to have produced stability in function for previous long periods, and, in these eyes, neuroprotection would not be appropriate.

DEBATE: NON-IOP LOWERING THERAPIES WILL BE THE FUTURE OF GLAUCOMA MANAGEMENT
CON:

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LEARNING OBJECTIVES

1. Describe the argument that the mechanisms of glaucomatous injury and how all of these mechanisms (vascular, mechanical, tissue remodeling, and neurodegenetation) are intimately related to the loading force within the eye (IOP)
2. Describe the relationship and differences between stress (the loading force; IOP) that is delivered to the posterior scleral and optic nerve and resultant tissue strain (the response of the tissue due to stress)
3. Describe that even at normal levels of IOP, significant tissue strain and deformation can occur that could result in compromise of the load bearing connective tissues of the optic nerve and generate significant axonal injury

CME QUESTIONS

1. The following are constant risk factors for the development of glaucoma
    a. Thin cornea
    b. Diabetes
    c. Female gender
    d. Myopia
2. True/False: Elevated stress (IOP) is required for potentially damaging tissue strain (deformation).
3. Focal acquired optic nerve pits are related to
    a. Lower rates of glaucoma progression
    b. Thick corneas
    c. Optic disc heme
    d. Alpha zone atrophy

KEYWORDS

1. Glaucomatous Optic Neuropathy
2. Intraocular Pressure
3. Lamina Cribrosa
4. Ocular Biomechanics

INTRODUCTION

Point-Counterpoint: IOP lowering therapies will always play a role in the future of glaucoma management.

Lowering of intraocular pressure (IOP) either with medications or surgical interventions has been the mainstay of glaucoma therapy for well over 100 years and remains the only proven method to retard or prevent the development or progression of the disease. However, despite the fact that IOP lowering therapy is available, patients still may progress despite lowering of IOP. In addition, patients can develop glaucoma even at a low IOP. These findings have stimulated the development of alternate hypotheses regarding the pathogenesis of glaucomatous through non-IOP related mechanisms. There is clear evidence that vascular changes that alter perfusion to the optic nerve, changes in the supportive tissues of the lamina cribrosa, immunologic and excitotoxic/neuro-degenerative changes all play an important role in the development of glaucoma. However I will argue in this debate that despite these insults, that IOP lowering therapy will always remain a valid and important treatment for glaucoma. This is because IOP load is integrally related to changes in the vasculature and the supportive cellular and connective tissue components of the lamina cribrosa and thus play a key role in the axogenic injury to the optic nerve that is critical to the development of glaucoma.

The lamina cribrosa provides structural and functional support to the retinal ganglion cell (RGC) axons as they pass from the relatively high-pressure environment within the eye to a lower pressure region in the retrobulbar cerebrospinal space.[1] To protect the RGCs in this unique anatomic region, the lamina has developed into a complex structure composed of a three- dimensional network of flexible beams of connective tissue, nourished by a capillary bed primarily arising from the short posterior cilliary arteries penetrating the immediate peripapillary sclera.[2] This intra-scleral and intra-laminar vasculature is unique in that it is encased in load-bearing connective tissue, either within the scleral wall adjacent to the lamina cribrosa, or within architecture of the laminar beams themselves.[3] Thus, this “end-organ” capillary bed is completely encased in load bearing connective tissues that is under constant strain (tissue deformation) that varies across every second, every hour and every day throughout life creating a unique

situation in which mechanical effects are inseparable from vascular and other non-IOP mechanisms of injury.

The anatomy of the lamina cribrosa and peripapillary sclera merits several considerations regarding the etiology of glaucomatous cupping and implies that the classic "mechanical" and "vascular" mechanisms of glaucomatous injury[4] are inseparably intertwined. For example, prior to structural damage, purely IOP-related stress could detrimentally affect the blood supply to the laminar segments of the axons by direct deformation of the capillary-containing connective tissue structures or due to changes in the extracellular matrix that may limit the diffusion of nutrients to RGC axons in the laminar region. Reciprocally, primary insufficiency in vascular supply to the laminar region could induce connective tissue changes that would serve to weaken the laminar beams, making them more prone to failure under similar levels of IOP- related mechanical stress.

To incorporate these concepts within a global hypothesis, a biomechanical model of glaucomatous optic neuropathy has been proposed.[2] This model proposes that IOP-related stress (force/cross sectional area) and strain (local deformation of the tissues) play an essential and causative role in the pathophysiology of the changes seen in all of the tissue types within the optic nerve head and in its blood supply. These not only include the lamina cribrosa, the scleral canal wall, and the peripapillary sclera, but also the cellular components of these tissues, including astrocytes, glial cells, endothelial cells, and pericytes, along with their basement membranes and the RGC axons. Regardless of the primary insult in glaucomatous injury, IOP-related stress and strain in the laminar connective tissues are key elements in this model and are dependent on the optic nerve head architecture and material properties of these connective tissues.

Applying this model to the theoretical question as to the future role of IOP-lowering therapy has important implications in that IOP will always be one of the primary drivers of injury even at low levels of IOP since significant tissue strain is still realized at the optic nerve head. For example, the classic observations that disc hemorrhages occur, does not necessarily imply a primarily vascular etiology. Disc hemorrhages could easily be explained due to remodeling and resultant rupture the laminar beams with the blood dissecting onto the disc surface within an axonal bundle. This could occur based on an entirely mechanical insult. That disc hemorrhages have been strongly associated with signs of significant laminar remodeling as in the case of acquired optic nerve pits lends some credence to this hypothesis. I am not arguing that other mechanisms are not playing an important role, simply that IOP related mechanism are still important to injury at all IOP levels.

Further evidence for the important role of the biomechanical model in the development of glaucoma can be seen in the many large multicenter prospective studies focused on identifying the risk factors associated with the development or progression of glaucoma. The results of the several randomized prospective trials have identified the risk factors associated with the development or progression of glaucoma (Table 1). Factors that appear most consistent across several studies include the level of IOP, age, central corneal thickness, increased optic disc cupping, and African ancestry, which are all independently associated with glaucomatous progression. It is important to note that all of these risk factors have a biologically plausible association that can be directly explained within a biomechanical model. These factors are all associated with either the level of IOP, the severity of disease (visual field severity), or factors that may relate to the biomechanical properties of the optic nerve head (age,[5] African ancestry,[6] corneal thickness,[7] increased cupping).

Table 1. Risk factors for glaucomatous progression

Risk Factor	Prospective Study
Increasing Age	AGIS, CIGTS, EMGT, OHTS, EGPS
African Ancestry	AGIS, CIGTS, CNGTS OHTS (Univariate)
Visual Field Severity	EMGTS, AGIS, OHTS, EGPS
Diabetes	AGIS, OHTS (Protective)
Disc Hemorrhage	EMGT, CNGTS, OHTS
Follow-up IOP	EMGT, CNGTS
Cup-Disc Ratio	OHTS, EGPS
Corneal Thickness	OHTS, EGPS
Pseudoexfoliation	EMGT
Initial IOP	EMGT
Female Gender	CNTGS
Male Gender	AGIS

AGIS, Advanced Glaucoma Intervention Study[8]; EMGT, Early Manifest Glaucoma Treatment Study[10]; CIGTS, Collaborative Initial Glaucoma Treatment Study[11]; CNTGS, Collaborative Normal Tension Glaucoma Study[12]; OHTS, Ocular Hypertension Treatment study[13]; EGPS, European Glaucoma Prevention Study[14]

Other factors that have been associated include diabetes, which can effect the material properties of connective tissues due to advance glycosylation end-products and disc hemorrhages, which as stated above could be secondary to structural remodeling of the lamina cribrosa in response to IOP-related or vascular injury. In short, all relevant risk factors for glaucoma can be explained within the context of a biomechanical model. Since IOP is a critical, but not exclusive, exposure input to this mode, lowering of IOP should remain a critical piece in the management of glaucoma.

CME ANSWERS

1. a
2. false
3. c

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North American Neuro-Ophthalmology Society

41st Annual Meeting

February 21-26, 2015
Hotel del Coronado • San Diego, California

ON-SITE REGISTRATION HOURS: (located in the Ballroom Foyer)

Saturday	2:00 p.m. – 8:00 p.m.
Sunday	6:30 a.m. – 5:30 p.m.
Monday–Thursday	6:30 a.m. – 12:30 p.m.

SOCIAL FUNCTIONS

SATURDAY, FEBRUARY 21

San Diego Zoo Safari Park- $110 **10:00 a.m. – 4:00 p.m.**

***Price includes admission and transportation. Departure location will be from the Hotel del Coronado Lobby.**

With over 2,000 acres of wildlife preserve including upwards of 4,000 rare and endangered animals housed in habitats replicating their native homelands, the San Diego Zoo Safari Park is a offering education and entertainment. Nairobi Village is home to two dynamic interactive exhibits: the Hidden Jungle, where you can mingle with exotic butterflies and tropical hummingbirds, and Lorikeet Landing, a walk-through aviary for feeding nectar to rainbow lorikeets. Nairobi Village also features an expansive gorilla grotto for a large troop of lowland gorillas and the Animal Care Center, which encompasses a baby animal nursery, exhibits for koalas and small primates, and a petting corral with exotic deer, antelope, and goats.

The Africa Tram Safari is an experience aboard an open air tram that runs on bio diesel. Complete with an interactive island research station, primate island, giraffe feeding station, and safari surprises, it brings people closer to the animals in a way not even an African safari can replicate! The Journey into Africa tour is designed to give you a glimpse of the amazing diversity found there.

Opening Reception **6:00 p.m. – 7:30 p.m.**

Please join us for the Opening Reception on the Sun Deck at Hotel del Coronado. All are welcome to attend the opening reception, which features complimentary cocktails and several food stations.

SUNDAY, FEBRUARY 22

Members-in-Training Program and Reception **5:30 p.m. – 6:30 p.m.**

New to Neuro-Ophthalmology? All students, residents and fellows are encouraged to attend!

MONDAY, FEBRUARY 23

WIN Luncheon **12:15 p.m. – 1:30 p.m.**

Join your colleagues for the Women in Neuro-Ophthalmology (WIN) Luncheon & Meeting. The lunch option listed below will be available for purchase for $35; however, all are welcome to attend even without the purchase of a lunch.

WIN Lunch Option: California Citrus Salad with Orange Balsamic Vinaigrette
Vegetable and Cheese Ravioli, Wild Mushrooms and Asparagus Cream, Asiago cheese Sauce
Fresh Rolls and Butter, Seasonal Fruit Panna Cotta
Coffee, Decaffeinated Coffee, Specialty 7 Herbal Teas, Ice Tea

Young Neuro-Ophthalmologist Forum **3:00 p.m. – 5:00 p.m.**

While all are welcome to attend, this forum is specifically designed for residents, fellows and Neuro-Ophthalmologists in the early years of their career. The YONO Committee has incorporated last year's positive, constructive feedback and present a re-vamped format. The revised forum will have multiple rotating roundtable discussions in small groups facilitated by YONOs, who have just walked in your footsteps, to mid-career folks, who can shed light on the next steps ahead.

3:00 p.m. – 4:00 p.m.	**All you ever wanted to know about becoming a Neuro-Ophthalmologist: For trainees, residents, and fellows**
4:00 p.m. – 5:00 p.m.	**So now I have a job, where do i go from here? For junior attendees in private practice or academics in their first 5 years out of training**

TUESDAY, FEBRUARY 24

***The USS Midway Tour, San Diego Zoo, and Balboa Park/Museum pricing includes admission, transportation, and a boxed lunch. All excursions will depart from the Orange Avenue lawn which is located to the left of the Hotel del Coronado front entrance.**

USS Midway Tour - $75 **12:15 p.m. – 4:15 p.m.**

Guests will have a once-in-a-lifetime opportunity as they step onto a genuine Naval Aircraft Carrier for a fascinating tour of the USS Midway. A coveted opportunity, the privilege of actually boarding one of these impressively immense ships is truly unique. Over ten football fields in length, the USS Midway was built as the largest seagoing vessel in the world—the first ship too big to cross the Panama Canal. Her patriotically inspiring history in service stands as a testament to United States military achievement. Guests will have the opportunity to explore the USS Midway, on a self-guided audio tour featuring 60 exhibits including 24 restored aircraft. The Midway docents, many of whom are Midway veterans, will provide interactive, storytelling at many of the areas on the ship. Wear comfortable shoes, suitable for stairs and ladders; a light jacket is recommended on the Flight Dec

San Diego Zoo - $100 **12:15 p.m. – 4:15 p.m.**

The San Diego Zoo is renowned all over the world for its expansive collection of the rarest animals on earth housed in an intimate setting of exotic botanical foliage. The visit will include a narrated bus safari, taking you into the lush, sweeping canyons and countless animal enclosures. Take a plunge into the arctic as you get a glimpse of the Polar Bears dancing in the cold ice-filled waters. Otherwise, take a stroll through Tiger River, a misty path where along the way you'll encounter hundreds of reptiles and mammals and possibly come within a clawing distance of a Sumatran Tiger. See the spectacular Gorilla Tropics, one of the most popular exhibits. Guests can board a thrilling ride on the skyfari aerial tram and enjoy a panoramic, bird's eye perspective. Apart from wildlife, the park houses an extensive and highly acclaimed collection of plants, orchids, palms, coral trees, and more.

