



JW Starr Pass Marriott



Tucson, AZ



February 27-March 3, 2016

*North American
Neuro-Ophthalmology Society*

1975-2016





North American Neuro-Ophthalmology Society

42nd Annual Meeting

February 27 - March 3, 2016

JW Starr Pass Marriott • Tucson, Arizona

SCHEDULE AT A GLANCE

SATURDAY, FEBRUARY 27

2:00 pm - 8:00 pm
8:00 am - 12:00 pm
3:00 pm - 5:00 pm
6:00 pm - 7:30 pm

Registration/Help Desk
NANOS Board Meeting
Botulinum Toxins: The Neuro-Ophthalmologists Guide Course [2 CME]
Opening Reception (All are Welcome)

LOCATION

Arizona Foyer
San Luis
Tucson Ballroom
Ania Terrace

SUNDAY, FEBRUARY 28

6:00 am - 6:45 am
6:30 am - 5:30 pm
6:30 am - 7:45 am
6:30 am - 2:30 pm
7:45 am - 5:00 pm
9:40 am - 10:10 am
11:50 am - 12:30 pm
12:30 pm - 2:00 pm
5:15 pm - 5:45 pm
5:15 pm - 5:45 pm
5:30 pm - 6:30 pm
5:45 pm - 6:15 pm
Evening

Yoga Class
Registration/Help Desk
Breakfast
Exhibits
FRANK B. WALSH SESSION [6 CME]
Coffee Break
Lunch
Poster Session I: Clinical Highlights in Neuro-Ophthalmology
Frank B. Walsh Committee Meeting
Fellowship Director's Meeting
Members-in-Training Program and Reception
Fellowship Committee Meeting
Dinner on your own

San Ignacio
Arizona Foyer
Arizona Ballroom
Arizona Ballroom
Tucson Ballroom
Arizona Ballroom
Arizona Ballroom
Arizona Ballroom
San Xavier
San Pedro
San Luis
San Pedro

MONDAY, FEBRUARY 29

6:00 am - 6:45 am
6:30 am - 5:30 pm
6:30 am - 7:30 am
6:30 am - 12:15 pm
7:00 am - 7:30 am
7:30 am - 9:30 am
9:30 am - 10:00 am
10:00 am - 12:00 pm
12:15 pm - 1:30 pm
1:30 pm - 3:30 pm
2:30 pm - 4:30 pm
3:00 pm - 5:00 pm
5:00 pm - 7:00 pm
8:45 pm - 10:30 pm

Yoga Class
Registration/Help Desk
Breakfast
Exhibits
NOVEL Editorial Board/Curriculum Committee Meeting
Journal Club [2 CME]
Coffee Break
Hot Topics: Today and Tomorrowland [2 CME]
Women in Neuro-Ophthalmology (WIN) Luncheon
Understanding OCT: Devices, Images, Artifacts, Real-time Scanning, and Interactive Cases [2 CME]
Teaching Neuro-Ophthalmology in the Developing World [2 CME]
Forum for New and Future Neuro-Ophthalmologists
SCIENTIFIC PLATFORM PRESENTATIONS: SESSION I [2 CME]
Night at the Movies: "Three Amigos"

San Ignacio
Arizona Foyer
Arizona Ballroom
Arizona Ballroom
San Pedro
Tucson Ballroom
Arizona Ballroom
Tucson Ballroom
Starr Circle Terrace
Tucson Ballroom
Arizona 8-10
Starr Circle Terrace
Tucson Ballroom
Tucson Ballroom

TUESDAY, MARCH 1

6:00 am - 6:45 am
6:30 am - 5:30 pm
6:30 am - 7:30 am
6:30 am - 12:15 pm
6:30 am - 7:30 am
7:30 am - 12:00 pm
9:15 am - 9:30 am
9:30 am - 10:00 am
12:00 pm - 6:00 pm
6:00 pm - 9:30 pm

Yoga Class
Registration/Help Desk
Breakfast
Exhibits
JNO Editorial Board Meeting
SCIENTIFIC PLATFORM PRESENTATIONS: SESSION II [3.75 CME]
Update: The Journal of Neuro-Ophthalmology
Coffee Break
Free Afternoon/Optional Excursions
Poster Session II: Scientific Advancements in Neuro-Ophthalmology

San Ignacio
Arizona Foyer
Arizona Ballroom
Arizona Ballroom
San Pedro
Tucson Ballroom
Tucson Ballroom
Arizona Ballroom

WEDNESDAY, MARCH 2

6:00 am - 6:45 am
6:30 am - 5:30 pm
6:30 am - 7:30 am
7:00 am - 7:30 am
7:30 am - 11:10 am
9:30 am - 9:50 am
11:10 am - 11:20 am
11:20 am - 12:00 pm
12:00 pm - 12:10 pm
12:15 pm - 1:30 pm
1:00 pm - 5:00 pm
1:30 pm - 3:30 pm
2:00 pm - 4:30 pm
4:00 pm - 5:00 pm
5:30 pm - 10:00 pm

Abstract Committee Meeting
Registration/Help Desk
Breakfast
Annual NANOS Business Meeting (all encouraged to attend)
Neuro-Imaging [3.25 CME]
Coffee Break
NOVEL Update
Jacobson Lecture [.75 CME]
Announcement of a New NORDIC Study
Research Committee Meeting Luncheon
Practical Introduction to Basic Statistics [4 CME]
3D Anatomy of the Orbit and Skull Base [2 CME]
Consortium of Pediatric Neuro-Ophthalmologists Meeting (CPNO)
International Relations Committee Meeting
Annual NANOS Reception and Banquet

Arizona Ballroom

San Pedro
Arizona Foyer
Arizona Ballroom
Tucson Ballroom
Tucson Ballroom
Arizona Ballroom
Tucson Ballroom
Tucson Ballroom
Tucson Ballroom
Signature Grill
Arizona 8-10
Tucson Ballroom
San Luis
San Pedro
Old Tucson

THURSDAY, MARCH 3

6:30 am - 12:00 pm
6:30 am - 7:30 am
7:30 am - 9:30 pm
9:30 am - 10:00 am
10:00 am - 12:00 pm

Registration/Help Desk
Breakfast
Ocular Motility [2 CME]
Coffee Break
Sports-Related Concussion: The Eyes Have It! [2 CME]

Arizona Foyer
Arizona Ballroom
Tucson Ballroom
Arizona Ballroom
Tucson Ballroom



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Please note that the following resources no longer appear in the NANOS syllabus and are available on the NANOS website: Committee listing, historical Board information, past faculty and meeting archives, award recognition, bylaws, and the membership directory.



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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 COMMERCIAL 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 30.75 AMA PR Category 1 Credits. 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 CME goal of the meeting is to improve the attendees' knowledge of neuro-ophthalmology basic science and practice. More specifically, the goals of the meeting are:

1) To achieve competence in neuro-ophthalmic diagnosis, treatment, and teaching; 2) To improve performance as physicians, teachers, and researchers by using information presented at the meeting to change clinical practice and instruction; and 3) To review research projects to investigate questions raised by the meeting's scientific sessions.

The expected results of our CME program, and of our annual meeting as its main CME activity, is that our members will increase their knowledge of neuro-ophthalmology and improve their skill in its practice, so that they can apply that knowledge and skill to enhance 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 sources translate professionals' need into current practices to improve competence in knowledge, diagnosis, performance, and treatment of neuro-ophthalmic diseases.

Approved by the NANOS CME Subcommittee and NANOS Board of Directors as of 2015



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(Donation Period: January 1, 2015-January 7, 2016)



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**NANOS would like to thank the following
Supporters and Exhibitors for their financial
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2016 Supporters:

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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.

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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.

First Name	Last Name	Designations	Commercial interest:	What was received:	For what role:
Laura	Balcer	MD, MSCE (P)	Biogen	Consulting Fees	Consultant for Development of Visual Outcome Measures
			Genzyme	Consulting Fees	Consultant for Development of Visual Outcome Measure
Jason J. S.	Barton	MD, PhD, FRCPC (F)	Vycor Medical Corporation	Financial Compensation	Scientific Advisory Board
Jeffrey	Bennett	MD, PhD (F) (P)	EMD-Serono, Questcor Pharmaceuticals, Alnylam Pharmaceuticals, Medimmune, Abbvie, Novartis Pharmaceuticals, Chugai Pharmaceuticals, Genzyme, Genentech	Consultant Fees	Consultant
			NIH, Guthy-Jackson Foundation, Novartis, Mallinckrodt	Research Support	Scientific Research
			Apsara Therapeutics	Stock, Royalty Payments	Patent on Aquaporin
Valérie	Biousse	MD (F) (P)	GenSight Biologics	Consulting Fees	Consultant
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			Bayer	Medicolegal Fees	Medicolegal Consultation
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			Genzyme	Honorarium	Consultant/Speaker
			Teva	Honorarium	Consultant
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Key: P = Planner; F = Faculty

All other faculty and planners have declared that they have no relevant financial disclosures.

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Christine	Glastonbury	MBBS (F)	Amirsys	Royalties and Prior Investor	Writing Books, Website Educational Material
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			Bionure	Stock Options and Consultancy	Scientific Advisory Board
			Mediimmune	Consultancy Payments	Adjudication Committee
			Mylan	Expert Witness Fees	Expert Witness
Randy	Kardon	MD, PhD (F)	Department of Veterans Affairs	Grant Support	Principal Investigator and Director of Iowa City VA Center of Excellence for the Prevention and Treatment of Visual Loss
			Department of Defense	Grant Support	Principal Investigator
			National Eye Institute	Grant Support	Co-Investigator
			Novartis	Consultant Fee	Steering committee for OCTiMS, an international multicenter study
Michael	Lee	MD (P)	Eli Lilly	Research Support	Site PI for Multicentered Observational Study of NAION
Leonard	Levin	MD, PhD (F)	Inotek	Consultant Fee	Consulting
			Merz	Consultant Fee	Consulting
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			Eli Lilly	Research Support	Site PI of Trial
Mark	Moster	MD (P)	Acorda Therapeutics	Research Support	PI for study of Dalfampridine in NAION
			Biogen	Honoraria	Speaking
Nancy	Newman	MD (P)	GenSight Biologics	Consulting Fees	Consultant
			Santhera	Consulting Fees	Consultant
			Trius Therapeutics	Consulting Fees	Consultant
Robert	Sergott	MD (F)	Biogen	Consulting fees; Speakers' Bureau	Consulting, Speaking and Teaching
			Lundbeck	Consulting Fees, Speakers Bureau	Consulting, Speaking and Teaching
			Teva	Speakers Bureau	Speaking and Teaching
			Merck	Consulting Fees	Consulting
Patrick	Yu-Wai-Man	BMedSci, MBBS, PhD, FRCPPath, FRCOphth (F)	Gensight	Honorarium	Consultant
David	Zee	MD (F)	Oxford University Press	Royalty	Author

Key: P = Planner; F = Faculty

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North American Neuro-Ophthalmology Society 42nd Annual Meeting

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Program Schedule

SATURDAY, FEBRUARY 27, 2016

2:00 pm - 8:00 pm	Registration/Help Desk	Arizona Foyer
8:00 am - 12:00 pm	NANOS Board Meeting	San Luis
3:00 pm - 5:00 pm	Botulinum Toxins: The Neuro-Ophthalmologists Guide Course [2 CME] <i>Co-Chairs: Khizer Khaderi, MD and Benjamin Frishberg, MD</i>	Tucson Ballroom

The use of botulinum toxins is a vital part of the Neuro-Ophthalmologist's toolkit. In this symposium, we will review neurotoxin pharmacology and compare and contrast the currently available agents, namely Xeomin (incobotulinum toxin), Botox (onabotulinum toxin), Myobloc (rimabotulinum toxin) and Dysport (abobotulinum toxin). We will discuss the relevant on label use of neurotoxins for treatment of blepharospasm, hemifacial spasm, and chronic migraine. There will be further discussion about off label uses that may be helpful for Neuro-Ophthalmologists. There will be demonstrations of proper dilution techniques, as well as injection techniques.

Upon completion of this course, participants should be able to: 1) Recognize the four available toxins and their current FDA approved uses; 2) Have a clear understanding about the safety and tolerability of the botulinum toxins; 3) Perform appropriate injections in the treatment of hemifacial spasm and blepharospasm; and 4) Have a better understanding of the use of botulinum toxin in the treatment of chronic migraine.