Balboa Park/Museums - $110 **12:15 p.m. – 5:15 p.m.**

Balboa Park is San Diego's premier colonial landmark. Stretching over 1,400 acres nestled in the hills of downtown, this urban park houses 85 cultural and recreational organizations, including seventeen museums. Balboa Park is a cultural Mecca, the largest concentration of museums and cultural institutions outside The Mall in Washington, D.C. A day pass with admission to your choice of any (4) museums – each guest can customize their day and select the museums they personally wish to visit. The museums include: Natural History Museum, Reuben H. Fleet Science Center, Mingei International Art Museum, Museum of Photographic Arts, Air & Space Museum, Centro Cultural de la Raza; World Beat Center, Hall of Champions Sports Museum, Model Railroad Museum, Automotive Museum, and the Veteran's Memorial Center Museum.

TUESDAY, FEBRUARY 24

Poster Session **6:00 p.m. – 9:30 p.m.**

This year's Poster Session will include a reception and dinner. Event is complimentary for attendees, but guests must purchase tickets. Tickets are available for purchase for $50 per person. The buffet will open at 6:00 p.m. Authors will present their posters between 6:45 p.m. and 8:15 p.m. Odd numbered posters: 6:45 p.m. – 7:30 p.m., Even numbered posters: 7:30 p.m. – 8:15 p.m.

WEDNESDAY, FEBRUARY 25

Annual NANOS Reception and Banquet **6:45 p.m. – 10:00 p.m.**

The Annual Meeting Banquet will take place on the Windsor Lawn and beach front of the Hotel del Coronado. Join your colleagues for a fun, casual evening of socializing, dining and beach side bonfires at the NANOS Annual Reception and Banquet. Guests and children are welcome. Event is complimentary for attendees but guests must purchase tickets. Tickets are available for purchase for $100 per person. Beach appropriate shoes are highly recommended.

GUEST MEETING LOUNGE AREA **Available 9:00 a.m. – 11:00 a.m.**

Sunday February 21-Wednesday, February 25

Relax and enjoy the company of other guests in the 'Garden Patio' located in the center of the Hotel del Coronado.

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M. Agarwal
J. Chacko
G. Kao
M. Ko (Chair, YONO)
C. Lueck (Chair, International Relations)
H. Moss
J. Peragallo
B. Wallace

STRATEGIC PLANNING COMMITTEE

L. Frohman (Chair)
N. Newman (Board Liaison)
J. Fick (Executive Director)
L. Levi (Chair, Board)

NANOS ARCHIVES
PAST MEETING SITES AND FACULTY

No Star = NANOS Member Speaker
* = Moderators (Excluding Walsh Program)
** = Non-Member Guest Speakers

1975 SANTA FE, NEW MEXICO
Cannon, Carlow, Daroff, Glaser, Hoyt

1976 SANTA FE, NEW MEXICO
Cannon, Carlow, Daroff, Glaser, Hoyt, Schatz

1977 PURGATORY, COLORADO
Appenzeller, Bicknell, Cannon, Carlow, Daroff, Glaser, N. Newman (CA), Schatz

1978 PURGATORY, COLORADO
Bicknell, Cannon, Carlow, Daroff, Glaser, Schatz, Snyder, A.E. Walker, Wray

1979 JACKSON HOLE, WYOMING
Bicknell, Carlow, Daroff, Glaser, Schatz, Van Dyk, Wilson, Younge

1980 SANTA FE, NEW MEXICO
Bicknell, Carlow, Daroff, Glaser, Hoyt, Schatz

1981 PARK CITY, UTAH
Carlow, Cobbs, Corbett, Dell'Osso, Ellenberger, Glaser, Kennerdall, Sanborn, Savino, Seigel, Schatz, Thompson, Wilson, Wirtschafter, Younge, Zauel

1982 LAKE DILLON, COLORADO
Bilaniuk**, Beck, Carlow*, Corbett, David, Dell'Osso, Ellenberger*, Goodwin, Hoyt, Johnson, Kupersmith, Maitland, Piepgras**, Selhorst*, Sharpe*, Shults*, Smith, Spector*, Wirtschafter*, Younge*, Williams*

1983 BIG SKY, MONTANA
Baloh**, Beck, Carlow**, Corbett, David, Dell'Osso, Ellenberger* Goodwin, Hoyt, Johnson, Kupersmith, Maitland, Repgrass**, Selhorst*, Sharpe*, Shults*, Smith, Spector*, Wirtscafter*, Younge*, Williams*

1984 SNOWBIRD, UTAH
Beck, Carlow*, Ellenberger*, Feldon, Goodwin, Kennerdell*, Kupersmith, Maitland, Newman, S., Sanborn, Savino*, Schatz*, Selhorst, Sergott, Sharpe*, Smith, C., Spector, Stryker**, Wirtschafter, Younge*, Zimmermann**

1985 SUNSHINE VILLAGE, ALBERTA
Beck, Carlow*, Corbett*, Dell'Osso, Feldon*, Garrity, Goodwin, Graf-Radford, Guy, Kennerdell, Kupersmith*, I. Levy, S. Newman, Pilley, Quigley**, Rosenberg, Sadun, Sharpe*, Silberberg**, C. Smith, Spector, Tomlinson, Wall, Wirtschafter, Younge*, Zackon, Zauel

1986 WHISTLER, BRITISH COLUMBIA
Carlow*, Corbett*, Cox, Dell'Osso, Feldon*, Goodwin, Guy, Hoyt*, Kennerdell, Knox, Kupersmith*, Lisberger**, Maitland, S. Newman, Pilley, Ranalli, Rodnitzky, Savino*, Sharpe*, Shults*, Sibony, Thompson, Wall, Wirtschafter*, Zimmerman**

1987 NORTHSTAR, CALIFORNIA
Beck, Berenstein**, Carlow*, Corbett*, Cox, Cummings**, Digre, Feldon, Goodwin, Guy, Hart, Hoyt*, Keltner, Kupersmith*, Lasjaunias**, Meckler*, Miller, S. Newman, Rosenberg, Sadun*, Sharpe*, Shults*, Thompson*, Wirtschafter*, Wall*, Younge

1988 CRESTED BUTTE, COLORADO
Aguago**, Baker, Beck, Carr**, Carlow*, Corbett*, Chu, Goodwin, Hart, Hoyt*, Kupersmith*, Maitland*, S. Newman*, Rizzo, Saul, Selhorst, Schiffman, Sharpe*, Shults*, Thompson*, Wall, Wirtschafter*

1989 CANCUN, MEXICO
Baker, Buckley, Carlow*, Corbett*, Daroff*, Digre, Drake**, Feldon, Goodwin*, Glaser*, Hupp, Kardon, Kupersmith*, S. Newman, Odel, Sadun, Schatz*, Schiffman, Selhorst, Sharpe*, Shults*, Slavin, Sibony, Spector, Thompson*, Wall*, Weinstein, Zackon

1990 STEAMBOAT SPRINGS, COLORADO
Baker, Beck*, Carlow*, Corbett*, Dell'Osso, Digre, Feldon*, Freeman**, Friedman, Frishberg, Green**, Grimson, Kupersmith*, Meckler*, Melvill Jones**, McCrary, N. Newman (CA), N. Newman (GA), S. Newman*, Odel*, Paige**, Rizzo, Sadun*, Selhorst, Sharpe*, Sibony, Spector*, Winterkorn, Wirtschafter, Younge, Zackon*

1991 PARK CITY, UTAH
Baker*, Benes, Bielory, Bienfang*, Brodsky, Burde, Carlow*, Corbett, Feldon*, Frohman*, Friedman, E., Good, Greenlee, Guy*, Hart, Hayreh**, Horton, Kosmorsky, Kupersmith*, McCrary*, Moster, S. Newman, Rizzo*, Sadun*, Selhorst, Sergott, Sharpe, Silberberg, Wall*, Wurtz*

1992 RANCHO BERNARDO INN, SAN DIEGO
Burde, Caplan**, Carter, Chung, Corbett, Digre, Fletcher, Friedman, Frohman, Gage, Goodwin, Hyslop**, Kardon, Kaufman, Kline, Kosmorsky, Kupersmith*, Labutta, S. Lessell, Maitland, Miller, Moster, Newman, N.(GA), S. Newman, Odel, Saul, Slavin, Thompson*, Thurston, Wall, Wirtschafter*

1993 BIG SKY RESORT, BIG SKY, MONTANA
Aitken, Baker*, Beck*, Calvert, Carlow, De Yoe**, Digre, Feldon*, Frohman*, Goodwin, Hoyt*, Hupp, C. Johnson, P. Johnston, Kaufman, Kupersmith*, Maitland, Meckler*, Moster, S. Newman, Rizzo*, Sadun, Schiffman*, Seiff, Sergott, Slamovits*, Tang, Troost*, Wall, Weiss*, Wirtschafter*

1994 TAMARRON RESORT, DURANGO, COLORADO
Barrett, Borchert, Caplan, Chung*, Fletcher*, Friedman*, Frohman*, Griffin**, Horton, Kardon*, Knox, Kosmorsky, Leavitt, Mishkin**, M. Rizzo*, Sargent, Saul, Seybold, Sharpe, Shults, Tranel, Selhorst*, Sogg*

1995 EL CONQUISTADOR, TUCSON, ARIZONA
Arnold, Baker*, Burde, Boghen, Cross, Currie, Daroff*, Frohman, Hamed, Jacobson*, Kattah*, Krauss, Lavin, S. Lessell, Maitland*, Massof**, McLoon**, Newman*, Peele, Porter**, J. Rizzo*, Sadun, Tang, Tomsak, Walker**, Waxman**, Wirtschafter, Wolf

1996 SNOWBIRD RESORT, SNOWBIRD, UTAH
Arnason**, Borchert*, Calvert*, Caplan, Chung, Cornblath, Digre, Eggenberger, Flectcher, Forman*, Friedman*, Good, Hart, Heckenlively**, Horton*, C. Hoyt, Johnston-NcNussen*, Kaufman*, Kosmorsky*, Kupersmith*, Miller, C. Shatz**, Purvin, Rubenfeld, Sawyer, Skarf, Slavin*, Verner**, I. Williams

1997 KEYSTONE RESORT, KEYSTONE, COLORADO
Caplan*, Cross*, Dion**, Eggenberger, Feldon, Fisher**, Fletcher, Fohman, Galetta, Jacobson, J. Johnston, Kawasaki, Kazim**, Kelly**, Meckler*, Morrow, Munzo**, N.J. Newman, S. Newman*, Paige*, Purvin*, A. Sadun*, Schiffman, Sternau**, Stafford**, Waitzman

1998 BUENA VISTA PALACE RESORT,ORLANDO, FLORIDA
Averbuch-Heller, Barton, Berman, Borchert*, Brodsky*, Chavis, Fitzgibbon, Gans, J. Johnston*, Kline*, Leavitt, Morrow*, Ransohoff**, Rubenfeld*, Sharpe, Soloman**, Sretavan**, Sundin**, Yee

1999 SNOWMASS VILLAGE RESORT, SNOWMASS, COLORADO

Arnold*, Barton, Borchert, Brodsky, Chung, Dreyer**, FitzGibbon*, Fletcher, Galetta*, Gutmann**, Halmagyi**, Hamilton, Johnson*, Kaufman, Lee, Levin*, Lippa**, Maitland, Morrow, Moster*, N.J. Newman, Sargent*, Smith*, Winterkorn, Zee, Zimmernan

2000 MT. TREMBLANT RESORT, TREMBLANT, QUEBEC

J.S. Barton, Brazis, Calvert, Caplan, Corbett, Cox, Cross, Eggenberger*, Friedman, Gamlin**, Garrity, Jacobson, Johnston-McNussen, Kardon*, M. Kazim**, Kennerdell, Krauss*, Kupersmith, A. Lee*, Leavitt*, Lincoff, Ptacek**, Purvin, M. Rosenberg*, Sargent, Skarf*, Wall*, Williams, Wirtschafter

2001 MISSION HILLS RESORT, RANCHO MIRAGE, CALIFORNIA

Anderson**, Arnold*, Balcer, Blake, Bryan**, Chung*, Egan, Eggenberger, FitzGibbon*, Galetta*, Garrity*, Gordon, Grossman**, Hedges, Krauss*, Legge, Levin*, Levi*, Lincoff*, Liu, Mahon, Miller, Mills, Rizzo, Rudick**, Sadun, C. Smith, Stafford, Sternau, Volpe*