6:00 pm - 7:30 pm	Opening Reception (All are Welcome)	Ania Terrace
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SUNDAY, FEBRUARY 28, 2016

6:00 am - 6:45 am	Yoga Class	San Ignacio
6:30 am - 5:30 pm	Registration/Help Desk	Arizona Foyer
6:30 am - 7:45 am	Breakfast	Arizona Ballroom
6:30 am - 2:30 pm	Exhibits	Arizona Ballroom
7:45 am - 5:00 pm	FRANK B. WALSH SESSION [6 CME] <i>Co-Chairs: Wayne T. Cornblath, MD and Jonathan Trobe, MD</i> <i>Neuroradiologist: Ashok Srinivasan, MBBS, MD</i> <i>Neuropathologist: Sandra Camelo-Piragua, MD</i>	Tucson Ballroom

This symposium 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 am - 12:30 pm	Lunch	Arizona Ballroom
12:30 pm - 2:00 pm	Poster Session I: Clinical Highlights in Neuro-Ophthalmology	Arizona Ballroom
	Authors will be standing by their posters during the following times:	
	Odd-Numbered Posters: 12:30 pm - 1:15 pm	
	Even-Numbered Posters: 1:15 pm - 2:00 pm	
5:15 pm - 5:45 pm	Frank B. Walsh Committee Meeting	San Xavier
5:15 pm - 5:45 pm	Fellowship Director's Meeting	San Pedro
5:30 pm - 6:30 pm	Members-in-Training Program and Reception (All Students, Residents and Fellows-in-Training are encouraged to attend)	San Luis
5:45 pm - 6:15 pm	Fellowship Committee Meeting	San Pedro
Evening	Dinner on your own	

Frank B. Walsh Session I
Moderators: Shlomo A. Dotan, MD & Lindsey DeLott, MD

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Frank B. Walsh Session II
Moderators: Marie D. Acierno, MD & Kristopher Kowal, MD

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Frank B. Walsh Session III
Moderators: Alberto Galvez-Ruiz, MD & Hilary Grabe, MD

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Frank B. Walsh Session IV
Moderators: Edward A. Margolin, MD, FRCSC & Kara Warden, MD

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"Not Right in the Head"

Melinda Y. Chang, Janet Lee, Robert A. Goldberg, Stacy L. Pineles

Stein Eye Institute, UCLA Los Angeles, CA, USA

History & Exam

A 55 year old man presented with eight months of progressive left orbital swelling. His past ocular history was significant for LASIK of the right eye with monovision. His past medical history was significant for melanoma of the left arm, treated by surgical excision, with two negative lymph nodes, as well as hypertension, diabetes mellitus, peripheral neuropathy, and peptic ulcer disease. On ophthalmologic examination, visual acuity at distance was 20/15 OD and 20/80 OS, pinholing to 20/25 OS. There was no afferent pupillary defect. Color plates were 15/15 in both eyes. Hertel exophthalmometry measurements were 20 mm OD and 26 mm OS. Motility was full in both eyes. The left upper eyelid was mildly edematous, and there was moderate conjunctival chemosis of the left eye. The remainder of the ophthalmologic examination was normal. He had no systemic symptoms. Per report, outside MRI of the brain showed diffuse orbital involvement on both sides, with no specific mass or infiltrative features. Initial laboratory tests, including HIV serology, c-ANCA, p-ANCA, and ANA, were all negative. A procedure was performed.

Financial Disclosures: Stacy Pineles: NIH/NEI Grant K23EY021762 Research to Prevent Blindness Walt and Lily Disney Award for Amblyopia Research Knights Templar Eye Foundation Oppenheimer Family Foundation

Grant Support: NIH/NEI K23EY021762 Research to Prevent Blindness Walt and Lily Disney Award for Amblyopia Research Knights Templar Eye Foundation Oppenheimer Family Foundation

"Not Right in the Head"

Answer

Final Diagnosis

Erdheim-Chester disease.

Summary of Case

The patient underwent biopsy of the left orbital lesion. Histopathologic examination showed chronic sclerosing orbititis with perivasculitis, focal occlusive vasculitis, xanthogranulomatous inflammation, and fat necrosis. Staining was negative for microbes, and flow cytometry demonstrated no lymphoproliferative disorder. The IgG4+/IgG+ plasma cell ratio was 12%. He was referred to a rheumatologist for further work-up. Quantiferon gold, ACE, SPEP, C3, C4, IgG, IgG4, RF, hepatitis B and C serologies, and antibodies to ds DNA, SSA, SSB, CCP, myeloperoxidase, and proteinase-3 were all unremarkable. He was treated with prednisone for non-specific orbital inflammation. Symptoms improved on 60 mg/day, but worsened on tapering below 30 mg/day. He was then started on methotrexate. However, vision in the left eye decreased to 20/200 and a left APD developed. He was switched to cyclophosphamide for possible ANCA-negative granulomatous polyangiitis. One month later, his family brought him to the ED because he was "not right in the head." Vision decreased to 20/25 OD and was stable at 20/200 OS. MRI brain and orbits showed enhancement of the intraconal fat bilaterally. Additionally, there were multiple foci of abnormal T2 hyperintense signal within the brainstem, cerebellum, and deep nuclei of the cerebrum. The pituitary gland was enlarged and enhanced heterogeneously. These findings were interpreted by neuroradiologists as consistent with lymphoma, and less likely sarcoid, granulomatous polyangiitis, nonspecific orbital inflammation, or Erdheim-Chester disease. A radionuclide bone scan showed significantly increased radiotracer activity throughout the lower extremities. The original biopsy specimen then underwent further immunohistochemistry, which was negative for anti-CD1a, strongly reactive for anti-CD 68, and partially reactive for anti-S100. BRAF V600E mutation analysis was positive. Based on radiologic and histopathologic findings, the patient was diagnosed with Erdheim-Chester disease.

Struggle/Dilemma of the Clinical Presentation Description

This case illustrates the difficulty in diagnosing Erdheim-Chester disease, a rare xanthogranulomatous disease. The laboratory work-up was negative, and the biopsy was non-diagnostic, so the patient was treated with prednisone for non-specific orbital inflammation. However, symptoms worsened on prednisone and methotrexate, and ANCA-negative granulomatous polyangiitis was suspected based on histopathology showing focal occlusive vasculitis. Symptoms continued to worsen on cyclophosphamide, which prompted further neuroimaging and immunohistochemistry to arrive at the final diagnosis.

Keywords: Erdheim-Chester Disease, Orbital Inflammation, Optic Neuropathy, Proptosis, Non-Langerhans Cell Histiocytosis

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Leopard Can't Change Its Spots

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History & Exam

An 8 year-old Caucasian female presented with bilateral conjunctivitis, photophobia, and blurred vision. Visual acuity was 20/50 OD and 20/60 OS. She had 2-3+ anterior chamber cell and flare OU, 1+ vitreous cells OU, 2+ optic disc edema OU, and macular edema OU. She was diagnosed with anterior uveitis, vitritis, and neuroretinitis. At home, she had a cat, a rabbit, and a dog. She had recent travel to Hawaii. She reported a recent transient erythematous maculopapular rash behind her ears and neck. A full work-up was negative for bartonellosis, brucellosis, leptospirosis, toxoplasmosis, Lyme disease, and tularemia. Normal studies included serum ACE, lysozyme, ANA, chest x-ray, and HLA-B27. Systemic treatment consisted of azithromycin and rifampin. Prednisolone acetate eyedrops were added with a slow taper over 4 months when ocular inflammation resolved and vision returned to 20/20 OU. A week later, she developed new fevers, headache, nausea, vomiting, seizures and altered mental status. She developed disseminated intravascular coagulopathy, and recurrence of maculopapular rash which progressed to toxic epidermal necrolysis (TEN). MRI of the brain demonstrated bilateral thalamic signal intensities. Extensive workup was again negative for bartonellosis, tularemia, rickettsioses, and rubeola. Normal studies included anti-NMDA, HSV, HHV-6, HHV-7, CMV, VZV, EBV, Mycoplasma, West Nile, Enterovirus, Typhus, HIV, NMO, MPO, PR-3, ANCA, ANA, HMPV, Adenovirus, Parainfluenza, Influenza. Parvovirus B19 CSF PCR was negative, but subsequent bloodwork had positive IgG and negative IgM, and positive serum PCR and bone marrow PCR at low levels with no pathologic evidence of acute parvovirus disease. Ferritin and soluble IL-2 were elevated, and natural killer cell count was low. A procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Leopard Can't Change Its Spots

Answer

Final Diagnosis

Hemophagocytic Lymphohistiocytosis (HLH).

Summary of Case

Bone marrow biopsy showed markedly increased histiocytes with increased erythrophagocytosis, platelet phagocytosis, and rare hemophagocytosis, consistent with a diagnosis of HLH.

The close temporal relationship between panuveitis and TEN, two inflammatory events with similar skin presentations, together with immunological findings of positive parvovirus IgG, and bone marrow parvovirus PCR indicative of a chronic type of infection, supported a chronic parvovirus infection. Although rare, HLH has been described as having uveitis as a symptom of the disease.¹ It is unclear why there was a delay between the eye findings and the systemic features of her illness. Parvovirus B19 has been described as the inciting factor in uveitis and HLH.^{2,3} Perhaps in our case there was a delayed activation of the immune system to parvovirus that initially incited inflammation in the eye and then progressed to a systemic inflammatory response, as shown by the elevated CRP. As her condition progressed from eye inflammation, she developed encephalopathy with MRI brain findings of bilateral thalamic signal intensities, which can be associated with viral infections. Along with her characteristic lab findings, the bone marrow pathology was critical in showing hemophagocytosis to help make the diagnosis. This case helps physicians remember to keep the rare diagnosis of HLH in mind when there are multiple systemic manifestations in conjunction with eye inflammation that all point to a possible autoimmune etiology. This patient was treated with systemic steroids along with aggressive fluid, airway, and burn management. Her symptoms gradually improved along with the recovery from critical status.

Struggle/Dilemma of the Clinical Presentation Description

To our knowledge, this is a unique case of bilateral neuroretinitis and pan-uveitis that insidiously progressed to systemic autoimmune reaction resulting in HLH. It provides a prolonged clinical picture of what may have all stemmed from a parvovirus infection. There was no way to predict that this patient would progress from the initial eye findings to a fulminant systemic scenario.

Keywords: Neuroretinitis, Panuveitis, Hemophagocytic lymphohistiocytosis, Parvovirus

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Is It or Isn't It?

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History & Exam

A 58-year-old woman with recurrent left idiopathic orbital inflammation (IOI) presented with one day of rapidly progressive bilateral proptosis, edema, right eye redness, photophobia, and blurry vision. Her right eye had previously been asymptomatic. Her left eye had macular scarring with reduced vision from presumed IOI-associated posterior uveitis. Past medical history was remarkable for lymph node and orbital biopsy during a previous episode of IOI that were negative for malignancy. Recently she had been diagnosed with asthma. Vision was 20/50 in the right eye and 20/200 in the left. Both eyes were proptotic, left 1mm more than right. She had non-tender bilateral upper eyelid edema with left medial canthal xanthelasma-like changes. The right eye had 3+ conjunctival injection, and 3+ anterior cell. Left eye slit lamp exam was normal except for iris synechiae. The dilated exam was normal in the right eye, but the left eye had macular pigment and a fibrotic scar without active inflammation. The nerves appeared normal, without pallor or edema. She was treated with IV solumedrol, topical steroids and cycloplegics to the right eye. Six hours later, right vision had deteriorated to 20/200. There was new hypopyon and corneal haze in the right eye. Orbital CT scan showed bilateral enlargement of the extraocular muscles and lacrimal glands, ethmoid sinus disease, but no abscess, mass or bony erosion. T1 MRI orbits with contrast showed bilateral enhancement of the retro-orbital fat and extraocular muscles including the tendons, but no optic nerve enhancement. The T2 MRI orbits showed straightening of the optic nerve, but no abnormal signal. Parotid and submandibular glands were enlarged. Thyroid function, TB, syphilis, ANA, RF, ANCA, ACE, Lysozyme, Chest X-ray were normal. Serum IgG4 levels were elevated. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Is it or isn't it?

Answer

Final Diagnosis

Adult onset asthma with periocular xanthogranuloma.

Summary of Case

Lacrimal gland biopsy revealed sclerotic tissue to gross inspection. Microscopic analysis revealed fibroadipose tissue, xanthogranulomas with Touton giant cells, lymphoid follicles and scattered plasma cells. Flow cytometry was negative for lymphoproliferative disorder. The IgG4+/IgG+ plasma cell ratio was 60% with 96 IgG4+ plasma cells per high power field, just under the diagnostic cut-off of 100 for IgG4 related orbital disease (ROD) (Deshpande, 2012). Given her asthma, dermatological and histopathologic findings, a diagnosis of adult-onset asthma with periocular xanthogranuloma (APX) was made. APX is a rare non-Langerhans histiocytosis belonging to a spectrum of xanthogranulomatous diseases including Erdheim-Chester disease and necrobiotic xanthogranuloma. The latter two are important to distinguish from APX due to their poor prognosis related to paraproteinemia and multiple myeloma. APX is rarely associated with lymphoproliferative disorders, diabetes, and lymphoplasmacytic sclerosing pancreatitis. APX signs include bilateral yellow-orange, elevated, indurated eyelid masses with inflammation of orbital fat, lacrimal glands and/or extra ocular muscles. There is no consensus on treatment, but immunosuppressive agents are mainstay treatment, and our patient was treated with high dose IV steroids followed by oral steroid taper. One week later, her right eye vision had improved to 20/50 with 1+ anterior cell. A unique feature APX in our patient was a marked anterior chamber reaction in the active eye with evidence of prior uveitis in the fellow eye. Although uveitis has been reported in IOI in children (Mottow-Lippa 1981) and rarely in adults (Xu 2013), it has not previously been described in association with APX. This case illustrates the arbitrary nature of cut off values for IgG4 ROD. An association has been described between xanthogranulomatous inflammation of the orbit and a prominent population of IgG4-positive plasma cells, suggesting that it is a variant of IgG4 sclerosing disease (Mudhar, 2011).