2002 COPPER MOUNTAIN RESORT, COPPER MOUNTAIN, COLORADO

Balcer, Borchert, Bose*, Calvert, Chung*, Cox, Cross*, DeAngelis**, Dell'Osso*, FitzGibbon, Forbes**, Gardner**, Giannini**, Golnick, Gordon*, Hood**, Jacobson, Jampol**, Keltner, Knox*, Leavitt*, Mahon**, Miller, Moster, S. Newman*, Odel, Pomeranz*, Purvin, Reader, Sawyer*, Schiffman, Tang, Vance**, Williams**, Younge*

2003 SNOWBIRD SKI RESORT, SNOWBIRD, UTAH

Balcer, Borchert, Bose*, Calvert, Chung*, Cox, Cross*, DeAngelis**, Dell'Osso*, FitzGibbon, Forbes**, Gardner**, Giannini**, Golnik, Gordon*, Hood**, Jacobson, Jampol**, Keltner, Knox*, Leavitt*, Mahon**, Miller, Moster, S. Newman*, Odel, Pomeranz*, Purvin, Reader, Sawyer*, Schiffman, Tang, Vance** Younge*

2004 ORLANDO, FLORIDA

Berger**, Balcer, Bennett, Berenstein**, Bose*, Brodsky, Calvert, Chavis, Cockerham, Cornblath*, Demer**, Eggenberger, Garrity, Ghatek**, Gordon*, Kawasaki*, Kosmorsky*, Krauss*, Leigh**, Levi, Liu*, Luciano**, Mahon**, Morrow, Moster*, S. Newman, Osborn**, Pomeranz*, Sergott, Tang, Turbin, Winterkorn*, Wong*

2005 COPPER MOUNTAIN RESORT, COPPER MOUNTAIN, COLORADO

Rorke-Adams**, Barton*, Borchert, Buckley, Caplan, Craigle**, Digre*, Donahue*, Egan*, FitzGibbon*, Friedman, Frishberg*, Galletta, Goadsby**, C.Hoyt**, Huna-Baron*, Kaminski**, Keltner, Kerrison*, Landau*, Lane**, Lewis**, Lombardo**, Mawn*, Miller, Parsa*, Repka, Rucker, Selhorst*, Tang, Trobe, Van Stavern*, Volpe, Weinstein, Zimmerman**

2006 JW MARRIOTT STARR PASS RESORT AND SPA, TUCSON, ARIZONA

Balcer*, Bose*, Calvert, Chambers**, Corbett, Craigle**, Curtin**, Digre, Eggenberger*, Friedman*, Fujimoto**, Gordon*, Hedges, III*, W. Hoyt*, Huxlin**, M. Johnston**, Kardon, Kaufman*, Kerrison*, Lessell, Liu, Lombardo**, Mejico*, N. Miller, Mindel*, Mokri**, M. Moster**, N. Newman, Odel, Pomeranz*, Purvin, Prystowsky**, Ray, Savino, Sergott, Newman-Toker, Trobe*, Wall, Warner, Hedley-Whyte**, Wray

2007 SNOWBIRD SKI RESORT, SNOWBIRD, UTAH

Acierno, Arnold, Balcer, Bennett*, Biousse, Bose*, Cockerham, Cornblath, Costello, Digre, Di Polo**, Eggenberger, Falardeau**, Feldon*, Freedman**, Frohman, Garrity, Gaskill**, Golnik, Gordon, Guy, Hauswirth**, Kirby**, LeBer**, Lee, Levin*, Lombardo**, McCulley, Miller, Mower**, Murphy**, Newman-Toker, Rucker*, Sadun, Stieber**, Trobe*, Van Gelder**, Wong, Workman**, Youngkin**

2008 RENAISSANCE ORLANDO AT SEAWORLD, ORLANDO, FLORIDA

Acierno*, Agarwal, Anderson*, Arnold, Biousse*, Bose*, Corbett, Cornblath*, Costello, Dennis, Duffy**, Eggenberger*, Farris, Frankel**, Friedman, Gordon, Hinton**, Inglese**, Jirawuthiworavong, Kelman, Kim**, Krauss, Lee*, Legge, Levi, Lombardo*, N. Newman*, S. Newman*, Newman-Toker*, Paulson**, Pelak*, Quiros, Rizzo, Selhorst*, Truwit**, Van Stavern, Volpe*, Wong*

2009 HYATT REGENCY LAKE TAHOE RESORT, LAKE TAHOE, NEVADA

Acierno, Arnold, Bazarian**, Biousse, Bollen**, Bose*, Costello, Daroff, Eggenberger, Ellis-Behnke**, Engle**, Fallon, FitzGibbon, Galetta, Glastonbury**, Golnik*, Gordon, Horton, Hoyt, Hwang, Le Ber, A. Lee*, Levin, Liao, Lombardo*, McCulley, Miller, N. Newman, Pomeranz, Repka, Rizzo*, Sadowski**, Sadun, Siatkowski*, Silva**, Subramanian*, Trauzettel-Klosinski, Trobe, Tychsen**, Volpe, Warner*, Wong*

2010 JW STARR PASS MARRIOTT RESORT & SPA, TUCSON, ARIZONA

Agarwal*, Balcer*, Bennett, Bonhomme, Brodsky, Chan, Cockerham, Cornblath, Costello*, Cross, Digre, Douglas**, Dreizin, Eggenberger, Feldon*, Foroozan, Friedman, Frohman*, Galetta*, Hedges, III, Jay, Johnston, Kardon*, Kawasaki, Keltner, Kline, Leavitt, M. Lee, Lombardo, Mejico*, Moster*, N. Newman, Pepin, Pruitt**, Purvin, Rubenfeld, Sadowski, Sadun, Schuman**, Shindler*, Subramanian, Trobe, Volpe, Wong

2011 THE FAIRMONT HOTEL VANCOUVER, VANCOUVER, CANADA

Acierno, Balcer, *Barton, Bennett, Borchert, Bruce, Cestari, Chacko, Chung, **Corbo, Cornblath, Costello, Digre, Eggenberger, Falardeau, *FitzGibbon, Galetta, Green, Horton, Jay, Kline, *Lam, *Landau, Le Ber, *Lee, Legge, Liao, Liu, Lombardo, *Miller, *Morrow, Mudumbai, *Odel, Phillips, Rizzo, Rucker, Savino, **Sharma, Shepherd, *Shin, **Spaide, Trauzettel-Klosinski, *Van Stavern, Warner, **Wingerchuk, Wong

2012 JW MARRIOTT SAN ANTONIO HILL COUNTRY RESORT AND SPA, SAN ANTONIO, TEXAS

Acierno, **Bazan, Borchert, *Brodsky, **Burns, Carelli, Carter, Dreizin, Eggenberger, FitzGibbon, *Fletcher, Friedman, **Gailloud, *Gordon, Jay, Johnston, **Kassam, Kattah, Kline, Kupersmith, Le Ber, *M. Lee, Legge, **Leigh, *Lincoff, *Liu, Lombardo, Mawn, *Miller, *N. Newman, S. Newman, Newman-Toker, Parsa, Pula, Roberts, *Sadun, Shindler, Stefko, *Subramanian, Thurtell , Trobe, Volpe, *Wong, Wray, **Zee

2013 SNOWBIRD SKI RESORT, SNOWBIRD, UTAH

*Agarwal, Arnold, Avery, Bennett, *Bhatti, *Biousse, *Bose, **Brat, *Bruce, **Chiang, *Costello, Digre, Dinkin, Falardeau, *FitzGibbon, Friedman, Frishberg, Frohman, *Galetta, **Hudgins, Jirawuthiworavong, Johnston-McNussen, **Kassam, Kedar, Ko, *Lam, *Lee, Liao, Mawn, *McCulley, Melson, Miller, Odel, Osborn, Phillips, *Prasad, *Quiros, Rucker, Sadun, Salzman, **Stoutenburg, *Subramanian, Thompson, Thurtell, G. Van Stavern, R. Van Stavern, **Vicchrilli, *Wall

2014 WYNDHAM RIO MAR BEACH RESORT, RIO GRANDE, PUERTO RICO

*Agarwal, *Balcer, *Biousse, **Blitz, *Borruat, Chung, Costello, Digre, **Eberhart, Eggenberger, *Falardeau, *Fraser, Friedman, *Frishberg, Galetta, Garrity, Golnik, Gordon, Kardon, Katz, Keltner, Kosmorsky, Krauss, Kupersmith, **LaFrance, Lee, Levin, Liu, Miller, *Moss, Newman, *Patel, *Purvin, *Rucker, Sadun, Sergott, Stefko, Subramanian, Thurtell, Trauzettel-Klosinski, *Trobe, Van Stavern, Volpe, *Wall, Warner, Yu-Wai-Man

NANOS ARCHIVES
PAST OFFICERS AND BOARD MEMBERS

1980-1982

President:	Thomas J. Carlow, M.D.
Vice-President:	Joseph Bicknell, M.D.
Secretary-Treasurer:	Donald Seelinger, M.D.

1983-1985

President:	Thomas J. Carlow, M.D.
Vice-President:	Peter Savino, M.D.
Secretary-Treasurer:	Brian Younge, M.D.
Member-at-Large:	Carl Ellenberger, M.D.
Board of Directors:	Robert Daroff, M.D.
	Joel S. Glaser, M.D.
	William F. Hoyt, M.D.
	Norman Schatz, M.D.

1986-1989

President:	Thomas J. Carlow, M.D.
Vice-President:	James A. Sharpe, M.D.
Secretary-Treasurer:	James Corbett, M.D.
Member-at-Large:	William T. Shults, M.D.
Board of Directors:	Robert Daroff, M.D.
	Joel S. Glaser, M.D.
	William F. Hoyt, M.D.
	Norman Schatz, M.D.

1990-1992

President:	Thomas J. Carlow, M.D.
President-Elect:	James A. Sharpe, M.D.
Vice-President:	James J. Corbett, M.D.
Secretary:	Mark J. Kupersmith, M.D.
Treasurer:	Stevcn E. Feldon, M.D.
Board of Directors:	Robert Daroff, M.D.
	Joel S. Glaser, M.D.
	William F. Hoyt, M.D.
	Norman Schatz, M.D.

1992-1994

President:	James A. Sharpe, M.D.
President Elect:	Steven E. Feldon, M.D.
Vice-President:	James J. Corbett, M.D.
Secretary:	Joseph Rizzo, M.D.
Treasurer:	Michael Wall, M.D.
Board of Directors:	Thomas J. Carlow, M.D.
	Robert Daroff, M.D.
	William F. Hoyt, M.D.
	Nancy J. Newman, M.D.
	William T. Shults, M.D.

1994-1996

President:	Steven E. Feldon, M.D.
President Elect:	Jonathan Wirtschafter, M.D.
Vice-President:	Alfredo A. Sadun, M.D.
Secretary:	John B. Selhorst, M.D.
Treasurer:	Kathleen Digre, M.D.
Board of Directors:	Thomas J. Carlow, M.D.
	James J. Corbett, M.D.
	Neil R. Miller, M.D.
	James A. Sharpe, M.D.

1996-1998

President:	Jonathan Wirtschafter, M.D.
President-Elect:	John Selhorst, M.D.
Vice-President:	Larry Frohman, M.D.
Secretary:	Gregory S. Kosmorsky, D.O.
Treasurer:	Deborah Friedman, M.D.
Board of Directors:	Steven E. Feldon, M.D.
	Neil Miller, M.D.
	H. Stanley Thompson, M.D.
	B. Todd Trost, M.D.
	James A. Sharpe, M.D.
Executive Vice-President:	Thomas J. Carlow, M.D.
Editor JNO:	Ronald M. Burde, M.D.

1998-2000

President:	John B. Selhorst, M.D.
President-Elect:	Neil Miller, M.D.
Vice-President:	Larry Frohman, M.D.
Secretary:	William Fletcher, M.D.
Treasurer:	Sophia Chung, M.D.
Board of Directors:	Kathleen Digre, M.D.
	Steven Feldon, M.D.
	H. Stanley Thompson, M.D. 97-99
	B. Todd Troost, M.D. 97-99
	D. Jacobson, M.D. 99-01
	J. Keltner, M.D. 99-01
	Jonathan Wirtschafter, M.D.
Executive Vice-President:	Thomas J. Carlow, M.D.
Editor JNO:	Ronald M. Burde, M.D.

2000-2002

President:	Neil R. Miller, M.D.
President-Elect:	Kathleen Digre, M.D.
Vice-President:	Joel Weinstein, M.D.
Secretary:	Deborah Friedman, M.D.
Treasurer:	Ralph Sawyer, M.D.
Board of Directors:	Larry Frohman, M.D.
	Daniel Jacobson, M.D. 99-01
	John Keltner, M.D. 99-01
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	Steven Newman, M.D. 00-02
	Valérie A. Purvin, M.D. 01-03
	John B. Selhorst, M.D. 00-02
Executive Vice-President:	Thomas J. Carlow, M.D.
Editor JNO:	Ron Burde, M.D. 01
	Jonathan D. Trobe, M.D. 02

2002-2004

President:	Kathleen Digre, M.D.
President-Elect:	Larry Frohman, M.D.
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Secretary:	Laura J. Balcer, M.D.
Treasurer:	Ralph A. Sawyer, M.D.
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Executive Vice-President:	Thomas J. Carlow, M.D.
Editor JNO:	Jonathan D. Trobe, M.D.