Struggle/Dilemma of the Clinical Presentation Description

This patient's second eye orbital involvement in the setting of recent-onset asthma made sarcoidosis a leading diagnostic consideration, though prior biopsy had not revealed it. While serum IgG levels were elevated, the orbital biopsy was borderline diagnostic for IgG4 related disease. Xanthogranuloma is a rare diagnosis and the patient had an anterior chamber reaction, which has not been described before for APX.

Keywords: Orbit, IgG4, Xanthogranuloma

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Not a Meatball

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History & Exam

In April 2015, a 10 year old girl was referred for a four day history of ptosis and double vision. On examination, visual acuity was 20/20-OU; near vision was 3pt OU. Visual fields showed subtle arcuate visual field changes. External examination revealed palpebral fissures of 6.5 and 9 with an upper lid range of 12 and 11. MRD was -1 and 4. Facial sensation was intact. Hertel with a base of 94 was 11.5 and 10. Pupils were 7.5 and 3.5. Motility revealed limitation in elevation and adduction on the right. Maddox rod demonstrated an exodeviation increasing on left gaze with a left hyper increasing on up gaze. Funduscopic examination revealed a view of 20/20 bilaterally with a cup-to-disc ratio of 0.1 and 0.2 with minimal hyperopic astigmatism. Imaging studies revealed a reason for her cranial nerve III palsy. A procedure was carried out.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Not a Meatball

Answer

Final Diagnosis

Recurrent giant cell granuloma of the sphenoid sinus and clivus.

Summary of Case

Endoscopic transphenoidal biopsy; giant cells were present; RANK-L +. Extended endonasal approach to the clivus cleared the sphenoid sinus. Pathology revealed giant cells with a background of mononuclear stromal cells. Two months later she developed new ptosis OS consistent with a left cranial nerve III palsy. MRI scan showed recurrent mass in the sphenoid and she underwent repeat transphenoidal resection. Post operatively, she was started on infusions of denosumab. Six month follow up demonstrated an essentially normal exam. The first pathologic description of this condition was in 1954 by Jaffe. Giant cell lesions are more common in children or young adults and women. While they have been described in long bones, they are not infrequent in the mandible and maxilla, but only 2% involve the cranium. When the sphenoid is involved, patients present with diplopia (most commonly VI), change in vision, and headaches. CT scan usually reveals lytic changes. MRI scanning demonstrates low intensity on both T1 and T2, usually with Gadolinium enhancement. Radiographically it can be difficult to distinguish giant cell tumors from giant cell granulomas, emphasizing continued need for pathology. Pathologic evaluation reveals fewer nuclei in giant cell granulomas than giant cell tumors. Although giant cell granulomas may recur, they do not, like giant cell tumors, metastasize (1-6% usually to lungs). Definite treatment is unfortunately yet to be defined. Surgical decompression can be helpful. Radiation therapy has been employed. Calcitonin may also play a role inhibiting osteogenesis reducing abnormal bone turnover. Curettage alone is associated with a high rate of recurrence. Because of the bone involvement and the positive RANK-L markers monoclonal antibodies (denosumab) have been postulated to alter osteoclastogenesis.

Struggle/Dilemma of the Clinical Presentation Description

This is an unusual appearance of a skull base mass in a child (differential and diagnostic aspects). Treatment options in rapidly recurrent lesions involving the sphenoid and clival bone.

Keywords: Diplopia, Skull Base, Osteolytic Lesion, Monoclonal Antibody Therapy, Endoscopic Biopsy

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Diplopic Uveitis

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History & Exam

33 year-old man presented with 3 days of binocular diplopia. Visual acuity was 20/30 OU and pupillary exam was normal. Motility testing demonstrated right partial 3rd nerve palsy (no adduction and limited supraduction with complete ptosis). There were +1/2 anterior chamber cells and few vitreous cells bilaterally. Fundoscopy was normal with mild bilateral cystoid macular edema on OCT. Of note, the patient was diagnosed with bilateral panuveitis six years ago for which no identifiable cause was found. He was treated with several topical and systemic immunosuppressants, but was receiving only adalimumab injections regularly for past two years; he continued to demonstrate low-grade panuveitis while on treatment. He recalled having three previous episodes of intermittent diplopia with right ptosis during last three years which spontaneously resolved. Urgent MRI/MRA revealed densely enhancing osteodestructive lesion around right sphenoid sinus, extending into adjacent meninges, right cavernous sinus and right superior orbital fissure; associated soft tissue thickening had low signal on T2. Radiological differential was between inflammatory or neoplastic entities. After short course of oral prednisone, motility deficits and ptosis resolved. One month later, diplopia recurred; right 6th nerve palsy was diagnosed. At the same time, central vision deteriorated to counting fingers with right RAPD. CT chest, abdomen and pelvis were normal. Extensive serological testing was unrevealing. Transphenoidal biopsy of skull base mass demonstrated inflammatory infiltrate with lymphocytes and slight increase in B cells, but was otherwise unrevealing. Bone marrow biopsy was normal. Adalimumab was discontinued and, two weeks after biopsy, acuity had improved to 20/40 OD; motility deficits had resolved. There were still +1/2 cells in AC bilaterally. CT brain and orbits demonstrated destructive changes in left sphenoid sinus and thickening of left cavernous sinus and orbital apex. Radiological differential was unchanged. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Diplopic Uveitis

Answer

Final Diagnosis

IgG4-related disease with sclerosing skull base lesion and bilateral panuveitis.

Summary of Case

The biopsy was reviewed again specifically looking for presence of granulomas (as adalimumab has been associated with increased risk of sarcoidosis) and IgG-4 disease. Serum testing for IgG-4 was negative but repeat immunohistochemical staining for IgG-4 demonstrated elevated plasma cells in the lesion relative to IgG staining (greater than 40% IgG-4/IgG ratio and greater than 30 IgG-4 positive plasma cells per hpf) in three different areas (Figures 13-14). This was consistent with diagnosis of IgG-4 related disease. While sclero-uveitis is one of the rare manifestations of IgG-4 disease, this is the first case of panuveitis without any scleral involvement associated with IgG-4 disease.

Struggle/Dilemma of the Clinical Presentation Description

History of adalimumab is associated with increased risk of lymphoma and sarcoidosis. However, despite repeated imaging and a biopsy which failed to produce a definitive diagnosis, there were only a few entities which could have explained both bilateral panuveitis and a skull base lesion. Clinical suspicion and insistence at having the biopsy re-examined has led to the discovery of final diagnosis.

Keywords: IgG-4 Disease, Panuveitis, 3rd Nerve Palsy, 6th Nerve Palsy, Skull Base Mass

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Looking for a Drop of Porcelain

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History & Exam

A 4 year old healthy boy presented with severe headache. A right subdural hygroma was seen on brain MRI and CSF evaluation showed a leukocytosis with elevated protein. A week later he developed left leg weakness and a repeat brain MRI showed progressive leptomeningeal enhancement and new punctate infarcts with spine imaging revealing diffuse thickening and enhancement along the thecal sac. CNS vasculitis was suspected and he was started on steroids. A brain biopsy showed a subdural hemorrhage with pathology showing intraluminal fibrin thrombi, fibrinoid necrosis of some vessels and perivascular hemorrhage suspicious for CNS vasculitis, however, a thrombotic etiology was favored on second opinion. Despite steroids, rituximab, cyclophosphamide, infliximab, and IVIG he continued to have recurrent radiologic strokes with progressive weakness in his left leg, new weakness in his left arm, and a new left homonymous hemianopsia. After two months, he was transferred to a large referral center and on transfer his exam showed a 25 lb weight gain from baseline, weakness in the left leg and arm, a left homonymous hemianopsia, and normal mental status. Two months after his initial presentation, he developed right eyelid ptosis, right eye mydriasis and double vision. On exam he had normal near visual acuity, a left homonymous hemianopsia, abduction, supraduction and infraduction defects in his right eye with a fixed and dilated right pupil. His dilated fundus exam was normal with no evidence of vasculitis or papilledema. He was diagnosed with an ischemic complete 3rd nerve palsy, either peripheral or central (radiologically occult). Two weeks later, he had onset of hematuria, urinary retention, and abdominal pain; thought to be a cyclophosphamide side effect. Additional ineffective treatments included aspirin and natalizumab and at 3 months from presentation, two raised circular lesions on his left lower abdomen and right foot developed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Looking for a Drop of Porcelain

Answer

Final Diagnosis

Degos disease.

Summary of Case

Dermatology described these as drops of porcelain suggestive of Degos disease, also known as malignant atrophic papulosis (MAP), which was confirmed by skin biopsy. He was started on treprostinil, however after progressive strokes and new encephalopathy, he was transitioned to palliative care. He died after 4 months from his presentation of gastrointestinal hemorrhage. His autopsy showed numerous cerebral strokes, mucin filled lesions on the bowel with perforation and hemorrhage, and hepatomegaly. This rare presentation of a child with cranial neuropathy, multifocal cerebral strokes, porcelain-like depressed infarcts of the skin, and gastrointestinal hemorrhage is classic for Degos disease. MAP is a multisystem obliterative vasculopathy first described in 1942 which has since been described in all ages from infants to adulthood^{1,2} with a male predominance of 3:1.³ Histology shows zones of skin necrosis due to vasculitis with little to no inflammatory reaction differentiating this from angitis. Mucosal lesions including the bulbar conjunctivae have been reported.² The vasculopathy may be from excessive vascular C5b-9 deposition and a type I interferon rich environment, however the causative trigger (virus, autoimmune, genetic, anomalous fibrinolysis) is unknown.⁴ There is currently no cure and with multisystem involvement it is fatal within 2 years often despite treatment with steroids, antiplatelet or antithrombin therapy, and biologics.³

Struggle/Dilemma of the Clinical Presentation Description

This case was difficult to diagnose with a cranial neuropathy and multi-cerebral infarcts in the absence of the gastrointestinal and dermatologic signs for the first 3 months of his neurologic presentation. The diagnostic dilemma neared futile as his brain ischemia progressed despite multiple autoimmune therapies for presumed central nervous system vasculitis. Cranial neuropathy with multiple cerebral infarcts that may look like vasculitis of the central nervous system can be the presenting symptoms for Degos disease.

Keywords: Cranial Nerve Palsy- Third, Homonymous Hemianopsia, Vascular Arterial (Ischemic Stroke)

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Many Small Lesions, One Big Problem

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History & Exam

A 73-year old hypertensive and hyperlipidemic man presented with 18 months of horizontal diplopia, worse at distance and gaze right, oscillopsia on left head turn, and unsteady gait. Six months prior to consult, he developed dysphagia, worse with liquids, and recurrent falls forced him to use a walker. He had memory impairment for three months. On exam, MoCA testing revealed score of 20/30, with both language and visuo-spatial deficits. Visual acuity was 20/40 OD, 20/30- OS. Mydriatic pupil OS, due to old injury, was present; no RAPD was found. Color plates were normal. Visual fields were full to confrontation. Left ptosis from old injury was present. He had nuclear sclerotic cataracts. Optic discs were pink & flat, with 0.2 cup/disc ratio. EOM revealed partial right abduction deficit, comitant left hypertropia, and upbeat nystagmus. Motor and sensory exams were unremarkable. He had dysmetria in his upper extremities, left worse than right. He had an ataxic gait, with tendency to fall to the left, and could not tandem walk. MRI of the brain showed numerous contrast-enhancing lesions, hyperintense on FLAIR, widely distributed in the brainstem, basal ganglia, cerebral and cerebellar hemispheres, in patterns suggesting perivascular localization. CSF analysis revealed elevated protein at 69 mg/dl, with 7 leukocytes per cmm. CSF cultures, cytology, and demyelination studies were all negative. No malignancies were discovered by CT scans of the chest, abdomen, and pelvis, or by whole-body PET scanning. A battery of autoimmune markers was negative. Vitamin E and B12 levels were normal. Lactic dehydrogenase, beta 2 microglobulin, ANCA, and HIV testing were all normal. Serum IgE was elevated, and absolute CD4 and CD8 counts were roughly at a third of low normal, and the CD4:CD8 ratio was high. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Many Small Lesions, One Big Problem

Answer

Final Diagnosis

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS).