2004-2006

President:	Larry Frohman, M.D.
President Elect:	Deborah I. Friedman, M.D.
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Editor JNO:	Jonathan D. Trobe, M.D.

2006-2008

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2008-2010

President:	Anthony C. Arnold, M.D.
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	Agnes M.F. Wong, M.D., Ph.D., OFRCS(C) 09-12
Executive Vice-President:	Thomas J. Carlow, M.D.
Editor JNO:	Lanning B. Kline, M.D.

2010-2012

President:	Preston C. Calvert, M.D.
President-Elect:	Leah Levi, M.D.
Vice President:	Edmond J. FitzGibbon, M.D.
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	Nicholas J. Volpe, M.D. 10-12
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Editor JNO:	Lanning B. Kline, M.D.

2012-2014

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President-Elect:	Nancy J. Newman, MD
Vice President:	Edmond J. FitzGibbon, MD
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	Ivy J. Dreizen, MD 11-14
	Lynn K. Gordon, MD, PhD 12-15
	Mark L. Moster, MD 13-16
	Peter A. Quiros, MD 13-16
Immediate Past President:	Preston C. Calvert, MD
Ex-Officio:	Thomas J. Carlow, MD
Editor JNO:	Lanning Kline, MD

NANOS RECOGNITION AND AWARDS
PRESENTED AT THE ANNUAL NANOS BANQUET DURING THE ANNUAL MEETING

RESIDENT FELLOW AWARD RECIPIENTS

Separate awards are given to the best work by a medical student, resident or fellow. Eligible candidates include any medical student, resident or individual in a fellowship program who is the first (presenting) author of work done as a student, resident or fellow respectively. The James A. Sharpe Fund supports the fellow award. Judging for the awards is based upon the candidate's platform or poster presentation at the annual NANOS meeting.

1983 Big Sky
David Zackon
Vertical Supranuclear Gaze Palsy and Intrathoracic Carcinoid Tumor

1984 Snowbird
Mary Stefanyszn
Optic Nerve Tumor in a Child

1985 Sunshine Village
Paul Ranalli
Ocular Motor Syndrome of the Superior Cerebellar

1986 Whistler
William Fletcher
Big Blind Spot Syndrome without Optic Disc Edema Artery

1987 Lake Tahoe
Steven Gross
A Child with Aminoaciduria and Retinal Degeneration

1988 Crested Butte
Jonathan Horton
Ocular Dominance Columns in Human Visual Cortex

1989 Cancun
Karl Golnik
Acute Visual Loss in a Young Male

1990 Steamboat Springs
Jonathan Horton
Occipital Visual Field Defects Respecting the Horizonal Meridian: Hallmark of Extrastriate Cortical Lesions

1991 Park City
Constance Fry
Is there Value in Evaluating Carotid Artery Patency in Patients with Anterior Ischemic Optic Neuropathy

1992 Rancho Bernardo
Ikyle Smith
Herteroplasmy in Leber's Hereditary Optic Neuropathy

1993 Big Sky
Kimerly Peele
The Role of Peripheral Visual Fields in IIH

1994 Durango
Aki Selky
Variability of the Relative Afferent Pupillary Defect: Effect of Stimulus Number, Duration, and step Size on the Confidence Limit Using Pupillography

1995 Tucson
Erkan Mutlukan
Red Color Desaturation, Brightness Perception Asymmetry and Light Detection Threshold Elevation in Optic Neuropathy: How Do They Inter-Relate?

1996 Snowbird
Nurhan Torun
Initial and Sinusoidal Vestibulo-Ocular Reflex Following Focal Brainstem Lesions

1997 Keystone
John M. Khoury
Can Humphrey Perimetry 24-2 Be Substitued for 30-2

1998 Orlando
Valérie Biousse, M.D.
Neuro-Ophthalmologic Manifestations of 145 Patients with Extracranial Internal Carotid Artery Dissections

1999 Snowmass
John Kerrison, M.D.
Congenital Motor Nystagmus Linked to Xq26-q27

2000 Mt. Tremblant
Agnes Wong, M.D.
Effects of Abducens Nerve Palsy on Listing's Law During Saccades and Fixation

2001 Rancho Mirage, CA
Gabriella Szatmary, M.D.
Can Sita Fast Be Used as a Reliable Alternative to Goldman Perimetry in Neuro-Ophthalmic Practice?

2002 Copper Mountain
Nicholas T. Monsul, M.D.
Dibutyryl Cyclis AMP Promotes Optic Nerve Regeneration

2003 Snowbird
Nitza Goldenberg-Cohen, M.D.
Defining the Retinal and Optic Nerve Response to Anterior Ischemic Optic Neuropathy (AION) Using a Mouse Model

2004 Orlando

- Fellow: *Guy V. Jirawuthiworavong, M.D., M.A.*
  Frequency of Antiretinal Antibodies in Normal Human Serum
- Resident: *Gregory F. Wu, M.D., Ph.D.*
  Visual Function and Disease Phenotype in Multiple Sclerosis
- Student: *A Quantitative Approach to Identifying Non-Organic*
  Contributions to Field Defects Using the Multifocal Visual Evoked Potential (mfVEP)

NANOS RECOGNITION AND AWARDS
PRESENTED AT THE ANNUAL NANOS BANQUET DURING THE ANNUAL MEETING
(CONTINUED)

2005 Copper Mountain

- Fellow: *Gabrielle R. Bonhomme, M.D.*
  Isolated Pediatric Optic Neuritis: Brain MRI Abnormalties and Risk of Multiple Sclerosis
- Resident: *Clare Fraser, M.B.B.S*
  Multifocal Visual Evoked Potentials in the Differential Diagnosis of Acute Optic Neuritis
- Student: *Christopher Rodarte, B.A.*
  A Quantitive Approach to Identifying Delayed Latencies in the Multifocal Visual Evoked Potential (mfVEP)

2006 Tucson

- Fellow: *Gregory Wu, M.D., Ph.D.*
  Regional MRI Abnormalities and Visual Dysfunction in Patients with Multiple Sclosis
- Resident: *Clare Fraser, M.B.B.S.*
  One Year Multiple Sclerosis Conversion Rates for Patients with Multifocal Visual Evoked Potential (MVEP) Latency Delay
- Student: *Michael D. Richards*
  Duration of Binocular Decorrelation Predicts the Intensity of Fusion Maldevelopment (Latent) Nystagmus in Strabismic Macaque Monkeys

2007 Snowbird

- Fellow: *Christopher C. Glisson, D.O.*
  Clinical Characteristics Associated with Neuromyelitis Optica (NMO) Antibody Seropositivity
- Resident: *Melissa W. Ko, M.D.*
  Assessment of Visual Dysfunction in Parkinson's Disease
- Student: *Bryn Burkholder*
  Low-Contrast Letter Acuity Loss Over Time in Multiple Sclerosis Correlates with Reductions in Retinal Nerve Fiber Layer Thickness and Macular Volume by OCT

2008 Orlando

- Fellow: *Thomas N. Hwang, M.D., Ph.D.*
  Reconstitution of Light-Evoked Responses through a Mechanism of NMDA Receptor Mobility across the Cell Membrane in a Tiger Salamander Model
- Resident: *Sashank Prasad, M.D.*
  Cross-Modal Language Processing in the Visual Cortex of the Congenitally Blind
- Student: *Matt Schlenker*
  The Translational Vestibulo-Ocular Reflex in Patients with Skew Deviation

2009 Lake Tahoe

- Fellow: *Divya Aggarwal, M.D.*
  Melanopsin Retinal Ganglion Cells: A New Class of Cells in Human Retina
- Resident: *Daniel Barthelmes, M.D., FEBO*
  Retinal Hemorrhages in High Altitude Mountaineers
- Student: *Sally C. Chang*
  MS Functional Composite Scores with a Visual Component Added Capture Axonal Loss in Patients with Multiple Sclerosis

2010 Tucson

- Fellow: *Robert Avery, D.O.*
  Reference Range of Cerebrospinal Fluid Opening Pressure in Children
- Resident: *Patrick Yu-Wai-Man, M.D.*
  Multi-System Neurological Disease is Common in Patients with OPA1 Mutations
- Student: *Jonathan Frandsen*
  Macular Carotenoids in Patients with Photophobia

2011 Vancouver

- Fellow: *Jennifer Graves, M.D.*
  Visual Pathway Axonal Loss in Patients with Benign Multiple Sclerosis
- Resident: *Patrick Yu-Wai-Man, M.D., Ph.D.*
  Efficacy and Safety of Idebenone in Patients with Leber's Hereditary Optic Neuropathy (LHON): Results of a 6-Month Randomized, Placebo-Controlled Trial (RHODOS)
- Student: *Joyce Ho*
  In Vivo Imaging of Murine Experimental Anterior Ischemic Optic Neuropathy

2012 San Antonio

- Fellow: *Patrick Yu-Wai-Man, BMedSci, MBBS, PhD, FRCOphth*
  Mitofusin 2 (MFN2) mutations cause mitochondrial DNA instability in Charcot-Marie-Tooth disease
- Resident: *Karen Schmitt, M.D.*
  Transmeningeal Drug Delivery to the Optic Nerve
- Student: *Mithu Storoni*
  The Use Of Magnetic Resonance Imaging To Distinguish Between NMO Spectrum And MS Related Optic Neuritis Based On The Appearance Of The Visual Pathways

2013 Snowbird

- Fellow: *Kimberly Winges, M.D.*
  The Ganglion Cell Layer Across the Vertical Meridian in Hemianopsia: I Get No Respect!
- Resident: *Cynthia Yu-Wai-Man, MBBS, FRCOphth*
  Extraocular muscle atrophy and central nervous system involvement in chronic progressive external ophthalmoplegia – a structural and spectroscopic magnetic resonance study
- Student: *Ali S. Saber Tehrani*
  Quantitative video-oculography for diagnosing stroke at the bedside in acute vertigo: an "ECG" for the eyes

2014 Puerto Rico

Best Abstract Awards

- James A. Sharpe-Fellow: *Krista I. Kinard, M.D.,*
  Chronic Migraine is Associated with Reduced Corneal Nerve Fiber Density and Length
- Resident: *Ajay E. Kuriyan, M.D.*
  Orbital Fibroblasts from Thyroid Eye Disease Patients Differ in Proliferative and Adipogenic Responses Depending on Disease Sub-Type
- Student: *Matthew A. Miller*
  A Comparison of Clinical Features of Pseudotumor Cerebri Secondary to Tetracyclines and Idiopathic Intercranial Hypertension

NANOS RECOGNITION AND AWARDS
PRESENTED AT THE ANNUAL NANOS BANQUET DURING THE ANNUAL MEETING
(CONTINUED)

THE THOMAS AND SUSAN CARLOW YOUNG INVESTIGATOR AWARD

This award was established to encourage and recognize basic or clinical research in neuro-ophthalmology by a NANOS candidate or active member. The originality, scientific merit and neuro-ophthalmic interest of a developing investigator's total body of work combined with a representative new research manuscript will be considered as criteria to determine the award recipient. The award is selected by the Research Committee during the Annual Meeting and need not be given annually. It is not open to NANOS Fellows.