Summary of Case

The differential diagnosis, based on the radiological findings of punctate and linear lesions suggesting *perivascular space involvement*, included Neuro-Behcet disease, primary CNS vasculitis, lymphomatoid granulomatosis, Erdheim-Chester disease, CNS lymphoma, neurosarcoidosis, paraneoplastic encephalitis and chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). A double-dose contrast MRI study revealed bilateral fronto-parietal and right occipital lesions, and a right frontal lesion was biopsied. Histopathology revealed lymphocytic and histiocytic perivascular infiltration, primarily with CD3+ T-lymphocytes and lesser numbers of CD20+ B-lymphocytes. No vasculitis, giant cells, or granulomas were found. Stains for viral, fungal, and acid-fast organisms were negative. No myelin loss was demonstrated. The patient was given a 5-day steroid pulse, and discharged on prednisone 60 mg daily. After one month of therapy, his gait ataxia and dysphagia improved, though his visual complaints were unchanged. His diplopia responded to prism glasses.

Struggle/Dilemma of the Clinical Presentation Description

Our patient's clinical presentation suggested a wide differential diagnosis of inflammatory, neoplastic, and infectious disorders. Laboratory evaluations were not diagnostic. MRI imaging narrowed the differential, but we felt histopathologic diagnosis was necessary. Pathology was mostly in surgically risky brain regions. Double-dose contrast MRI uncovered pathology in brain areas that we could safely biopsy.

Keywords: Autoimmune Diseases, CNS Vasculitides, Abducens Nerve Palsy, Upbeat Nystagmus

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Heart of Darkness

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History & Exam

An 18 year-old woman presented to the emergency department in October 2014 with three days of blurred vision in her left eye. Past medical history included a hypoplastic right heart status-post orthotopic heart transplant at 2 months of age, chronic kidney disease with BK viremia since 12 years of age, and recurrent post-transplant lymphoproliferative disorder (PTLD, diagnosed at 15 years of age, with two subsequent recurrences). Medications included tacrolimus, leflunomide, trimethoprim/sulfamethoxazole, atorvastatin, amlodipine, and 81 mg aspirin. Review of systems was notable only for mild nasal congestion and cough for the past four weeks. Visual acuity was 20/20 in the right eye, 20/40 in the left, with a mild APD. Ishihara plates were full in the right eye, 2/11 in the left. Automated perimetry revealed an inferonasal depression in the left eye. There was no proptosis or ptosis. The anterior segment examination was normal; posterior segment revealed tortuous vasculature in both eyes and mild nasal disc elevation in the left eye, along with a fan-shaped intraretinal hemorrhage nasal to the disc margin. MRI brain and orbits without contrast (contrast withheld in setting of renal dysfunction) demonstrated a 0.7 x 0.5 cm mass along the medial aspect of the left orbital apex, possibly contiguous with the optic nerve. Lumbar puncture on admission demonstrated a normal opening pressure with no malignant cells. Patient was started on dexamethasone and then rituximab for presumed PTLD recurrence. At 1 week, steroids were tapered and the exam was stable. At 2 weeks, visual acuity worsened to 20/200, and there was a 3+ RAPD. Repeat MRI was unchanged.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Heart of Darkness

Answer

Final Diagnosis

Epstein-Barr Virus-associated smooth muscle tumor (EBV-SMT) of the left optic nerve.

Summary of Case

Systemic steroids were restarted and orbital radiation was initiated. That month, vision worsened to LP and optic nerve pallor developed. Despite aggressive medical and radiation therapy, worsening clinical course prompted family and team to proceed with pterional craniotomy for intracranial tumor resection. Microscopic examination demonstrated a mass of spindle cells, focally arranged in intersecting fascicles. EBV-encoded RNA (EBER) stain was EBV-positive. Immunohistochemical studies revealed smooth-muscle-actin (SMA) positive lesional cells. EBV-SMT are rare (122 reported since 1970) and typically manifest under immunosuppression (commonly post-solid-organ transplantation, also with HIV). 29 cases have been reported in children following solid-organ transplantation.¹ In contrast to other EBV-associated-malignancies (Burkitt lymphoma, Hodgkin disease, nasopharyngeal carcinoma), malignant potential of these tumors is uncertain. Mean age of onset is 39 years, 68% of patients have multiple tumors, which are typically well-differentiated, exhibit slow mitotic activity, and are locally invasive. It is unclear if these represent metastases or loci of infection.² Liver, lungs, brain, and GI tract are typical sites for EBV-SMT, though orbital cases have been reported. They include: two HIV-positive patients in their 40s – one with a fusiform orbital mass surrounding the optic nerve, the other with a retro-orbital mass; a 52-year old renal transplant patient with two iris lesions; and a 12-month-old status-post two liver transplants with a posterior orbital mass extending intracranially.³ No established treatment pattern exists, but it may include surgical resection, chemotherapy/radiation, antiviral therapy, and reduced immunosuppression. Patient remains NLP in the left eye. Repeat MRI is scheduled.

Struggle/Dilemma of the Clinical Presentation Description

Differential diagnosis was originally lymphomatous optic nerve infiltrate with history of recurrent PTLD, versus a question of a compressive lesion/extrinsic lymphomatous deposit. The diagnosis was also limited by the patient's chronic kidney disease (no IV contrast possible). Management and treatment dilemma arose with precipitous vision loss despite aggressive chemotherapy, radiation, and steroids. There was a question of simply observing versus repeating treatment, decreasing immune suppression, or performing biopsy of the lesion to obtain a tissue diagnosis.

Keywords: None.

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A Night at the Met

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History & Exam

A 73-year old woman with no headache history presented to the emergency department with several days of right-sided, retro-ocular, and vertex headaches and inability to see the left side of the TV screen-- all beginning 1 week after cataract surgery. Evaluation by her ophthalmologist was unrevealing. Eight years earlier, she had been diagnosed with stage 1a lung adenocarcinoma and had undergone wedge resection. One year later, she developed hematuria and left arm edema. A bladder scan showed increased uptake, and she was diagnosed with metastatic stage 3 bladder cancer. She was considered in remission from both malignancies. On our examination, she was normotensive. Visual acuities were 20/20 OD and 20/25 OS. Color vision was normal. Pupils were symmetric and brisk without APD. She had a left homonymous hemianopia to confrontation. The remainder of the examination was normal. Brain CT showed a 2 cm right occipitotemporal hemorrhage with surrounding edema. Brain MRI was consistent with an acute hematoma, showing subtle patchy rim enhancement and a suggestion of smooth thin dural or leptomeningeal enhancement over the right hemisphere. Gradient echo MRI showed no microhemorrhages. CT angiogram (to look for an underlying AVM), and CT of the chest/abdomen/pelvis (to look for primary malignancy) were negative. Three weeks later, she developed prosopagnosia. Brain MRI showed several new lesions adjacent to the original hemorrhage. There were new hemorrhages in the original lesion and more prominent peripheral enhancement. Echocardiogram to exclude marantic endocarditis was unremarkable. Digital cerebral angiography was normal. A procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

A Night at the Met

Answer

Final Diagnosis

Amyloid beta-related angiitis.

Summary of Case

Brain biopsy revealed gliosis, microglial activation, and histiocytic infiltration in addition to hemosiderin pigment and granulation tissue. Thickened vascular channels, many displaying a variably abundant mixed inflammatory infiltrate, were consistent with vasculitis. Amyloid-beta stains demonstrated widespread immunoreactivity within intraparenchymal and leptomeningeal blood vessels, with focal transmural involvement. Immunostains for amyloid-beta were positive. PCR tissue analysis, sent to the CDC, disclosed no infectious agents. A diagnosis of amyloid-beta-related angiitis (ABRA) was made. While cerebral amyloid angiopathy is common, rarely it can elicit an inflammatory response. There are two forms: inflammatory cerebral amyloid angiopathy, which is primarily perivascular, and the exceedingly rare amyloid-beta related angiitis (ABRA), which features frank vessel wall inflammation and granulomatous destruction. The amyloid deposits are thought to incite the vasculitic reaction. Regarded as a close variant or subtype of primary CNS angiitis, ABRA is histopathologically distinct in that amyloid co-localizes with inflammatory changes, a feature not seen in PACNS. Both conditions respond variably to immunotherapy and there is some suggestion of a better response to immunotherapy in ABRA. Our patient was treated with prednisone 60 mg/day for several weeks and transitioned to azathioprine. She has clinically improved with resolution of enhancement on MRI.

Struggle/Dilemma of the Clinical Presentation Description

1) Given her history, hemorrhagic metastases were high on the differential; 2) Radiographic findings were not characteristic of any condition (wrong location for hypertensive hemorrhage, no signs of amyloid angiopathy on gradient echo, oddly clustered and rapidly progressive lesions for metastatic disease, hemorrhage not typical of PACNS); 3) Conventional cerebral angiogram was normal; 4) ABRA is exceedingly rare and extremely challenging to diagnose.

Keywords: Vision Loss: Visual Field, Prosopagnosia, Cerebral Amyloid Angiopathy, Amyloid-Beta Related Angiitis, Intracerebral Hemorrhage

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It is, is it not?

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History & Exam

A 44-year-old man presented with visual loss, confusion, apraxia, and left-sided weakness. His medical history included retinal vasculopathy, chronic kidney disease, hypertension, and hypertensive cardiomyopathy that had presented over the preceding six years. The retinal vasculopathy had been termed “posterior uveitis with retinal vasculitis.” The condition had been treated with several immunosuppressive medications, including prednisone, cyclosporine, mycophenolate mofetil, adalimumab, methotrexate, and interferon-alpha. Additional treatments included retinal laser photocoagulation, intravitreal glucocorticoids, and bevacizumab. The patient had undergone two kidney biopsies, which were reported to show focal segmental glomerulosclerosis with thrombotic microangiopathy and mild nephrosclerosis. No tubulointerstitial disease was present. His father had died at age 36 years from Hodgkin lymphoma. His paternal uncle had died in his early forties from unclear causes, accompanied by renal dysfunction. The patient denied any history of oral, genital, or skin lesions, sicca symptoms, musculoskeletal, respiratory or gastrointestinal symptoms. He had undergone extensive diagnostic evaluations, including two brain biopsies, at another hospital. Glucocorticoids had been prescribed for cerebral edema. After five weeks, the patient was transferred to our institution for further management. On arrival, physical examination was remarkable for an irregularly irregular pulse and 3+ pitting edema of the lower extremities. Best-corrected visual acuity was 20/80 in the right eye and 20/50-1 in the left eye. There was bilateral dyschromatopsia. A relative afferent pupillary defect was not present. Slit lamp examination showed moderate bilateral symmetrical optic disc pallor, epiretinal membranes, cotton wool spots, retinal arteriole obstruction with sclerosis and resulting ghost vessels, and extensive pan-retinal photocoagulation scars. Neurological examination was remarkable for nonspecific visual field defects on confrontation testing, mild left lower facial weakness, mild left pronator drift, and unsteady gait. Cognitive abnormalities documented five weeks earlier were no longer present. Brain MRI revealed a right temporo-parieto-occipital tumefactive lesion with vasogenic edema extending through the splenium of the corpus callosum and the left periventricular white matter. Laboratory evaluations for systemic and CNS-related autoimmunity and inflammation, HLA-B51 antigen, and analysis of blood and cerebrospinal fluid for various infectious agents were negative. Specimens from the two brain biopsies demonstrated a vasculopathy with abnormally thickened vessel walls and focal necrosis of the white matter with areas of dystrophic calcification. Because the retinal vasculopathy, in combination with the tumefactive cerebral lesion, raised the possibility of Behçet disease or other inflammatory conditions, high-dose dexamethasone, weekly adalimumab, and daily cyclophosphamide were initiated. Decrease in the vasogenic edema with resolution of the mass effect was noted after 10 weeks of dexamethasone. His vision, however, continued to deteriorate. We took a direct approach toward reaching a diagnosis.

Financial Disclosures: The authors had no disclosures.

Grant Support: None

It is, is it not?

Answer

Final Diagnosis

Retinal vasculopathy with cerebral leukodystrophy due to a novel mutation of TREX1 gene.