1997 *Leonard A. Levin, M.D., Ph.D.*
Induction of Gene Expression after Retinal Ganglio Cell Anatomy

1998 *Jason J.S. Barton, M.D.*
Ocular Tracking of Step-Ramp Targets by Patients with Unilateral Cerebral Lesions

1999 *Wolf Lagrese, M.D.*
Neuroprotection with Memantine, Cerestat and Riluzole in a Rat Model of Acute Retinal Ischemia

2000 *Sean Donahue, M.D.*
Skew Deviation and Inferior Oblique Palsy

2002 *Valérie Biousse, M.D.*
The Eyes of Mito-Mouse

2003 *Agnes M.F. Wong, M.D., Ph.D.*
Early Versus Delayed Correction of Infantile Strabismus in Macaque Monkeys: Effects on Cerebral Ocular Motor Circuits

2004 *John B. Kerrison, M.D.*
Candidate Gene Analysis in X-linked Congenital Nystagmus

2005 *Steven F. Stasheff, M.D., Ph.D.*
Alterations in Spontaneous and Light Evoked Ganglion Cell Activity During Retinal Degeneration in Roll Mice

2006 None

2007 *Fiona Costello, M.D., FRCP*
Retinal Nerve Fiber Layer Measurements in Optic Neuritis: Determining the Role of OCT in Predicting Visual Recovery and the Future Risk of MS

2008 *Kenneth Shindler, M.D.*
Orally Administered SIRT1 Activator SRT501 is Neuroprotective for Retinal Ganglion Cells and Suppresses and Neurological Dysfunction in a Mouse Model of Multiple Sclerosis

2009 *Michael S. Salman, Ph.D., MRCP*
Characteristics of the Cerebellar Dysplasia in Type II Malformation as Revealed by Ocular Motor Functions

2010 None

2011 *Y. Joyce Liao, M.D., Ph.D.*
Laser-Assisted Transplantation of Stem Cells into the Adult Eye

2012 *Beau B. Bruce, M.D., M.S.*
Non-mydriatic Ocular Fundus Photography Read by Emergency Department (ED) Physicians: FOTO-ED Study

2013 *Robert A. Avery, D.O.*
Hand-Held Optical Coherence Tomography During Sedation Detects Visual Acuity and Visual Field Loss in Young Children with Optic Pathway Gliomas

2014 *Patrick Yu-Wai-Man, B.Med.Sci., M.B.B.S., Ph.D, FRCOphth,*
The Molecular and Neuro-Ophthalmological Features of Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)

THOMAS CARLOW DISTINGUISHED SERVICE AWARD

This award is given by the Executive Board to those who have provided a sustained and substantial service to the North American Neuro-Ophthalmology Society. It is named after, and honors, the NANOS Founder, Thomas Carlow, who contributed an immeasurable amount of his time and energy founding and then nurturing NANOS.

2000 *Susan Carlow*
Thomas J. Carlow, M.D.
Robert B. Daroff, M.D.
Joel S. Glaser, M.D.
William F. Hoyt, M.D.
David L. Knox, M.D.
Norman J. Schatz, M.D.

2002 *Ronald M. Burde, M.D.*

2004 *James A. Sharpe, M.D.*
H. Stanley Thompson, M.D.
Jonathan D. Wirtschafter, M.D.

2005 *Steven E. Feldon, M.D., MBA*

2006 None

2007 *John B. Selhorst, M.D.*
Neil R. Miller, M.D.

2008 *Kathleen B. Digre, M.D.*

2009 *Mark J. Kupersmith, M.D.*

2010 *Larry Frohman, M.D.*

2011 *John L. Keltner, M.D.*

2012 *Deborah I. Friedman, M.D., M.P.H.*

2013 None

2014 *Anthony Arnold, M.D.*

WILLIAM F. HOYT LECTURE

2001 *Thomas J. Carlow, M.D.*
Oculomotor Ophthalmoplegic Migrane: Is it Really Migrane?

2002 *H. Stanley Thompson, M.D.*
The Vitality of the Pupil: A History of the Clinical Use of the Pupil as an Indicator of Visual Potential.

2003 *Simmons Lessell, M.D.*
The Neuro-Ophthalmic Complications of Radiation

2004 *Creig S. Hoyt, M.D.*
What Do We Really Know About Amblyopia?

2005 *Neil R. Miller, M.D.*
Advances in the Diagnosis and Managment of Optic Nerve Sheath Meningiomas

2006 None

2007 *Joel S. Glaser, M.D.*
Romancing the Chiasm

NANOS RECOGNITION AND AWARDS
PRESENTED AT THE ANNUAL NANOS BANQUET DURING THE ANNUAL MEETING
(CONTINUED)

WILLIAM F. HOYT LECTURE (CONTINUED)

2008 *Peter J. Savino, M.D.*
Evaluation of the Retinal Nerve Fiber Layer: Descriptive or Predictive

2009 *Norman J. Schatz, M.D.*
The Troubles I've Seen

2010 *Jonathan Trobe, M.D.*
Papilledema: The Vexing Issues

2011 *Steven A. Newman, M.D.*
Interventional Neuro-Ophthalmology, an Addition Not an Oxymoron

2012 *Alfredo A. Sadun, M.D., Ph.D.*
Are We There Yet? Has Neuro-Ophthalmology Reached the Paradigm Shift?

2013 *Nancy J. Newman, M.D.*
Neuro-Ophthalmology in Review: Around the Brain With 50 Fellows

2014 *Mark J. Kupersmith, M.D.*
Optical Imaging of the Optic Nerve: Beyond Documenting RNFL Loss

BEST FRANK B. WALSH SESSION PAPER PRESENTATION BY A FELLOW

2004 *Margaret M. Wong, MBBS, FRCS, FRCOphth*
Frozen Eyes and Muscle Cramps

2005 *Kevin M. Barrett, M.D.*
An Obvious Case of Giant Cell Ateritis

2006 *Jennifer T. Scruggs, M.D.*
A 68 Year-Old Woman with New Onset Vertical Diplopia and Pain

2007 *Thomas N. Hwang, M.D., Ph.D.*
A Case of Bilateral Optic Nerve Atrophy

2008 *Beau Bruce, M.D.*
What?!?

Thomas Hwang, M.D.
My Orbits Are Melting

2009 *Sashank Prasad, M.D.*
Hear No Evil, See No Evil

2010 *Rebecca Stacy, M.D.*
A Bitter-Sweet Diagnosis

2011 *Clare Fraser, M.D.*
Bad Eyes, Bad Walking and Bad Judgment

2012 *Lindsey DeLott, M.D.*
CSEye

2013 *Chantal J. Boisvert, M.D.*
OMG, I can't C

2014 *Dane A. Breker, M.D.*
Muscle Bound or Unbound?

PILOT GRANT RESEARCH AWARD

The NANOS Pilot Research Grant Program provides a one-year, non-renewable source of funding to help principal investigators generate preliminary data that will lead to additional funding from other national agencies or foundations.

2007 *Deborah M. Grzybowski, M.D., Ph.D.*
An in-vitro model of CSF outflow through the arachnoid membrane for IIH

2008 *Kimberly Cockerham, M.D., F.A.C.S.*
Thyroid Eye Disease Clinical Manifestations Measurements: Comparing Clinical Examination with Laboratory Values of Thyroid Antibodies and Magnetic Resonance Imaging

Nitza Goldenberg-Cohen, M.D.
Intraocular Injection of Growth Factors to Enhance Differentiation of Bone Marrow Derived Stem Cells Following Ischemic Injury

2009 *Prem S. Subramanian, M.D., Ph.D.*
Pilot Study to Measure Diplopic Fields and the Correlation of Diplopic Field Characteristics with Visual Function Quality

2010 *NONE*

2011 *Steven Roth, M.D.*
Mechanisms of Perioperative Ischemic Optic Neuropathy

2012 *Y. Joyce Liao M.D., Ph.D.*
Stat1 Pathway Insuffciency as a Mediator for Giant Cell Arteritis Pathogenesis

2013 *Byron J. Lam, M.D.*
Obesity and Spinal Canal Compliance in Idiopathic Intracranial Hypertension

2014 *Beau Bruce, M.D., M.S.*
Non-Mydriatic Ocular Fundus Photography for the Acute Risk Stratification of Patients with Transient Ischemic Attack and Minor Stroke

FIGHT FOR SIGHT/NANOS POSTDOCTORAL FELLOWSHIP AWARD

This award was established by Fight for Sight (FFS) and the North American Neuro-Ophthalmology Society (NANOS) to fund a Summer Student Fellowship for ophthalmology residents or fellows interested in pursuing neuro-ophthalmology research.

2008 *Arun Sundaram, M.D.*
Saccadic Roles of the Human Subthalamic Nucleus and Globus Pallidus

2009 *Zoë Williams, M.D.*
Diffusion tensor magnetic resonance imaging of the optic nerve in patients with congenital and acquired optic disc elevation

2010 *Karen E. Schmitt, M.D.*
In vitro determination of the potential of a novel nanosponge to penetrate optic nerve dura and arachnoid mater for delivery of a fluorescent marker, a surrogate for various neuroprotective drugs

NANOS RECOGNITION AND AWARDS
PRESENTED AT THE ANNUAL NANOS BANQUET DURING THE ANNUAL MEETING
(CONTINUED)

FIGHT FOR SIGHT/NANOS POSTDOCTORAL FELLOWSHIP AWARD (CONTINUED)

2011 None

2012 None

2013 *Linus Da-Shih Sun, M.D., Ph.D.*
Quantitative Eye Movements to Evaluate Corollary Discharge

2014 None

DANIEL M. JACOBSON LECTURE

2008 *James J. Corbett, M.D.*
Familial Idiopathic Intracranial Hypertension

2009 *Robert B. Daroff, M.D.*
Reflections and Advice from an Aging Academic

2010 *Deborah I. Friedman, M.D., M.P.H.*
IIH with Dan, and Beyond

2011 *Kathleen B. Digre, M.D.*
Neuro-ophthalmologic Disorders in Pregnancy

2012 *Jonathan Trobe, M.D.*
The Lasting Scientific Contributions of Dr. Daniel Jacobson

2013 *H. Stanley Thompson, M.D.*
Neuro-Ophthalmology at Iowa

2014 *Leonard A. Levin, M.D., Ph.D*
Three Questions and Four Answers

ARTICLES OF INCORPORATION NORTH AMERICAN NEURO-OPHTHALMOLOGY SOCIETY

(A Non-Profit Corporation)

BYLAWS

ARTICLE I - OBJECTIVES

The North American Neuro-Ophthalmology Society (NANOS), also called the Society, exists for and is dedicated to the following purposes:

1) Support for those principles, policies and practices that seek the attainment of the best in neuro-ophthalmologic patient care.

2) The pursuit of excellence in medical education, especially as it concerns the neuro-ophthalmologic sciences.

3) The pursuit of scientific and clinical knowledge in fields related to neuro-ophthalmology.

4) The communication of scientific and scholarly information through scientific meetings and publications.

5) Provision for communication with other groups and their representation for neuro-ophthalmologic opinion to best achieve and preserve the purposes of the Society.

6) The advancement of clinical neuro-ophthalmology.

ARTICLE II - MEMBERSHIP

Section 1 - Classes of Membership
Membership in NANOS shall consist of ten classes: Fellow, International Fellow, Active Member, International Active Member, Candidate, International Candidate, Associate Member, Honorary Member, Senior Fellow Member and Senior Member. There shall be no restriction regarding the number of members in any given category. All candidates for membership and all members shall be in compliance with the NANOS ethics statement. Violation of the NANOS ethics statement will render an applicant ineligible for membership.

Section 2 - Fellows may be elected only from among physicians nominated by the Membership Committee:

1) who have been certified in Neurology by the American Board of Psychiatry and Neurology, or in Neurosurgery by the American Board of Neurosurgery, or in Ophthalmology by the American Board of Ophthalmology, or in Neurology by the American Osteopathic Board of Neurology and Psychiatry, or in Ophthalmology by the American Osteopathic Colleges of Ophthalmology and Otolaryngology, Head and Neck Surgery, or in Neurology, Neurosurgery or Ophthalmology by the Royal College of Physicians and Surgeons of Canada; and

2) whose chief interest is directed toward practice, teaching or research in Neuro-Ophthalmology; and

3) who have been Active Members of NANOS for no less than three years; and

4) who have attended no less than five annual NANOS or Frank Walsh meetings in five separate calendar years; and

5) who have demonstrated special achievement in clinical Neuro-Ophthalmology; and

6) who have completed a year of Neuro-Ophthalmology Fellowship or have practiced clinical Neuro-Ophthalmology or have performed research in Neuro-Ophthalmology for three years. An exception may be the election of certain other members of unusual accomplishment, at the discretion of the Executive Board of NANOS upon recommendation by the Membership Committee.

Section 3 - International Fellows may be elected only from among physicians outside the United States and Canada upon nomination by the Membership Committee:

1) whose chief interest is directed toward practice, teaching or research in Neuro-Ophthalmology; and

2) who have been International Active Members of NANOS for no less than three years; and

3) who have attended no less than five annual NANOS or Frank Walsh meetings in five separate calendar years; and

4) who have demonstrated special achievement in clinical Neuro-Ophthalmology; and

5) who have completed a year of Neuro-Ophthalmology Fellowship or have practiced clinical Neuro-Ophthalmology or have performed research in Neuro-Ophthalmology for three years. An exception may be made for the election of certain other members of unusual accomplishment, at the discretion of the Executive Board of NANOS upon recommendation by the Membership Committee.

Section 4 - Active Members may be elected from among physicians nominated by the Membership Committee who have been certified in Neurology by the American Board of Psychiatry and Neurology, or in Neurosurgery by the American Board of Neurosurgery, or in Ophthalmology by the American Board of Ophthalmology, or in Neurology by the American Osteopathic Board of Neurology and Psychiatry, or in Ophthalmology by the American Osteopathic Colleges of Ophthalmology and Otolaryngology, Head and Neck Surgery, or in Neurology, Neurosurgery or Ophthalmology by the Royal College of Physicians and Surgeons of Canada.

Section 5 - International Active Members may be elected from among physicians outside the United States and Canada upon nomination by the Membership Committee:

1) who have graduate d from a foreign medical school recognized by the World Health Organization (WHO) and who show evidence of having passed the requirements for license to practice medicine in their home country or country of residence; and

2) who have completed postgraduate training in Neurology, Ophthalmology or Neurosurgery who are certified by the licensing authority in their country or by an internationally-recognized agency that grants accreditation in these specialties,

OR

1) who have been recognized specialists in Neuro-Ophthalmology in their country for at least five years; and

2) have achieved distinction in clinical practice, teaching or research.

Section 6 - Candidate Members may be elected from among physicians nominated by the Membership Committee:

1) who have graduated from a recognized School or College of Medicine in the United States or Canada, or College of Osteopathic Medicine in the United States, or a foreign medical school and are in a fellowship program in neuro-ophthalmology of at least 12 months duration, or a residency in ophthalmology or neurology or a similar field in the United States or Canada, and

2) who are engaged in postgraduate studies directed toward qualification to be certified in Neurology by the American Board of Psychiatry and Neurology, or in Neurosurgery by the American Board of Neurosurgery, or in Ophthalmology by the American Board of Ophthalmology, or in Neurology by the American Osteopathic Board of Neurology and Psychiatry, or in Ophthalmology by the American Osteopathic Colleges of Ophthalmology and Otolaryngology, Head and Neck Surgery, or in Neurology, Neurosurgery or Ophthalmology by the Royal College of Physicians and Surgeons of Canada.

The duration of Candidate Membership status may not extend beyond seven (7) years from the date the Candidate Member began postgraduate training, except that a Candidate Member may, upon written request and authorization from the NANOS Board, extend his/her Candidate Membership due to active military service for a period of time, equal to the time such Candidate Member spent in active duty military service during the Candidate Membership period. In no event shall a Candidate Member be allowed to maintain Candidate Membership status for a period of more than ten (10) years.

Candidate Members shall be transferred to Active Membership upon certification in Neurology by the American Board of Psychiatry and Neurology, or in Neurosurgery by the American Board of Neurosurgery, or in Ophthalmology by the American Board of Ophthalmology, or in Neurology by the American Osteopathic Board of Neurology and Psychiatry, or in Ophthalmology by the American Osteopathic Colleges of Ophthalmology and Otolaryngology, Head and Neck Surgery, or in Neurology, Neurosurgery or Ophthalmology by the Royal College of Physicians and Surgeons of Canada. The transfer of status from Candidate Member to Active Member will automatically occur after written receipt of notification from the appropriate board or entity and subsequent independent confirmation by NANOS that the Candidate Member has obtained the required certification.

Candidate Members who are ineligible for Active Membership may apply for election to Associate Membership at the end of their period of eligibility for Candidate Membership.

Section 7 - International Candidate Members may be elected from among physicians outside the United States and Canada upon nomination by the Membership Committee:

1) who have graduated from a foreign medical school recognized by the World Health Organization (WHO) and who show evidence of having passed the requirements for license to practice medicine in their home country in their home country or country of residence; and

2) who are engaged in postgraduate studies directed toward qualification in the clinical specialties of Neurology, Neurosurgery, or Ophthalmology.

The duration of International Candidate Membership status may not extend beyond seven (7) years from the date such International Candidate began postgraduate training, except that an International Candidate Member may, upon written request and authorization from the NANOS Board, extend his/her International Candidate Membership due to active duty military service for a period of time, equal to the time such International Candidate Member spent in active duty military service during the initial International Candidate Membership period. In no event shall an International Candidate Member be allowed to maintain International Candidate Membership status for a period of more than ten (10) years.

International Candidate Members shall be transferred to International Active Membership upon completion of a postgraduate training program in Neurology, Ophthalmology or Neurosurgery that is recognized by the licensing authority in their country or by an internationally recognized agency that grants accreditation in these specialties. The transfer of status from International Candidate Member to International Active Member will automatically occur after written receipt of notification from the appropriate board or entity and subsequent independent confirmation by NANOS that the International Candidate Member has satisfactorily completed the required training program. International Candidate Members who are ineligible for International Membership may apply for election to Associate Membership at the end of their period of eligibility for Candidate Membership.

Section 8 - Associate Members may be elected upon nomination by the Membership Committee from among the following:

1) Physicians who have graduated from any medical school recognized by the World Health Organization (WHO), who show evidence of having passed the requirements for license to practice medicine in their home country or country of residence and who are practicing in clinical specialties of Neurology, Neurosurgery or Ophthalmology or in other fields related to Neuro-Ophthalmology; or

2) Persons, including physicians or holders of an advanced degree, practicing or engaged in non-clinical fields relating to Neuro-Ophthalmology.

Section 9 - Honorary Fellows may be elected upon nomination by the Membership Committee from among distinguished persons including physicians in clinical Neuro-Ophthalmology or cognate fields and other holders of an advanced degree. Nominating for this category must bear the signature of two sponsors who must be Fellows.

Section 10 – Senior Fellow Members may be elected upon nomination by the Membership Committee from among Fellows who are the age of 65 or older, disabled, or are fully retired from the active practice of clinical Neuro-Ophthalmology or research.

Section 11 – Senior Members may be elected upon nomination by the Membership Committee from among Active or Associate Members who have been Society Members for a period of no less than five years, are the age of 65 or older, disabled, or are fully retired from the active practice of clinical Neuro-Ophthalmology or research.

Section 12 - Voting and Holding Office in NANOS

Only Members in the following classes of Membership are entitled to vote on any matter in person or by proxy during any Annual or Special Business Meeting of the Society or by electronic voting, as provided in Article III, section 6: Fellows, International Fellows, Active Members, International Active Members, Senior Fellow Members, and those Senior Members who had voting privileges in their most recent previous category of Membership. NANOS Fellows and Members who have the right to cast votes in person or by proxy or electronically will

be designated as "eligible voters" and the group of eligible voters may be referred to as the "Voting Membership" in these Bylaws and in official Society documents. Voting privileges may be suspended at the discretion of the Executive Board if an eligible voter is found to be in violation of the NANOS ethics statement.

The only classes of Members entitled to hold any elected office in NANOS shall be Fellows and Senior Fellows. Violations of the NANOS ethics statement will render Members ineligible for holding an elected NANOS office until otherwise decided by the Executive Board. Elected officers found to be in violation of the NANOS ethics statement may be removed from office at the discretion of the Executive Board.

Section 13 - Procedure for Application to Membership

Application for membership shall be made in writing on the application form provided by the Executive Office, supplying in detail all information required, and signed as the name is to appear in the membership records.

Application for Fellowship must include the written recommendation of two Fellows. Application for International Fellowship must include a written recommendation from two Fellows or International Fellows. Application for International Membership must include a written recommendation from two Fellows, International Fellows or International Members. Applications for other classes of membership must bear the signature of two sponsors who are Fellows in NANOS.

Completed applications will be forwarded to the Membership Committee for review to assure applicants meet the criteria for membership. Recommendations regarding either approval or rejection for all categories of membership must be approved by a two-third vote of the eligible voters in attendance at the annual meeting.

Section 14 - Fees, Dues and Assessments

1) The dues, assessments, and other fees for each class of membership shall be established annually by the Executive Board.

2) Annual dues shall be established on the basis of the fiscal year. The dues for a year shall be payable on the first of January for the fiscal year beginning January 1 of that year and shall be considered delinquent if not paid by March 15 of the current fiscal year. Assessments and fees shall be payable at the time or times that the Executive Board shall determine.

3) Assessments, or other fees shall be payable by Honorary Members, Senior Fellow Members, or Senior Members at the discretion of the Executive Board.

Section 15 - Termination of Membership

Policies regarding late or non-payment of dues, including penalties and suspension or termination of membership, shall be established by the Executive Board.

Section 16 - Disciplinary Action

The Executive Board shall have the duty to consider disciplinary action for any violation of the NANOS Ethics Statement or for any professional misconduct on the part of any Member of NANOS for which similar disciplinary action has been taken by a State, County, or official governmental Board of Medical Examiners, Board of Professional Medical Responsibility, or like body. Such disciplinary action may be in the form of censure, suspension or expulsion from NANOS; and if the Member be an Officer of NANOS, that Member shall be removed from office regardless of whether the Member is otherwise censured, suspended or expelled. For purposes of this section, the word "censure" means that the individual shall be advised in writing that his or her professional conduct is not consistent with the objectives of NANOS and that such conduct should be changed; the word "suspended" means that the individual shall be advised in writing that his or her privileges as a Member of NANOS have been temporarily suspended or terminated until the professional misconduct has been corrected to the satisfaction of the State Board of Medical Examiners, Provincial, or other professional bodies supervising professional conduct; "expulsion" means that the Member shall be advised that the Member's membership in the Society is terminated. A Member suspended or terminated, as a result of disciplinary action, may apply to have Membership reinstated after a period of one year.

ARTICLE III - MEETINGS AND VOTE OF FELLOWS AND MEMBERS

Section 1 - Annual Meetings

Annual Meetings of the Society shall be held each year at the place or places and on the date or dates designated by the Executive Board. The primary purpose of the Annual Meetings shall be to provide educational courses and forums for the presentation of scientific papers. There shall be not less than one (1) business session at each annual meeting of NANOS, run according to the Order of Business as provided in Article III, Section 4.

Section 2 - Special Meetings

Special scientific and business meetings of NANOS may be called by the Executive Board for the times and places it may designate.

Section 3 - Notice

Notice of each Annual Meeting of the Society shall be given to all Society members, as provided in Article VI, Section 2, not less than 90 days prior to the date on which the meeting is to begin. Notice of special scientific and business meetings of the Society shall be given, as provided in Article VI, Section 2, at least 30 days prior to the date on which the meeting is to begin.

Section 4 - Order of Business

The order of business at the annual business meeting shall be:

1) Reading of minutes of preceding meeting

2) Reports of Officers and Executive Board

3) Reports of Committees

4) Unfinished Business

5) New Business

6) Report of Nominating Committee and Elections, if not performed by electronic vote.

Section 5 - Quorum

At any annual or special business meeting of the Society, a quorum shall consist of not less than 10% of the voting membership, except as required by further provisions in these Bylaws.

Section 6 - Vote

If a quorum is present, a majority vote of the eligible voters present shall be required to constitute an action by the eligible voters on any

matter, unless otherwise provided by applicable law, the Articles of Incorporation, or these Bylaws. A member may vote either in person or by proxy executed in writing and signed by the member. Every proxy shall be dated, but need not be sealed, witnessed or acknowledged. No proxy shall be valid after 11 months from its date, unless otherwise provided in the proxy. At all meetings of members, the proxies shall be filed with and verified by the Secretary of the Society.

The Voting Members may vote electronically on special matters as approved by the Executive Board. For purposes of electronic voting, the entire Voting Membership shall be deemed present during the voting process. Notice of special matters subject to an electronic vote shall contain a detailed explanation of the matters to be voted on by the Voting Membership and shall be provided electronically to all Voting Members as provided in Article VI, Section 2. An adequate time period will be offered to submit an electronic vote, and the dates for submitting an electronic vote will be clearly stated. Appropriate security measures will be employed to ensure a fair and accurate balloting process.

Section 7 - Standing Rules

The Standing Rules of the Society are contained in the document attached to these Bylaws in effect on the effective date of the adoption of the Bylaws. The Standing Rules of NANOS may be amended or revised from time to time as provided therein, but may not be inconsistent with the Articles of Incorporation or Bylaws of NANOS.

Section 8 - Parliamentary Authority and Rules of Order

The deliberations of NANOS, its Executive Board, and all committees shall be governed by the rules contained in the then current edition of Robert's Rules of Order Revised (Robert's Rules) except in instances where Robert's Rules are contrary to or otherwise inconsistent with the Articles of Incorporation, Bylaws, Standing Rules, or the customary practices and procedures of NANOS. In such event the Articles of Incorporation, Bylaws, Standing Rules, or the customary practices and procedures of NANOS shall govern.

ARTICLE IV – EXECUTIVE BOARD

Section 1 - Elected Board Members of the Society shall be:

1) Officers: President, President-Elect, Vice-President, Treasurer, and Secretary.

2) Other Members of the Board – of which there will be five (5).

3) Immediate Past President – serves on the Board for two (2) years following President term.

- Non-elected, non-voting members of the Board shall be:

1) The founder, Dr. Thomas Carlow, until such a time as he indicates he no longer wishes to serve on the Board or can no longer serve;

2) The Executive Vice President of the Society, when such a person has been appointed by the Board;

3) The Editor of the Journal of Neuro-Ophthalmology.

Section 2 - Election

Election of Officers shall be held by electronic vote during even-numbered years. Officers shall serve a term of two (2) years, commencing on July 1 following the Annual Meeting at which they were elected. Other Members of the Executive Board (not Officers) shall serve a term of three (3) years, or until a successor is elected, commencing on July 1 following the Annual Meeting at which they were elected. The immediate Past President shall serve a term of two (2) years immediately following the term of President.