Summary of Case

We performed a PubMed search for the most prominent features: “vasculopathy”, “retinopathy”, “nephropathy”, and “cerebral calcifications.” The first matching entity that came up was **retinal vasculopathy with cerebral leukodystrophy** (RVCL), a rare, autosomal dominant vasculopathy caused by mutations of the *TREX1* gene.¹

² *TREX1* gene analysis for our patient demonstrated a frameshift mutation c.830-833dupAGGA. RVCL is characterized by a vasculopathy that causes varying degrees of retinopathy, cerebral infarction, nephropathy, and hepatopathy. It is caused by C-terminal frameshift mutations of the three-prime repair exonuclease-1 (TREX1), the major mammalian 3' to 5' DNA exonuclease. Reports of RVCL describe 7 mutations in more than 70 patients.¹

⁴ The *TREX1* mutation described here is novel but presumably leads to a similar molecular abnormality with cellular mislocalization of the enzyme. The pathophysiologic link between TREX1 mislocalization and the vasculopathy remains elusive.¹

Struggle/Dilemma of the Clinical Presentation Description

A multisystem condition with retinal involvement and the impression of inflammation led to a diagnosis of a Behçet-like disease. The absence of indicators of underlying inflammation was misattributed to chronic immunosuppressive therapy. Despite the concerning family history, the patient's age delayed the consideration of its genetic nature. Improvement of brain imaging abnormalities with dexamethasone was misinterpreted as a sign of cerebral inflammation, but the same effect is observed in vasogenic edema from any cause.

Keywords: Vasculopathy, Retinopathy, Cerebral Calcifications, Nephropathy, Retinal Vasculopathy with Cerebral Leukodystrophy

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In The Thick of It

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History & Exam

A 38 year-old woman with a history of premature birth with significant developmental delay was sent for neuro-ophthalmic evaluation for excessive head movements with gaze shifting. As an adult, she was verbal and able to take the bus alone to a day program. Over the past two years, language and cognitive skills deteriorated and she developed slowed movement and a hand tremor. Hand-eye coordination was reportedly impaired. Her paternal grandfather and his family from China were reported to have an undiagnosed neurological problem. On examination, she was largely non-verbal, perseverative and bradyphrenic. She was able to follow only simple commands and recalled 0/3 objects at 5 minutes. Examination further revealed symmetric parkinsonism with a rest tremor, lower cranial dystonia, frontal release reflexes, and marked gait ataxia. She confabulated answers during acuity testing and often appeared not to be looking at the chart, but was able to properly identify numbers on the 20/400 line of the near card. She blinked to threat in both hemifields of each eye. Pupils were poorly reactive. She had cortical cataracts with central posterior subcapsular opacities OU and optic nerves were pale temporally. Motility range was full, but she had profoundly increased saccadic latency and made large head movements with saccade attempts. Smooth pursuit was saccadic and much more difficult to elicit with the head stationary. She was unable to accurately reach for an object presented in her peripheral vision. MRI brain without gadolinium showed severe confluent white matter changes in temporal and occipital white matter, extending into the splenium of the corpus callosum and thalami. The corticospinal tracts, ventral brainstem, and cerebellum were markedly abnormal. There was mild cerebellar atrophy and moderate cerebral and vermian atrophy.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

In The Thick of It

Answer

Final Diagnosis

Cerebrotendinous Xanthomatosis (CTX).

Summary of Case

Our patient had widespread cortical dysfunction, including profound saccadic dysfunction. Leukodystrophy evaluation was planned, including very-long-chain fatty acids, arylsulfatase A, and mitochondrial testing. However, review of a video made during gait testing drew attention to the extreme thickening of her Achilles tendons, making cerebrotendinous xanthomatosis (CTX) the leading diagnostic suspect. Genetic testing revealed a mutation in the *CYP27A1* gene, confirming CTX. She underwent cataract surgery and there was immediate improvement in acuity to 20/30 OU. Therapy for CTX was initiated with chenodeoxycholic acid. Within months, she showed significant improvement in cognitive abilities, spontaneous speech, parkinsonism, biparieto-occipital dysfunction, and gait imbalance. Our patient demonstrates classical findings of CTX. Though rare, it is extremely important to diagnose, as this is one of the few treatable leukodystrophies. Further, it has a recognizable pathognomonic sign that can easily be missed on examination – Achilles tendon thickening. Leukodystrophies are a large, heterogeneous group of conditions, which cause significant diagnostic challenges¹. CTX is an autosomal recessive disorder, affecting 3-5 per 100,000 people worldwide, being more common in the Moroccan Jewish population (affecting 1 in 108). CTX is caused by *CYP27A1* gene mutations, affecting the enzyme 27-hydroxylase and leading to lowered chenodeoxycholic acid levels. As a result, cholestanol and bile alcohols produce xanthomas and can accumulate in numerous organ systems, including brain, heart, skeletal system and the eyes. Four clinical criteria are used in diagnosis; intractable diarrhea, presenile cataracts, tendinous xanthomas, and neurologic abnormalities (typically in third decade). Particularly suggestive are extrapyramidal disease (81%), cognitive impairment (66%), ataxia (56%), spastic paraparesis, and MRI evidence of dentate nuclei signal alterations². Seizures and polyneuropathy are also possible. Ophthalmologic manifestations include bilateral cataracts, optic disc pallor, and palpebral xanthelasma³⁻⁶. Chenodeoxycholic acid is the mainstay of therapy. Early recognition is critical, as delay in therapy is associated with a poor outcome⁷.

Struggle/Dilemma of the Clinical Presentation Description

Our patient had baseline developmental delay with recent regression, a multisystem neurological disorder, cataracts, and leukodystrophy, raising a broad differential diagnosis. Initially, adrenoleukodystrophy, Leigh's disease and mitochondrial disorders were considered until the pathognomonic profound Achilles tendon thickening of CTX was recognized. In hindsight, bilateral cataracts and cerebellar (dentate nuclei) involvement were also strongly suggestive. Our case highlights the importance of general physical examination (Achilles tendon thickening) in this treatable leukodystrophy.

Keywords: Cerebrotendinous Xanthomatosis (CTX), Metabolic/Storage Diseases, Achilles Tendinous Xanthoma, Cataracts, Dentate Nuclear Signal Alterations

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When a WEINO Goes Blind

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History & Exam

A 16 year old male presented to an outside center with binocular horizontal diplopia. His symptoms began approximately six months prior when he noticed difficulty reading. He was seen by an optometrist and prescribed reading glasses. His vision was 20/66 in the right eye and 20/25 in the left eye. He had previously been diagnosed with amblyopia as a child. There was no family history of ophthalmic or neurologic issues. Over the next two months he lost the ability to adduct the right eye. At the emergency department, a brain MRI revealed a large T2 high signal area involving the dorsal midbrain. He denied any visual changes at that time but OCT revealed RNFL loss temporally. He was diagnosed with bilateral internuclear ophthalmoplegia (INO) and treated with intravenous methylprednisolone for three days followed by a course of oral steroids. Despite this treatment and a course of IVIG the following month, he continued to deteriorate. He developed upbeat and downbeat nystagmus with a >50 prism diopter exotropia in primary gaze with adduction and downgaze paresis and 70% limitation of upgaze in both. At the same time he noticed a decrease in the vision of his right eye (CF OD, 20/30 OS). He was uncertain of the tempo of onset as he had been patching his right eye due to the diplopia. There was no pain on eye movements. Neurological examination was unremarkable for other focal deficits. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

When a WEINO Goes Blind

Answer

Final Diagnosis

Leber's hereditary optic neuropathy (LHON) with Leigh-like syndrome, LHON-Plus.

Summary of Case

The MRI and magnetic resonance spectroscopy tests were evaluated and a lactate peak and peripheral rim of restricted diffusion were identified, these coupled with the decreased vision and OCT findings were consistent with a mitochondrial disorder. Genetic testing revealed the m.11778G>A mtDNA mutation, associated with LHON. The patient was placed on Thiamine (200mg daily) and Coenzyme Q10 (300mg daily) which was switched to Idebenone (900mg TID) upon discovery of the LHON mutation. Further brain MRI after 5 months revealed a decrease in the size of the area of enhancement in the dorsal midbrain. His bilateral INO, however, did not improve and he developed a central scotoma bilaterally, consistent with LHON. Seven months after onset his best corrected vision was 20/150 OD, 20/100 OS. He was unable to identify any Ishihara color plates with the right eye but was able to see 6/14 plates with the left using eccentric fixation. There was no RAPD. The slit lamp examination and the remaining neurological examination was within normal limits. Eight months after onset he developed subacute bulbar symptoms and sudden hypercarbic respiratory failure requiring intubation. MRI showed increased hyperintense changes involving the brainstem and the spinal cord extending to T1. Idebenone was maintained at 900 mg daily. Levetiracetam was added because of multifocal myoclonus, as well as L-arginine, dexamethasone and antioxidants: thiamine, riboflavin, vitamin C, E, alpha-lipoic acid. A ketogenic diet was also started. He made no respiratory effort until day 7 into his admission, but managed extubation on day 8. He continued to improve, but had reduced visual acuity to 2/36 bilaterally. Rapamycin was started on a trial basis, but he developed pyrexia and abdominal side effects as a complication. The patient was discharged from hospital on day 21, and continued to recover and returned to school despite severe vision impairment.

Struggle/Dilemma of the Clinical Presentation Description

The patient's presentation was suggestive of multiple sclerosis, neuro-myelitis spectrum disorders or mitochondrial disease. MtDNA testing revealed the m.11778G>A LHON mutation on a K1a haplogroup. The bilateral brainstem involvement is more typical of a Leigh-like phenotype rather than LHON, although there are a few similar case reports of LHON with central nervous system involvement (1,2). Complete sequencing of mtDNA and whole genome failed to reveal additional mutations, including MT-ATP6 and SURF1.

Keywords: Diplopia, Optic Atrophy, Optic Nerve, Extraocular Muscles, Optic Neuropathy

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The Good, The Bad, and The Ugly

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History & Exam

A 37-year-old man with a history of hearing loss presented to the Neuro-Ophthalmology clinic in 2014 with 1 month of decreased vision in the left visual field. He also reported a period of binocular horizontal diplopia, similar in all directions of gaze, which had since resolved. Past medical history revealed progressive hearing loss since 2003, resulting in complete hearing loss by 2009. Bilateral cochlear implants restored his hearing. He took no medications and had no allergies. He had a normal neuro-developmental history. There was no family history of stroke or hypercoagulable disease, but several relatives had early hearing loss requiring the use of hearing aids. He was single and employed as an engineer. He denied any alcohol, tobacco, or drug use. His neuro-ophthalmic examination showed VA 20/25 OU with correction. He was highly myopic, with a manifest refraction of -14.25 +150 x 115 OD, and -14.75 +050 x 045 OS. He identified 11/11 color plates OU. Pupils were 5mm OU, reactive, with no RAPD. Motility was full and alignment showed a 10 prism diopter esophoria in all cardinal directions of gaze. Saccades were normal. Anterior slit lamp examination revealed no abnormalities. Dilated fundus examination revealed myopic optic disc pallor OU. The cup to disc ratio was 0.2 OU. Both maculae were flat. The periphery showed myopic changes without angioid streaks, peripheral retinal emboli, or Gass plaques. Goldmann visual fields showed a left homonymous hemianopsia, more complete in the left eye. Head CT showed a right medial occipital hypodensity. Follow-up head CT five weeks later showed resolution of the occipital lesion, but also a new right posterior frontal hypodensity. In the setting of his profound hearing loss and recent visual symptoms, additional testing was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

The Good, The Bad, and The Ugly

Answer

Final Diagnosis

MELAS due to the 1644 G->A mutation in mitochondrially encoded tRNA valine.

Summary of Case

Bloodwork showed a normal CBC and BMP. LDL was 128, ESR was 6 mm/hr, and CRP was 0.4 mg/L. A1c was 5.3%, and RPR, FTA-Abs, SPEP, ANA, Rheumatoid Factor, APC-resistance testing, Cardiolipin Abs, and Beta-2 glycoprotein Abs were negative. Ferritin was 202 ng/mL. Leukocyte alpha-galactosidase activity was normal. However, lactate was elevated at 2.6 mmol/L (nl 0.5-1.5), and pyruvate was elevated at 0.10 mmol/L (nl 0.03-0.08), with a Lactate/Pyruvate ratio 26 (nl 10-30). Transesophageal echocardiogram showed normal cardiac function without masses or thrombi. CT angiography of the head and neck revealed no areas of stenosis. Repeat Head CT 6/2014 showed resolution of the previously seen medial occipital lesion, but also a new hypodensity in the posterior frontal lobe, likely correlating with an episode of transient left arm weakness. Given the patient's deficits in vision and hearing, blood was sent for mitochondrial DNA testing for point mutations and deletions, including testing for MELAS, which was negative. Muscle biopsy was also performed, which showed reduced cytochrome oxidase staining in many muscle fibers, but normal mitochondrial enzymatic testing. In addition, there were no fibers with increased staining on succinate dehydrogenase, and no ragged-red fibers on Gomori trichrome. The muscle was subsequently sent for comprehensive mitochondrial genomic analysis by next-generation sequencing, (Baylor test #2085), which revealed a pathogenic 97.7% heteroplasmic 1644G->A point mutation in mitochondrially encoded tRNA valine, confirming the diagnosis of MELAS.

Struggle/Dilemma of the Clinical Presentation Description

The primary challenge in this case was determining and confirming the unifying diagnosis for the patient's symptoms, especially in the setting of the negative mitochondrial genetic testing performed on blood and the limited abnormalities present on muscle biopsy. The concept of heteroplasmy (i.e. selective tissue involvement) was also important to consider, given that mutations may sometimes be limited to, and randomly distributed throughout, affected tissues.

Keywords: Vision Loss, Hearing Loss, Combined Vision and Hearing Loss, Mitochondrial Disorders

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Eyes and Bowels Bottled Up

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History & Exam

A 56 year-old man presented with diplopia and ptosis. Actually he was more concerned about severe constipation that had started about the same time. Abdominal x-rays had shown stool loading; laxatives had been ineffective. Our exam showed bilateral ptosis with complete ophthalmoplegia in both eyes. Pupils were normal, as was the rest of the ophthalmic examination. He had mild hypophonia but an otherwise normal neurologic exam, including intact muscle stretch reflexes. Acetylcholine receptor antibody titers were abnormal: binding 6.39 nmol/L (normal < 0.02nmol/L), striational 1:30270 (normal \leq 1:60), modulating 95% loss of function (normal 0-20%). To investigate his constipation, we performed abdominal CT, which showed dilated loops of small bowel without apparent obstruction. Within days of starting treatment with pyridostigmine (60mg 5x/day), his constipation was relieved, and CT showed resolution of the dilated bowel loops. But his eye signs persisted.

A procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Eyes and Bowels Bottled Up

Answer

Final Diagnosis

Myasthenia gravis with dysautonomic intestinal pseudo-obstruction and thymoma.

Summary of Case

The procedure was a chest CT that revealed a thymic mass. Substernal surgery extirpated a stage B3 thymoma. Myasthenia, usually with thymoma, can rarely affect the autonomic nervous system, causing intestinal pseudo-obstruction. In a review of 12 patients with myasthenia and dysautonomia, 10 had gastrointestinal dysmotility, 6 had cardiovascular symptoms and 2 had pupils fixed to light.(1) Eight had thymoma, 3 with positive anti-ganglionic antibodies. Two additional cases of GI dysmotility, thymoma, and myasthenia have since been reported, (2,3) one with negative skeletal acetylcholine receptor antibodies, the other with moderately positive skeletal antibodies and borderline elevated anti-ganglionic antibodies, which most resembles our case. We speculate that the intestinal pseudo-obstruction in our case was related either to occult anti-ganglionic antibodies (this test is only 50% sensitive in myasthenic dysautonomia) or a high titer of anti-skeletal muscle antibodies cross-reacting with enteric plexus receptors, given a 60% sequence homology shared by the extracellular domains of the two distinct receptor types.(4)

Prior to thymectomy, our patient had received prednisone, intravenous immunoglobulin, plasmapheresis, and pyridostigmine for 6 weeks, but eye movements and ptosis improved only minimally. Two weeks after thymectomy, these eye signs disappeared. The tumor showed extra-thymic involvement, so he underwent radiotherapy of 50.4 Gy. On maintenance mycophenolate mofetil 1gm/day, he has remained asymptomatic for 18 months.

Struggle/Dilemma of the Clinical Presentation Description

The profound ophthalmoplegia and markedly elevated acetylcholine receptor antibody titer in this patient were striking but compatible with myasthenia gravis. What vexed us was trying to link myasthenia to constipation—the patient's more troubling symptom. Our concept was that myasthenia gravis does not affect the autonomic nervous system. But we were wrong. It can, with the small bowel the main target. Even more rarely, myasthenia may present with autonomic manifestations!

Keywords:

Myasthenia Gravis, Dysautonomia, Intestinal Pseudo-Obstruction

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Avengers Assemble!

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History & Exam

A five-year-old otherwise healthy boy presented with a two-week history of behavioral changes, nausea, vomiting, headache, and subacute vision loss bilaterally. Six weeks prior to presentation to our hospital, he had presented to an outside hospital with esotropia and blurred vision in both eyes. At that time, he had bilateral 4+ optic nerve edema. MRI demonstrated a right mesiotemporal lobe arachnoid cyst. Opening pressure on lumbar puncture was elevated, and the patient underwent an arachnoid cyst fenestration. He improved clinically for two weeks but subsequently had a rapid decline in vision and mental status. Repeat MRI showed global enhancement of the leptomeninges, especially of the right mesiotemporal lobe near the arachnoid cyst, and enhancement of both optic nerves and the optic chiasm. Repeat lumbar puncture showed an opening pressure >55cm H₂O. He was transferred to our hospital for further care. Initial ophthalmologic examination at our hospital revealed 20/400 visual acuity in the right eye and 20/800 visual acuity in the left eye. Visual fields were constricted to approximately 10-degree nasal islands bilaterally. Motility and alignment were normal. Ophthalmoscopy revealed bilateral 4+ optic disc edema with surrounding peripapillary retinal edema. Given the significant bilateral vision loss, an optic nerve sheath fenestration was attempted, but engorgement of the ophthalmic vessels prevented completion of the procedure. Repeat lumbar puncture showed an opening pressure again of >55cm H₂O. An extraventricular drain was placed and dura was biopsied, revealing benign dense connective tissue. An infectious, autoimmune, and paraneoplastic laboratory work-up was unrevealing, and CSF cytology was negative for malignancy and infection. Repeat MRI brain and spine revealed a possible primary tumor involving the right mesiotemporal lobe and hippocampus and multifocal areas of leptomeningeal enhancement outlining the spinal cord conus, raising a question of metastatic disease. Spinal cord arachnoid biopsy was performed, showing histiocytic infiltration with reactive changes. An additional procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Avengers Assemble!

Answer

Final Diagnosis

Pediatric malignant spindle cell neoplasm with epithelioid features consistent with malignant peripheral nerve sheath tumor with leptomeningeal dissemination.

Summary of Case

A temporal lobe biopsy showed an infiltrative malignant spindle cell neoplasm with epithelioid features. The immunohistochemical profile was consistent with an epithelioid malignant peripheral nerve sheath tumor (MPNST). A ventriculoperitoneal shunt was placed and palliative craniospinal radiation was recommended. MPNSTs are rare and aggressive sarcomas that originate from peripheral nerves or cells associated with nerve sheaths. MPNSTs typically originate in the trunk and extremities but sporadically arise intracranially. MPNSTs are staged and treated as malignant soft tissue sarcomas, and management of locally advanced tumors is challenging. The clinical course, management, and optimal treatment of epithelioid MPNSTs are not defined in pediatric cases.

Struggle/Dilemma of the Clinical Presentation Description

This is a rare case of a malignant spindle cell neoplasm affecting the optic nerves and chiasm. This case illustrates the difficulty in identifying a rare disease that masquerades as more common diseases. In this case, non diagnostic dural and spinal biopsies delayed diagnosis. Further investigations led to a subsequent temporal lobe biopsy which established the diagnosis of epithelioid MPNST with leptomeningeal dissemination.

Keywords: Papilledema, Increased Intracranial Pressure, Intracranial Tumors, Optic Nerve Tumors, Vision Loss

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Growing Up Too Fast

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History & Exam

A 7 ½ year old boy presented in 2000 with precocious puberty (development of pubic hair, acne and rapid linear growth). Work-up included a brain MRI revealing a suprasellar mass, consistent with a visual pathway glioma. On ophthalmologic evaluation, he was noted to be 20/25 OU with a normal funduscopy exam. He was started on leuprolerin with improvement in his symptoms and followed with serial MRIs, showing slow increase in the size of the tumor. Two years after diagnosis, he was offered radiation therapy, but the family deferred treatment. Serial visual field testing showed a stable temporal defect in the right eye and mild nasal depression in the left eye, consistent with left optic tract involvement. He was lost to follow-up from August 2008 until June 2015 when he presented to the ER with 2 months of progressive right upper and lower extremity weakness. He denied any recent changes in his vision. Eye exam showed 20/20 acuity in both eyes, normal color vision, 2+ temporal pallor in both eyes and an incomplete right homonymous hemianopia on visual field testing. Repeat MRI showed a partially cystic and partially nodular enhancing mass, centered in the region of the left hypothalamus versus left optic tract, with associated infiltration of adjacent structures including the left thalamus and inferior left basal ganglia. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: An unrestricted departmental grant from Research to Prevent Blindness.

Growing Up Too Fast

Answer

Final Diagnosis

Chiasmal/hypothalamic ganglioglioma.

Summary of Case

The patient underwent craniotomy with cyst fenestration and partial resection of the tumor including biopsy. The pathology showed a ganglioglioma (WHO Grade I), with an infiltrative cellular neoplasm composed of glial cells containing irregular and hyperchromatic nuclei, along with dysplastic ganglion cells and neurons. Frequent eosinophilic granular bodies were present. Definite Rosenthal fibers, mitotic figures, necrosis and microvascular proliferation were not present. Immunohistochemistry was done and was positive for MAP-2 (microtubule associated protein-2), mGFAP (Glial Fibrillary Acidic Protein), Neurofilament 2F11. Ki-67 stained only 2% of cells. There was some focal reactivity for CD34. OncoPlex Single Gene analysis demonstrated positivity for BRAF p. V600E mutation. An outside institutional review of the slides agreed with the diagnosis. Following surgery, he had resolution of his right sided weakness. His right homonymous hemianopia remained unchanged. Treatment options of BRAF inhibitor versus radiation therapy were presented. He had no findings concerning for neurofibromatosis type 1.

Struggle/Dilemma of the Clinical Presentation Description

Gangliogliomas are exceedingly rare tumors involving the optic pathway, with only 23 cases reported in the literature. More typically, they occur within the temporal lobe, and present with seizures. The patient was initially diagnosed with an optic pathway glioma, a diagnosis typically made based on symptoms and imaging findings, without pathologic confirmation. Due to the rarity of gangliogliomas, there is little guidance on appropriate treatment of these tumors.

Keywords: Ganglioglioma, Optic Pathway Glioma, Optic Tract, Precocious Puberty

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Masquerade

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History & Exam

A 68 year-old man from Nicaragua, with a past medical history of diabetes and hypertension, presented with a one-year history of right-sided headaches, diplopia, and a four-month history of sudden vision loss in his right eye. In Nicaragua, a head CT and an angiogram had revealed a sphenoid wing and cavernous sinus lesion, suspected to be a meningioma, as well as occlusion of the right internal carotid artery. He was sent to the United States for possible radiation treatment. At the time of presentation in the United States, the patient also reported involvement of the left eye. He had no light perception in the right eye and a constricted visual field in the left eye. A right afferent pupillary defect was noted, along with decreased sensation in the V1 distribution on the right side. A procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Masquerade

Answer

Final Diagnosis

Invasive aspergillosis mimicking sphenoid wing meningioma.

Summary of Case

The patient underwent right pterional craniotomy with removal of the sphenoid lesion, dura, and an intraparenchymal component. Frozen specimens showed fungal hyphae concerning for mucormycosis. For that reason, he underwent exenteration of the right cavernous sinus, right cavernous carotid, and right optic nerve, and removal of the anterior and posterior clinoid processes. The procedure included complex skull base reconstruction with right abdominal fat graft. The globe itself was not violated. Therapy with amphotericin B and posaconazole was initiated. Postoperative ocular examination demonstrated no light perception in the right eye and 20/40-2 in the left eye. The right pupil was fixed and dilated with a large afferent pupillary defect by reverse. There was slight temporal constriction of the visual field in the left eye by confrontation. The right eye had complete ptosis and ophthalmoplegia, and the external appearance of the left eye was normal with full extraocular movements. Despite the preliminary pathologic diagnosis of mucormycosis, permanent sections demonstrated dense plasmacytic infiltrates, scattered regions of necrosis, and hyphae with positive GMS-staining and positive immunostaining for *Aspergillus*. The patient completed a course of amphotericin and was switched from posaconazole to voriconazole for long-term treatment of invasive aspergillosis.

Struggle/Dilemma of the Clinical Presentation Description

Imaging mimicking meningioma 2. Symptom chronicity atypical of a fungal infection.

Keywords: None.