When there is only one candidate running for office, the affirmative vote of a majority of the Eligible Voters present and voting shall be required for the election to any office. When there are two or more candidates for one office, a plurality vote of the Eligible Voters present and voting shall be sufficient for the election to that office. If a tie occurs, there shall be a runoff election between just the two tied members. If in the runoff election, the tie is not broken, then the Executive Board shall vote to break the tie. If the tie is not broken at the level of the Executive Board, then the Executive Vice President shall be asked to cast a vote as the Board re-votes.

Each member may vote for only one candidate for each office or Board seat.

With exception of the President, President-Elect, and immediate Past President, the Members of the Board may be nominated for consecutive terms in the same office. The terms of Board Members and Officers shall be staggered so that the term of half of the Board Members and Officers will expire during any single election year.

One Fellow will be designated Parliamentarian by the Chair of the Executive Board. The Parliamentarian shall be responsible for ensuring adherence to the stated Parliamentary Authority and Rules of Order during all Executive Board and Annual Business Meetings.

Section 3 - Nominations

Prior to each electronic vote or Annual Meeting at which elections are to be held, the Executive Board, acting on the recommendation of the Nominating Committee, shall nominate Fellows of NANOS for each vacancy that occurs on the Executive Board. NANOS Members shall be notified of the names of all nominees at least thirty (30) days prior to the electronic vote or Annual Meeting. In the event of death or withdrawal from candidacy of any of these nominees, the Executive Board shall designate a substitute nominee at any time before the election and shall announce that designation before the election. In addition, nominations for positions on the Executive Board may be made from the Voting Membership, provided that at least thirty (30) days before the date of the election, a written petition, signed by twenty (20) or more eligible voters, has been filed with the Chair of the Executive Board together with a signed statement by the nominee setting forth willingness to serve if elected.

Section 4 - President

The President shall preside at all business sessions of the membership of NANOS; shall act as chief spokesman of NANOS to the public, the press, legislative bodies, the medical community at large and federal, state, and local governmental and private agencies and organizations; shall work with the Chair of the Executive Board to ensure that basic NANOS policies and programs are formulated and executed; shall not serve consecutive terms as president; is responsible for making appointments to replace members rotating off standing committees; and may create ad hoc committees and appoint NANOS representatives to civic, professional, and governmental organizations as may be required to execute the business and affairs of NANOS.

Section 5 - President-Elect

The President-Elect shall automatically become the President of NANOS upon expiration of the President's term; shall, in the absence or disability of the President, have and perform the duties and responsibilities of the President; shall in the event of a vacancy in the office of President,

however occurring, fill the vacancy in the office of President for the unexpired portion of the President's term and also serve a full term as President; shall assist the President in the performance of his or her duties whenever requested to do so; and shall have all other duties and responsibilities that the President or the Executive Board may determine.

Section 6 - Vice President

The Vice President shall, in the event of a vacancy in the office of both the President and the President-Elect, however occurring, have and perform the duties of the President; shall have all other duties and responsibilities that the President or Executive Board may determine.

Section 7 - Treasurer

The Treasurer shall serve as Chair of the Finance Committee; ensure that NANOS maintains accurate financial records; review NANOS expenditures and financial status on a regular basis to ensure overall financial integrity; submit the financial accounts of NANOS to an annual independent audit; submit annual state and federal tax returns to the Internal Revenue Service; develop and present financial recommendations to the Executive Board; and perform other duties assigned by the President or Executive Board.

Section 8 - Secretary

The Secretary shall ascertain that records are maintained for all business meetings and Executive Board meetings of NANOS; ensure that copies of the minutes of each meeting are provided to the President and other Officers and Directors as appropriate; maintain current copies of the Association Rules and Bylaws for use by the President and the Executive Board; perform other duties assigned by President or Executive Board.

Section 9 - Members of the Executive Board (other than Officers)

Members of the Board shall have all duties and responsibilities that the President or the Executive Board may determine.

Section 10 - Immediate Past President

The Immediate Past President shall be a member of the Executive Board and shall have all duties and responsibilities that the President or the Executive Board may determine.

Section 11 - Vacancies

In the event of incapacitation, withdrawal, demise, resignation or removal of any Officer or Member of the Executive Board, except the President-Elect, the President, with a majority approval of the Executive Board, shall appoint a successor who will hold the appointed office until a successor has been elected.

In the event of incapacitation, withdrawal, demise, resignation or removal of the President-Elect, the Nominating Committee shall be reconvened to name a nominee for that position to present for election by the voting membership of NANOS at the next annual business meeting.

Section 12 - Removal from Office

Any Member of NANOS elected by the Voting Membership may be removed from office by the affirmative written ballot of two-thirds of the Board Members whenever, in their judgment, the removal will serve the best interests of NANOS. Ratification of removal from office of such Member must be approved by a majority vote of eligible voters in attendance at the next Annual Meeting.

ARTICLE V - EXECUTIVE BOARD

Section 1 - Authority

The Executive Board shall manage all the business and affairs of NANOS. The Chair of the Executive Board will be a current member of the Executive Board and will be elected every two (2) years by a majority vote of the Members of the Board. The Executive Board shall have all powers and responsibilities conferred upon the Board of Directors of a nonprofit corporation by the State of New Mexico, as now or hereafter amended, except as those powers or responsibilities may be limited by the Articles of Incorporation or these Bylaws. The Executive Board shall have the final responsibility and authority for all actions and policies that are recommended or adopted by any and all standing and ad hoc committees, sections, representatives to professional and governmental organizations, agents, and employees; and no action or policy shall be the action or policy of NANOS unless and until it is adopted, ratified, or approved by the Executive Board.

The Executive Board shall appoint, when in its opinion the affairs of NANOS justify such action, an Executive Vice-President, who shall function in the usual capacity of such office when those functions are not contrary to the Articles of Incorporation and Bylaws of the Society. The Executive Board shall determine the duties and salary, if provided, of such an Executive Vice-President and policies pertaining to that office. The Executive Vice-President is a non-voting member of all NANOS Committees and may be appointed as a voting member of Committees at the discretion of the President.

Section 2 - Members of the Executive Board

The members of the Executive Board shall number not more than eleven (11) elected members and shall consist of all the Officers and other Members of the Board elected by the voting membership. The Executive Vice-President and the Editor of the Journal of Neuro-Ophthalmology shall be non-voting "ex officio" members of the Executive Board. The founder of the Society, Dr. Thomas J. Carlow, shall sit as a non-voting ex-officio member of the Executive Board, until he notifies the Executive Board in writing of his resignation.

Section 3 - Meetings

The Executive Board shall meet during the Annual Meeting. Special Meetings of the Executive Board may be called by the President or at the written request of four (4) Members of the Board addressed to the Secretary at no less than twenty (20) calendar days' notice in advance of the proposed special meeting.

Section 4 - Notice

Notice of each Meeting of the Executive Board shall be given, as provided in Article VI, Section 2, by the Executive Vice-President, or, if such position is vacant, by a designee of the Executive Board, not less than fifteen (15) calendar days prior to the date on which the meeting is scheduled to be held. The matters to be discussed and voted upon at any duly called meeting of the Executive Board shall not be limited to those set forth in the Notice of the Meeting.

In the event that an electronic vote shall be held for the Election of Executive Board members, the Voting Membership shall be notified of the names of all nominees at least thirty (30) days prior to the date on which the vote is to be held, as provided in Article IV, Section 3.

Section 5 - Quorum

Five (5) Voting Members of the Executive Board shall constitute a quorum for the purposes of transacting Executive Board business and affairs on behalf of NANOS.

Section 6 - Manner of Acting

A majority vote of the Executive Board Members present and voting at a meeting at which a quorum is present shall be the act of the Executive Board, unless the vote of a larger number is required by applicable law, the Articles of Incorporation, or these Bylaws.

Section 7 - Written Action

Any action that the Executive Board could take at a duly called meeting of the Board may be taken by a written action signed by two-thirds of the Board Members. The same written action need not be signed by all Board Members, and each may sign a separate counterpart of the written action, but all Board Members shall be notified in writing at least twenty (20) calendar days in advance of the matter to be voted on.

Section 8 - Telephone Conference

Any action that the Executive Board could take at a duly called meeting of the Board may be taken during a telephone conference of the Board Members. A quorum must participate in the telephone conference in order to transact business. A notice of two (2) business days is required to all Executive Board members in order to schedule a telephone conference of the Board for the purpose of transacting NANOS business.

ARTICLE VI - MISCELLANEOUS

Section 1 - Fiscal Year

The fiscal year of NANOS shall be from January 1 to December 31.

Section 2 - Notice and Waiver of Notice

Notice is deemed given by a Fellow or member of NANOS to NANOS or to an Officer of NANOS when it is in writing and mailed or delivered to NANOS or to the Officer at the principal executive office of NANOS. In all other cases, notice is deemed given to a Fellow or Member of NANOS when it is communicated to the Fellow or Member orally, in person or by telephone, or in writing by mail, fax, email, telegram or otherwise delivered to the person at the person's last known address. Notice by mail is deemed to be given when it is deposited with the official government postal authority with sufficient postage affixed. Whenever any notice is required to be given by law, the Articles of Incorporation, or these Bylaws, a waiver of the notice may be executed, whether before, during, or after the time stated therein, and the waiver shall constitute the equivalent of receiving the notice.

Section 3 - Indemnification

To the full extent permitted by any applicable law, any person who is or was a director, officer, employee or agent of NANOS shall be indemnified by NANOS against any and all liability and reasonable expense incurred by reason of the person being or having been a director, officer, employee or agent of NANOS, or by reason of any action taken or not taken in the course and scope of the person's service as such director, officer, employee or agent of NANOS, in the event that such person was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, wherever brought, whether civil, criminal, administrative or investigative, other than an action by or in the right of the corporation. Such person shall be entitled to reimbursement by the Society of reasonable expense in advance of the final disposition of a proceeding in accordance with, and to the full extent permitted by, any applicable law.

The rights of indemnification provided in this section shall not limit, but shall be in addition to, any other right to which such director, officer, employee or agent may otherwise be entitled by contract, law or statute, or otherwise; and in the event of such person's death, such rights shall extend to such person's heirs, legal representatives, or successors. The foregoing rights shall be available whether or not the claim asserted against such person is based upon matters which antedate the adoption of this section.

NANOS, its Directors and Officers, shall be fully protected in making any determination under this section, or in making, or refusing to make any payment under this section, in reliance upon the advice of counsel.

NANOS may, to the full extent permitted by applicable law, purchase and maintain insurance on behalf of any person who is or was a Member of the Executive Board, an officer or employee of this corporation or a Member of a Committee of this corporation against any liability asserted against such person in such capacity.

If any provision of this section shall for any reason be determined to be invalid, the remaining provisions hereof shall not be affected thereby but shall remain in full force and effect.

ARTICLE VII - AMENDMENTS

These Bylaws may be amended, altered or repealed by the vote of at least two-thirds of the eligible voters, either by physical presence at a meeting or by electronic ballot of all of the eligible voters, provided that any proposed amendment 1) has been submitted in writing to the Executive Board and 2) notice thereof has been provided to each Fellow and other Voting Member at least one month prior to the date on which it will be voted upon. Bylaw amendments may be proposed only by Members of NANOS who are eligible voters as defined by these Bylaws. These Bylaws shall be subject to a complete review every ten years.

ARTICLE VIII - PUBLICATIONS

Section 1 - Publications Committee

The Publications Committee shall maintain liaison between the Executive Board of NANOS, and the Publisher and Editor of the Journal of Neuro-Ophthalmology. Members of the Publications Committee shall be appointed by the President each cycle to serve a two-year term, and may be reappointed for two additional terms to serve a maximum of six years. At least one (1) member of the Publications Committee shall be a Member of the Executive Board of NANOS.

Section 2 - Journal of Neuro-Ophthalmology

1) The governance of affairs of the Journal of Neuro-Ophthalmology is the responsibility of the Executive Board of NANOS. The Executive Board of NANOS shall report on the affairs of the Journal of Neuro-Ophthalmology to the membership each year at the time of the annual meeting. This report may be either by a member of the Executive Committee or by the Editor, or by the Chair of the Publications Committee, whichever is deemed appropriate to the Executive Board.

2) The Editor shall be appointed by the President upon recommendation of the Publications Committee for a term of four (4) years, renewable once. The Executive Board shall have the option, at its discretion, of extending the Editor's term for one additional one (1) year term to allow the Board time to locate and obtain a new Editor. An individual nominated for editorship of the Journal of Neuro-Ophthalmology must be a Member of the Society at the time he/she assumes the editorship.

The Editor shall serve at the pleasure of the Executive Board, and will be a non-voting, "ex officio" member of the Board. The Editor may be asked to step aside by the Executive Board with two (2) months notice. This period may be lengthened or shortened by mutual assent of the Executive Board and Editor.