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A Case Of Progressive Orbital Cellulitis in an Immunocompetent Patient

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History & Exam

A 74 year-old woman presented 2/7/2015 with left orbital swelling/discomfort. Imaging revealed paranasal sinus and orbital soft tissue abnormalities suggestive of inflammatory/infectious disease. She received intravenous vancomycin/meropenam but worsened. Medical history was notable for paroxysmal atrial fibrillation, arthritis, cervical intraepithelial neoplasia (grade 3). Visual evaluation at the time revealed a normal right eye and a left eye with NLP vision and IOP of 78mmHg. She underwent an emergent left lateral canthotomy bedside on 2/7/15, and ENT performed an anastrotomy, ethmoidectomy, sphenoid sinustomy, and frontal sinusotomy on 2/08/2015, with negative bacterial and fungal cultures. She also had left carious molars and necrosis of the mandibular bone, which was debrided; cultures showed light growth of both non-candida yeast and candida and fluconazole was started. The following week, she had a seizure and MRI showed cavernous sinus thrombosis which was treated with anticoagulation. Despite intravenous antibiotics and fluconazole, she worsened. Repeat MRI showed enhancing soft tissue throughout the left orbit and paranasal sinuses, numerous lytic skull lesions and pachymeningeal enhancement. CT showed intermediate pulmonary nodules, mild mediastinal/hilar lymphadenopathy, and subpleural reticulations in both lungs. Orbital biopsy revealed granulomatous inflammation without organisms; scalp biopsy showed many CD68+ histiocytes. Neuro-ophthalmological examination on 4/16/2015 was notable for persistent left orbital pain, numbness over V1 and V2 distributions, left orbital soft tissue swelling, and complete ptosis of the left upper eyelid. The right eye had 20/20 acuity; the left eye was phthisical with NLP vision. On the left there was 2+ diffuse conjunctival injection, corneal edema and haze, firm globe to palpation; iris neovascularization and near complete angle closure; there was no view behind the iris. Humphrey automated visual field testing of the right eye was reliable and showed a mean deviation score of -6.05dB, with generalized depression of sensitivity. Dilated stereoscopic funduscopy on the right was essentially normal.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

A Case Of Progressive Orbital Cellulitis in an Immunocompetent Patient

Answer

Final Diagnosis

Apophysomyces variabilis orbital and skull infection.

Summary of Case

A 74 year-old woman presented with frontal and maxillary sinus pain, left facial swelling, and left-sided headaches. Initial diagnosis was orbital cellulitis, but she worsened on intravenous antibiotic/antifungal agents. Neuroimaging showed a left orbital invasive process, paranasal sinuses, skull base, and calvarium, with cavernous sinus thrombosis. Left orbital exploration yielded cultures of *Staphylococcus warneri*. Initial histopathological analysis revealed abundant CD68+ histiocytes; a single section showed fungal forms that were considered contaminants. Biopsy of the left preauricular collection, scalp lesions, and right calvarium vertex bone confirmed fungal etiology and excluded a histiocytic neoplasm. She was started on vancomycin and Ambisome, which was switched to isavuconazole due to side effects. No gram positive pathogens were isolated so she received ertapenem for 1 month and was continued on outpatient isavuconazole. The case is nearly unique in finding, in an immunocompetent patient, lytic calvarial lesions that developed after onset of an orbital syndrome, initially assumed to be infection because of associated paranasal sinus disease. The subacute course was not consistent with bacterial infection, and early fungal studies were negative. This case exemplifies the challenge of documenting a fungal infection, and how persistent diagnostic steps are required to secure a diagnosis. The atypical course also raised questions about Erdheim-Chester disease, ANCA vasculitis, IgG4 related disease or malignancy. The following were negative: IgG 4, ANCA, V600E BRAF mutation for Erdheim-Chester, and other rheumatologic studies. Ultimately, biopsy of the left preauricular collection, scalp lesions, and right calvarium vertex bone revealed chronically inflamed fibrous tissue and bone with broad-based fungal hyphae seen individually and in clusters, compatible with *Mucorales*. Further speciation showed the organism to be *Apophysomyces variabilis*. *Apophysomyces variabilis* is a soil fungal organism in the order of *Mucorales* that infects immunocompetent humans and is thought to be contracted cutaneously. This is a rare but emerging pathogen that should be considered in cases of refractory orbital disease.

Struggle/Dilemma of the Clinical Presentation Description

The dilemma faced in this case was whether to presumptively treat the patient for Erdheim-Chester based on disease progression and the presence of histiocytes on pathology. Other features such as symptom time course were suggestive of an infectious etiology, although initial biopsies did not reveal a clear answer, and potentially treating for Erdheim Chester in the presence of an alternate etiology could have led to a worse outcome so this was a challenging decision.

Keywords: Monocular Vision Loss, Eyelid Ptosis, Orbital Cellulitis, Headaches, Fungal Infection

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North American Neuro-Ophthalmology Society

42nd Annual Meeting

February 27 - March 3, 2016
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Poster Session I: Clinical Highlights in Neuro-Ophthalmology

Sunday, February 28, 2016 • 12:30 pm – 2:00 pm

Authors will be standing by their posters during the following times:

Odd-Numbered Posters: 12:30 - 1:15 pm

Even-Numbered Posters: 1:15 - 2:00 pm

**Please note that all abstracts are published as submitted.*

Poster #		Presenting Author
Category: Disorders of the Anterior Visual Pathway (Retina, Optic Nerve, and Chiasm)		
1	Compressive Optic Neuropathy from Salivary Gland Tumor of Sphenoid Sinus	Nafiseh Hashemi
2	Unexpected Pathologic Diagnosis of Primary Dural B Cell Marginal Zone Lymphoma	Alberto G. Distefano
3	Bilateral Epstein-Barr Virus Optic Neuritis in a Lung Transplant Patient	Yen C. Hsia
4	Purtscher's Retinopathy as a Manifestation of Hemophagocytic Lymphohistiocytosis	Dov B. Sebow
5	Central Retinal Vein Occlusion, Paracentral Acute Middle Maculopathy, and Cilioretinal Vein Sparing with Acquired Shunt in a Patient with Antiphospholipid Syndrome and Cryoglobulinemia	Dov B. Sebow
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Poster 1

Compressive Optic Neuropathy from Salivary Gland Tumor of Sphenoid Sinus

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Introduction:

We present compressive optic neuropathy from salivary duct carcinoma of minor salivary gland origin, arising primarily from the sphenoid sinus.

Methods:

Case Report

Results:

A 59-year-old Hispanic man presented with an acute right, pupil-sparing CN III palsy. PMH included tubular adenoma of the colon, HTN, DM II, and NPDR. BCVA was 20/70 OD and 20/50 OS without RAPD. He had bilateral NPDR. Non-contrast CT head showed a non-expansile ground glass trabeculation of the right sphenoid sinus felt to represent interrupted pneumatization. Contrasted brain MRI/MRA redemonstrated this lesion with no other intracranial or vascular abnormality. CRP, TSH, ESR, ACE, ANA, Lyme Ab, SSA/B were normal. He was diagnosed with an ischemic CN III palsy and strict glycemic control was recommended. He presented to neuro-ophthalmology clinic 4 months later with one-month of blurry vision OD. His 3rd nerve palsy had resolved. He now had CF vision OD and stable acuity OS. A right RAPD was present. DFE showed right optic atrophy. Contrasted MRI of the brain and orbits showed a heterogeneous, enhancing, expansile mass emanating from the sphenoid sinus involving the right orbital apex. CT orbits was concerning for osteosarcoma. Pathology showed a carcinoma that stained positively for pancytokeratin, CAM 5.2, androgen receptors, PSAP, PSA, and CK-7. CD31, CD34, PAX8, TTF1, chromogranin, P63, S-100, CK5-6, and synaptophysin were negative. PSA was 3.54. Clinical examination revealed a 35-gram prostate without nodularity. CT and PET/CT showed diffuse osteoblastic metastatic disease. There were no other lesions seen systemically. Positive staining for CK-7 and androgen receptors supported a salivary duct origin¹. His tumor was determined to be an adenocarcinoma of minor salivary gland origin, arising from the sphenoid sinus, stage T4dN0M1.

Conclusions:

This is an uncommon case of prostate marker positive ductal adenocarcinoma, arising from minor salivary glands of the sphenoid sinus, resulting in compressive optic neuropathy.

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Keywords: Neuroimaging, Tumors, Skull Base, Optic Neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 2

Unexpected Pathologic Diagnosis of Primary Dural B Cell Marginal Zone Lymphoma

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Introduction:

Several infiltrative and neoplastic conditions may have similar features on MRI as meningioma. A biopsy should be obtained when clinically indicated to exclude diagnoses that may require a different treatment from meningioma.

Methods:

We present a single case report of severe vision loss of the left eye. Clinical, neuro-radiologic, and histopathologic findings will be presented.

Results:

A 54 year-old man presented with six weeks of progressive, painless decrease in vision of the left eye. The right eye lost vision to no light perception four years prior secondary to an ophthalmic artery occlusion. Brain MRI with contrast at that time was negative. Cataract extraction with intraocular lens implant of the left eye was performed locally, but post-operatively vision continued to decline to count fingers at one foot. Repeat MRI showed a suprasellar mass compressing the chiasm and intracranial optic nerves on the right more than the left and meningeal tail. A craniotomy for the presumed planum meningioma was performed. Histologic examination and immunohistochemical stains were consistent with a low-grade marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. No evidence of concomitant meningioma could be found. The patient received radiation therapy for the remainder of the unresectable tumor as well as intrathecal chemotherapy. Vision of the left eye improved to 20/250 post-operatively with a remaining paracentral inferotemporal visual field defect.

Conclusions:

This case highlights the difficulty in evaluation of a patient with a previous ophthalmic artery occlusion of the right eye with a previously negative MRI complicating clinical evaluation of new vision loss in the left eye. Repeat imaging and acquiring tissue for pathology should be obtained in complex cases of vision loss. In addition, extranodal marginal zone B-cell lymphoma should be considered in the differential diagnosis of a lesion radiographically appearing as a meningioma.

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Keywords: Neuroimaging, Tumors, Optic Neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 3

Bilateral Epstein-Barr Virus Optic Neuritis in a Lung Transplant Patient

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Introduction:

In organ transplant patients, atypical optic neuritis necessitates a broad differential, including post-transplant lymphoproliferative, inflammatory, toxic, and infectious causes.

Methods:

Case report

Results:

A 57-year-old female presented with acute onset headache, malaise, and left eye vision loss. Medical history was significant for systemic scleroderma necessitating lung transplantation six years prior. Daily medications included prednisone and sirolimus, and prophylactic sulfamethoxazole/trimethoprim and valganciclovir. On examination, BCVA was 20/20 OD and 20/400 OS, with a 3+ left APD. Fundus examination revealed bilateral disc edema with nerve fiber layer hemorrhages, more severe on the left. Brain MRI showed enlargement of the retrobulbar left optic nerve and sheath along with subtle nerve enhancement. Whole body PET/CT was unremarkable. Serum testing, including for NMO-IgG, RPR, ACE, and ANCA, was unremarkable. CSF analysis showed mild lymphocytic pleocytosis, elevated protein, and negative cytology. With viral PCR results pending, vision in the right eye dropped steadily to counting fingers, and the APD was now detected on that side. Right disc edema worsened and lipoproteinaceous macular fluid appeared. Cytomegalovirus, herpes simplex virus, and varicella zoster virus DNA was absent from CSF and serum. PCR analysis showed 10,400 copies/mL of Epstein-Barr virus (EBV) DNA in the CSF, but none in the serum. The patient was treated with intravenous acyclovir for six weeks, followed by long-term oral valacyclovir. After initiating targeted treatment, vision improved slightly as CSF EBV titer decreased steadily, most recently to 2,600 copies/mL at 6-month follow up.

Conclusions:

EBV optic neuritis is rare with few reported cases¹⁻³, mostly involving immunocompetent patients developing optic neuropathy after contracting infectious mononucleosis. In patients with atypical optic neuritis, it is important to include EBV in the differential, even when the patient is immunocompetent or has negative blood titers. This case is unique given the bilaterality with both neuroretinitis and retrobulbar optic neuritis.

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Keywords: Optic Neuritis, Epstein-Barr Virus, Neuroretinitis

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Poster 4

Purtscher's Retinopathy as a Manifestation of Hemophagocytic Lymphohistiocytosis

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Introduction:

Hemophagocytic Lymphohistiocytosis (HLH) is an inflammatory disease whose diagnostic criteria include fever, cytopenia, and hemophagocytosis in the bone marrow. Often incited by viral infections, it leads to uncontrolled activation of macrophages and a subsequent cytokine storm. We describe the case of a 52-year-old previously healthy Hispanic woman who presented with bilateral vision loss and purtscher's retinopathy secondary to HLH.

Methods:

Upon presentation, the patient underwent comprehensive ophthalmologic assessment, including color fundus photography and spectral-domain optical coherence tomography (SD-OCT).

Results:

The patient was admitted for worsening fever and found to have elevated transaminases, a pericardial effusion, and pulmonary edema. MRI of the brain revealed bilateral, near-symmetric subcortical white matter T2/FLAIR hyperintensities of the occipital lobes. She developed progressive pancytopenia, elevated serum ferritin, triglycerides and LDH as well as elevated soluble Interleukin 2 receptor alpha (sIL2Ra) levels. Epstein-Barr virus and Cytomegalovirus levels were elevated on quantitative PCR. Bone marrow biopsy showed hemophagocytosis, confirming the diagnosis of HLH. The fundus exam revealed patchy, polygonal areas of retinal whitening and edema with associated flame-shaped hemorrhages scattered throughout the posterior pole. The areas of retinal whitening corresponded to inner retinal edema on SD-OCT. These findings were consistent with purtscher's retinopathy. On subsequent exam when the patient was more alert, she was noted to have hand motion vision in both eyes.