The Editor is accountable directly to the Executive Board. The Editor will prepare an annual report to the Executive Board. The Editor will report annually to the Executive Board through the Publications Committee, or as frequently as events may dictate. There shall be a broad range of editorial autonomy; however, it should be understood that the Editor will share major business and financial decisions with the Executive Board. Major business and financial decisions include but are not limited to such matters as the choice of a publisher, the frequency of the publication, and similar business and financial matters. The Editor, with the advice of the Editorial Board, shall have complete and final authority over all editorial content, selection, modification, and quality matters. Working relationships with the publisher shall be completely within the authority of the Editor. Editorial operations shall not be subject to direct review by the Executive Board or by the membership of NANOS.

3) Members of the Editorial Board shall be approved by the Executive Board of NANOS upon recommendation of the Editor. The terms of Members of the Editorial Board will be determined by the Editor and shall not exceed five (5) years. The Editor shall have authority to recommend the appointment of Associate Editors and Editors for specific topics whose terms on the Editorial Board will be determined by the Editor, but shall automatically expire when the Editor vacates his position. When appropriate, the Editor will recommend Corresponding Editors from other countries who will be regular members of the Editorial Board and have similar responsibilities.

4) The Publications Committee will meet annually with the Editor, and the publisher, examine the product in order to review editorial and publishing practices and prepare an advisory report to the Executive Board of NANOS. The Executive Board of NANOS shall in turn advise the Editor of the findings. A function of the Publications Committee will be to provide constructive criticism.

The Publications Committee shall also be responsible for advising the Executive Board of NANOS in regard to the selection of the Editor. In relation to this duty, the Publications Committee shall poll the entire membership of NANOS to solicit nominations for the position of Editor.

5) Relationship to NANOS: The Journal of Neuro-Ophthalmology will serve as the official journal of NANOS.

6) Budgetary commitments between the publisher and NANOS are the responsibility of the Executive Board of NANOS. Contractual relations with the publishers shall be made by the President as recommended by the Chair of the Publications Committee with the approval of the Executive Board. Financial considerations of the Journal of Neuro-Ophthalmology shall be part of the regular reporting function to the Executive Board of NANOS by the Chair of the Publications Committee. The Editor shall be reimbursed by NANOS and the publisher for all secretarial and clerical expenses of maintaining the Editor's office. In addition, the Editor shall be provided with an honorarium, to be determined by the Publications Committee and approved by the Executive Board of NANOS. The Executive Board of NANOS will be responsible for negotiating these fiscal matters with the publisher and the Editor.

7) Subscriptions to the Journal of Neuro-Ophthalmology will be provided to all dues-paying Members of NANOS.

ARTICLE IX - USE OF THE SOCIETY NAME, INITIALS AND LOGO

Regulation of the use of the Name of the Society (North-American Neuro-Ophthalmology Society), its initials (NANOS) and its Logo shall be determined by the Executive Board. Use of these without written consent of the Board is strictly prohibited. Penalties for unapproved use of the Society name, initials and logo shall be determined by the Executive Board.

STANDING RULES OF THE NORTH AMERICAN NEURO-OPHTHALMOLOGY SOCIETY

I. CREATION OF STANDING COMMITTEES OF NANOS

Standing Committees of NANOS may be created by a majority vote of the Executive Board. These Standing Committees shall provide the ongoing functions vital to the Society on a long term basis. The scope of responsibility of each Standing Committee shall be established by the President on the advice of the Executive Board.

II. EXISTING STANDING COMMITTEES OF NANOS

The Chair of a Standing Committee shall be appointed by each new President when taking office. Chairpersons of all Standing Committees, except for the Nominating Committee whose Chair shall be the Board Chair, shall be appointed by the President to serve a two-year term, and may be re-appointed for two additional terms to serve a maximum of six years. An incoming President, at his/her sole discretion, may elect to extend the maximum term of an outgoing Committee Chair to allow such outgoing Committee Chair to serve in the capacity of a member of such committee for one additional two-year term.

Members of the Nominating Committee shall include one Past President of NANOS, two Chairpersons of Standing Committees, three Executive Board Members, and three additional Members who will be Fellows of NANOS, but not members of the Executive Board. The Executive Vice-President, when such a person has been appointed by the Board, is a non-voting member of the Nominating Committee unless appointed as a voting member by the Board Chair. The Committee is selected by the Board Chair and the Committee Members are vetted by the Executive Board.

With exception of the Nominating Committee, whose Members are selected by the Board Chair, Members of Standing Committees shall be subject to re-approval as each new President takes office. Members of Standing Committees shall serve for a maximum of six years, or three two-year terms, and terms of membership shall be staggered so that no more than one-third of the Committee Members have terms ending in the same year. As provided by Article IV, Section 4, the President is responsible for making appointments to replace Members rotating off Standing Committees.

III. STANDING COMMITTEES OF NANOS

Educational Arm

Meeting – Foster communication among the main component Committee Chairs on the NANOS annual meeting.

Continuing Medical Education – Develops and maintains a continuing medical education program for all NANOS meetings; develops recommendations and monitors all activities related to NANOS continuing medical education activities.

Curriculum – Develop the definitive neuro-ophthalmology curriculum.

Patient Information – Expand patient educational materials for the NANOS website.

Web Education – Use the internet, and other appropriate social media vehicles, to educate neuro-ophthalmologists and other providers of healthcare about neuro-ophthalmic topics and issues.

NOVEL – Encourage growth and development of the Neuro-Ophthalmology Virtual Education Library, creating, guiding and prioritizing activities. The Chair of the NOVEL Committee or delegate(s) will also be a member(s) of the following NANOS committees: Curriculum, Development, Archives, and AAN.

NOVEL Editorial Board – Peer review new collections for content.

Fellowship – Addresses issues concerning professional standards for neuro-ophthalmology, especially the training requisite to be recognized by NANOS as a neuro-ophthalmologist and advises the Board and membership on matters pertaining to these issues. The Chair of this Committee represents NANOS on these issues to relevant external agencies, specialty boards and associations.

Financial Arm
Finance – Prepares yearly budget for review and approval of Executive Board; supervises investments and accounts; reviews existing fiscal policies and develops recommendations for improving the financial status of NANOS.

Audit – Provides information for external audit, reviews the external audit and presents recommendations to the NANOS Executive Board.

Development – Develop a plan for funding goals of NANOS, obtain grants and donations from private companies and individuals and work with Research Committee to obtain funding for research.

Practice Arm
Practice Support – Addresses developing concerns regarding the availability of financial, personnel, and support resources required for the delivery of quality neuro-ophthalmic practice, both in the academic and private practice spheres. Assists in identifying and circulating best practices, both clinical and administrative.

Productivity/Compensation - Performs, likely with outside vendor, productivity and salary surveys, gathers and disseminates external standards, monitors appropriate interpretation of and application of these standards.

Carrier Relations – Collects and circulates information about major multistate carrier specific policies, coding tips, changes in Medicare rules, etc.

Informatics – Collects and disseminates information relevant to EMR and other forms of electronic data transfer/sharing in neuro-ophthalmology.

Advocacy – Monitor proposals to change that which impacts neuro-ophthalmic care, be it compensation models from CMS, national standards for certification or scope of care, etc. and then to disseminate and promote the viewpoint of NANOS regarding these issues.

Research Arm
Research – Promotes and facilitates research endeavors in neuro-ophthalmology, and advises the Board in the selection of recipients of specific NANOS research awards.

Publications – Advises the Board on the selection of an Editor of the Journal of Neuro-Ophthalmology, meets annually with the Editor and the publisher, and prepares an advisory report to the Executive Board; roles of the Publications Committee are described in Article VIII.

Member Services Arm
Young Neuro-Ophthalmologists (YONO) – Address the needs of potential neuro-ophthalmologists (students, residents, fellows) and NANOS members in their first several years of practice.

Women in Neuro-Ophthalmology (WIN) – Mentors female members of NANOS; guides and advises women planning careers in Neuro-Ophthalmology.

International Relations – Develops and recommends policies and procedures for fostering cooperative relationships between NANOS and physicians and organizations outside the United States and Canada.

Membership Recruitment and Retention – Find and implement ways to increase and retain membership, in conjunction with the Young Neuro-Ophthalmologists Committee (YONO).

Organizational Arm
AAO – Liaise with AAO and NANOS.

AAN – Liaise with AAN and with the NONO section of AAO.

Preferred Practice Patterns – Contribute topics on Preferred Practice Patterns (AAO Compendium of Evidence-based Eye Care; AAN Practice Guidelines as appropriate).

Patient Advocacy Groups Liaison – Develop relationships with Patient Advocacy Organizations in order to foster clinical, educational and research collaborations.

NANOS Management Arm
Executive – Serves to advise the Executive Board in the management of all the business and affairs of NANOS. Consists of 5-8 members, including the President, Past President, President-elect, Treasurer, Executive Vice President, when such a person has been appointed by the Board, and up to three (3) additional Board members.

Bylaws – Develops and recommends changes in the NANOS bylaws to the Executive Board.

Archives – Compiles, researches and maintains the written archives of NANOS.

Ethics – Serves to facilitate awareness and discussion of ethical issues that may arise in the practice of neuro-ophthalmology and to educate, consult, and advise on ethical issues.

Membership – Assures that proper membership status is provided for all present and potential NANOS members; recommends methods for strengthening membership activities within NANOS.

Nominating – Nominates a slate of Executive Board members consistent with NANOS Bylaws for election as allowed by the voting membership of NANOS.

Strategic Planning – To coordinate strategic planning for NANOS by providing continuity and institutional memory of our long range goals and their implementation, monitoring our progress toward those goals, and organizing periodic NANOS Executive Board Strategic Planning Retreats (SPRs).

IV. CREATION OF AD HOC COMMITTEES OF NANOS

Ad Hoc Committees may be appointed as the need arises by the President to carry out a specific task that is not the assigned function of an existing Standing Committee of NANOS. The Ad Hoc Committee's charge and date of expected report should be specified by the President, The Ad Hoc Committee and Members of all Ad Hoc Committees shall be appointed at the discretion of the President.

Ad Hoc Committees shall submit to the President reports as deemed appropriate by the President. The Chair of each Ad Hoc Committee shall be responsible for all reports.

V. COMMITTEE LONGEVITY

Standing Committees will continue to exist indefinitely at the discretion of the Executive Board. When, in the judgment of the Executive Board, a Standing Committee is no longer necessary, it may discharge the Standing Committee by majority vote of all Executive Board Members.

Ad Hoc Committees are discharged automatically 1) upon the acceptance of their final report by the Executive Board or 2) upon completion of the current President's term of office. Ad hoc committees may be discharged at any time by the President.

VI. REPRESENTATIVES TO CIVIC, PROFESSIONAL, AND GOVERNMENTAL ORGANIZATIONS FROM NANOS

Representatives shall be appointed by the President to the following organizations and to all others as deemed necessary:

American Academy of Neurology

American Society of Neuroimaging

American Academy of Ophthalmology

Canadian Neurological Society

Canadian Ophthalmological Society

International Neuro-Ophthalmological Society

International Perimetry Society

World Federation of Neurology

A position taken or expressed by a representative shall not be deemed the position of NANOS unless and until it is adopted, ratified, or approved by the Executive Board.

Representatives shall submit to the Executive Board an annual report and special reports as deemed appropriate by the representatives or as requested by the President.

VII. ELIGIBILITY REQUIREMENTS FOR COMMITTEE MEMBERS AND REPRESENTATIVES

All Members of NANOS Committees and NANOS representatives to organizations shall be NANOS Fellows, Senior Fellows, or Active Members. Exceptions to this include the International Relations Committee, Membership Committee, and Patient Education Subcommittee, on which International Members may serve.

Other classes of NANOS Membership may, upon receipt of approval from the NANOS Board, be appointed by the President to serve on NANOS Standing Committees and NANOS Ad Hoc Committees and NANOS representatives to organizations.

Nonmembers of NANOS may, with the specific approval of the President, serve as consultants on committees; however, they shall not vote on matters of administration or policy affecting NANOS.

VIII. ANNUAL AND SPECIAL REPORTS OF STANDING COMMITTEES, SPECIAL COMMITTEES, AND REPRESENTATIVES TO ORGANIZATIONS

Standing Committees, Ad Hoc Committees, and representative to organizations shall submit to the Executive Board an annual report and such special reports, from time to time, as deemed appropriate by the Committee, representatives or the Executive Board.

The chair of each committee and representative to each organization shall be responsible for submitting all reports. All reports shall be in writing.

IX. AMENDMENTS AND REVISIONS

These Standing Rules may be amended or revised by the Executive Board of NANOS.

NANOS Membership Roster (as of 1/5/2015)

Member Types: A = Associate, C = Candidate, F = Fellow, FS = Fellow Senior,
IF = International Fellow, IM = International Member, M = Active, S = Senior
Board Certifications: O = Ophthalmology, N = Neurology,
NO = Completed Neuro-Ophthalmology Fellowship Training (includes year certified/training complete)

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