Conclusions:

This report represents a rare case of purtscher's retinopathy as a manifestation of HLH. Since patients with HLH can develop DIC secondary to cytokine storm, it is reasonable to propose that they are also at risk of developing a purtscher's retinopathy from this consumptive coagulopathy. HLH has previously been shown to have various neurologic and neuro-ophthalmologic manifestations, including encephalopathy and nystagmus. This disorder, along with other cytokine storm diseases, should be included in the differential of purtscher's retinopathy as well.

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Keywords: Neuro-Ophth & Systemic Disease, Retina, Vascular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 5

Central Retinal Vein Occlusion, Paracentral Acute Middle Maculopathy, and Cilioretinal Vein Sparing with Acquired Shunt in a Patient with Antiphospholipid Syndrome and Cryoglobulinemia

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Introduction:

Paracentral Acute Middle Maculopathy (PAMM) is a recently described entity resulting from ischemia in the intermediate and deep capillaries of the retina, and can be associated with central retinal vein occlusion (CRVO). We describe the first reported case of CRVO with PAMM and cilioretinal vein sparing in the setting of two pro-thrombotic diseases; antiphospholipid syndrome (APS) and type II cryoglobulinemia.

Methods:

A 50-year-old man presented with intermittent loss of vision in his right eye. Color photography, SD-OCT and fluorescein angiography were performed to confirm the diagnosis.

Results:

On presentation, visual acuity was 20/HM OD, 20/30 OS with an RAPD OD. Fundus examination OD revealed vascular tortuosity, few scattered flame-shaped hemorrhages, as well as retinal whitening around the macula. SD-OCT revealed thickening of the middle layers of the retina that correlated with these areas of whitening. Laboratory testing revealed that the patient had APS and type II cryoglobulinemia. A discrete area superotemporal to the disc OD was spared from the PAMM-induced macular whitening. This area corresponded to the distribution of a single vein on FA leading to the superior edge of the optic disc where it anastomosed to an optociliary shunt vessel that had developed since previous fundus photos in 2008. As the patient's CRVO progressed and subsequently stabilized after treatment in the following months, this area of venous sparing remained the only functional, non-ischemic retinal tissue in his macula. Presumably, this vein possessed privileged and uncompromised blood flow by circumventing the occluded venous circulation and emptying instead through the shunt vessel at the disc margin.

Conclusions:

PAMM should be considered in the differential diagnosis of retinal whitening and is thought to occur in CRVO secondary to altered capillary pressure. This is also the first description of venous sparing of the retina, which can occur in a CRVO if a cilioretinal vein is present.

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Keywords: Retina, OCT, Vascular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 6

A Case of Wyburn-Mason Syndrome

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Introduction:

Wyburn-Mason syndrome is rare Phakomatosis which characterizes neuro-oculo-cutaneous involvement. The symptoms and signs are variable according to the location and size of arterio-venous malformation (AVM). We present 6 year-old boy with near blind vision in his right eye which reveals marked vascular malformation on the optic disc and extend to the orbit, nasal cavity and perichiasmal area.

Methods:

Case presentation

- Ophthalmologic exams: VA, Ref. fundus photo, FAG, OCT, VEP
- Neuro-radiologic evaluation: Transfemoral cerebral angiography

Results:

On fundus examination, right optic disc and posterior pole are blocked with severely tortuous and engorged retinal vessels which show early filling in FAG. OCT reveals vascular shadow underneath the ganglion cell layer and disrupted retinal layer contour. Transfemoral cerebral arteriography finds 2.5x4.0cm AVM nidus which extends to the right orbit, perichiasm and hypothalamus.

Conclusions:

Multidisciplinary approach is needed to diagnosis Wyburn-Mason syndrome. In case of optic nerve and macular involvement, vision threatening should be considered. With full understanding of this entity, we can differentiate diagnosis from Von Hippel-Lindau disease, Sturge-Weber syndrome, Retinal cavernous hemangioma and vasoproliferative retinal tumor.

References: None.

Keywords: Phakomatosis, AVM, Optic Disc

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 7

Debulking Optic Nerve Gliomas for Disfiguring Proptosis: A Globe-Sparing Approach by Lateral Orbitotomy Alone

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Introduction:

Optic nerve gliomas (ONG) with disfiguring proptosis and severe vision loss usually require a combined intraorbital and intracranial tumor resection. Incomplete tumor removal (Spicer et al.) and associated morbidity using this surgical approach suggests that a less invasive approach may be preferred.

Methods:

A retrospective case review of 3 patients with sporadic (not secondary to NF1) ONG manifesting profound vision loss and disfiguring proptosis who were treated at our institution. All patients underwent a lateral orbitotomy alone with a globe sparing resection of just the orbital intraconal portion of the ONG

Results:

Three ONG patients, all previously treated with chemotherapy, underwent debulking surgery between 12 and 13 years of age. One patient's ONG extended from the orbit to the chiasm. The second patient had intracanalicular extension, and the third case was isolated to the orbit. All were treated via a lateral orbitotomy alone for removal of the orbital, intraconal portion of the optic nerve and tumor, leaving a stump of tumor 2-3 mm posterior to the globe and tumor in the prechiasmal optic nerve. All 3 tumors were pilocytic astrocytoma (WHO Grade I). The average follow-up was 24 months (range 8-40 months). All patients had a significant reduction in proptosis with outstanding cosmetic results, blindness in the operated side, but normal retinal perfusion. Temporary post-operative complications which improved included esotropia and decreased corneal sensation. Follow-up imaging thus far reveals no tumor progression.

Conclusions:

Disfiguring proptosis due to ONG can be improved via a lateral, orbitotomy-only, debulking surgical procedure utilizing a less invasive approach rather than attempting complete tumor removal. The implication of leaving tumor near the globe or at the proximal optic nerve or chiasm following orbital debulking warrants further study

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Keywords: Optic Nerve Glioma

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 8

Longitudinally Extensive Spinal Cord Lesion in Leber's Hereditary Optic Neuropathy Due to the M.3460A Mitochondrial DNA Mutation

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Introduction:

Leber's hereditary optic neuropathy (LHON) is an inherited mitochondrial disorder characterized by optic nerve degeneration leading to progressive visual loss. Prior reports have described multiple sclerosis (MS) associated with all three primary LHON mutations (m.11778A>G, m.3460A>G, and m.14484T>C). Furthermore, neuromyelitis optica (NMO) has been reported in a patient with nt11778 LHON mtDNA mutation.

Methods:

We report a patient with 3460- point mutation for LHON who developed a longitudinally extensive spinal cord lesion with negative work-up including anti-NMO antibodies.

Results:

A 43-year-old female presented with progressive bilateral visual loss over 8 weeks. She reported a family history of visual loss. Brain MRI showed a mild central pontine enhancement. Genetic testing confirmed the 3460-point mutation for LHON. She had progressive decline in vision over a year with visual acuities of 20/300 OU and bilateral optic nerve pallor. The patient received Idebenone on a compassionate basis and recovered some visual acuity, improving to 20/250 OD and 20/150 OS after one year of treatment. Two years after her initial vision loss, she complained of lower limbs spasms, and neurological examination revealed a decrease in position and vibration sense in the lower limbs. MRI of the spine showed a posterior predominant longitudinally extensive spinal cord lesion that extended throughout the cervical cord and most of the thoracic cord. CSF composition was within normal range with negative oligoclonal bands. An extensive work-up was done to rule out other possible causes of her spinal cord lesion. Anti-NMO antibodies, inflammatory, metabolic, infectious, and paraneoplastic work up was negative.

Conclusions:

We report a case of LHON positive mutation associated with a spinal cord lesion. Our case report raises the possibility that the spinal cord lesion and even the previously reported MS-like lesions could be related to mitochondrial dysfunction and secondary axonal transport failure rather than an acquired inflammatory etiology.

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Keywords: Neuroimmunology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 9

Growth of an Optic Disc Vascular Anomaly for Twelve Years

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Introduction:

Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) is an uncommon idiopathic disorder in otherwise healthy young women in the third and fourth decades. It is characterized by aneurysmal dilations of the arteries of the disc and retina with peripapillary exudates, arterial sheathing and irregular venous dilation. The clinical course is unpredictable, ranging from benign self-limited form to severe visual loss due to an exudative or ischemia maculopathy. The long-term course of the disorder is not well documented

Methods:

Case report.

Results:

A 52 years-old female presented with normal acuity but an inferior field defect OS in April 2002. Funduscopy examination was normal OD but revealed a large vascular structure involving the optic disc with an overlying small hemorrhage and a large exudate adjacent to the disc OS. FA showed late staining of the disc. MRI/MRA and blood studies for systemic inflammatory disorders and infections were negative. The retinal abnormalities and visual field loss resolved leaving the vascular anomaly of the disc. The patient was seen in 2010 with normal visual testing but enlargement of the disc abnormality; OD was normal. In 2014 symptoms recurred OS. Exam showed Va 20/40, Ishihara 11/12 and nonspecific depression on perimetry. There was a dilated elongated segment of artery at the disc OD. OS showed vitreous hemorrhage obscuring the disc. FA revealed staining of the disc, the superior macroaneurysm and a segment of an inferior arteriole OD. There was staining of the optic disc with marked capillary nonperfusion peripherally OS.

Conclusions:

This is the longest followup of a patient with IRVAN. There was slow progression of the vascular abnormalities of the disc OS and development of similar abnormalities on the disc OD before a vitreous hemorrhage and marked capillary nonperfusion developed in the originally involved eye 12 years after initial presentation.

References:

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Keywords: Retina, Vascular Disorders, Visual Fields, Optic Neuropathy, Tumors

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 10

Retreatment with Ethambutol After Toxic Optic Neuropathy

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Introduction:

Ethambutol is an important component of the treatment for mycobacterial infections. Toxic optic neuropathy is a dose-dependent side effect of ethambutol treatment, occurring in approximately 5-6% of patients at 25mg/kg/day and in 1% at 15mg/kg/day. When optic neuropathy is suspected, ethambutol is typically withdrawn. Some patients require retreatment for mycobacterial infections, but the safety of ethambutol retreatment in a patient who previously developed and recovered from ethambutol-induced optic neuropathy or chiasmopathy has not been established.

Methods:

We reviewed the medical record of a 59-year-old woman who was diagnosed with pulmonary *Mycobacterium avium* complex (MAC) infection and developed ethambutol-induced optic neuropathy 7 months into treatment, recovered vision after ethambutol was discontinued, and required retreatment for pulmonary MAC infection 10 years later.

Results:

The patient's initial ethambutol toxicity was noted 7 months into therapy at a dose of 22mg/kg/day. She developed dyschromatopsia and decreased acuity to 20/80. She required retreatment for pulmonary MAC infection 10 years later. At time of neuro-ophthalmologic consultation before reinitiation of ethambutol, her vision was 20/20 OU with no residual dyschromatopsia. She was retreated with ethambutol at 25mg/kg 3 days per week for 14 months and copper supplementation without recurrence of optic neuropathy.

Conclusions:

Retreatment of mycobacterial infections with ethambutol after prior ethambutol-induced optic neuropathy is a controversial topic with very little data in the literature and most neuroophthalmologists recommend against retreatment. Though further research is required, our case shows that recurrent toxicity can be avoided when a lower dose is used.

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Sadun AA, Wang MY. Drug-related mitochondrial optic neuropathies. *J Neuroophth*. 2013;33:172-178.

Keywords: Optic Neuropathy, Neuro-Ophth & Infectious Diseases, Ethambutol

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 11

Multifocal Electroretinogram Findings in Two Patients with Idiopathic Neuroretinitis

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Introduction:

Neuroretinitis is a rare pathology of the optic disc vasculature, resulting in edema of the disc and macula with intra- and sub-retinal effusions. To date, full field electroretinogram (ERG) analysis has been described in several patients with neuroretinitis. Our purpose is to describe multi-focal ERG findings in two patients with idiopathic neuroretinitis, which to our knowledge has not been previously described.

Methods:

A retrospective analysis of two cases.

Results:

Two patients, ages 59 (female) and 31 (male), presented with unilateral subacute vision loss and eye pain. Both were found to have a visual acuity of 20/200 OD and optic disc edema on initial examination and subsequently developed macular exudates in a stellate pattern one to two weeks after presentation. Laboratory testing was negative for Bartonella Henselae and Quintana antibodies, rapid plasma reagin (RPR), Tuberculosis (Quantiferon Gold), and Borrelia Burgdorferi. Optical coherence tomography (OCT) showed intraretinal exudates and sub-retinal fluid accumulation in both patients. Automated visual field analysis showed significant hemifield deficits in both patients. Patient 1 had a dense inferior altitudinal defect, while patient 2 had a dense superior altitudinal defect. Multifocal ERG in both patients showed significant waveform amplitude and latency abnormalities centrally and nasally in the distribution of edema and subretinal fluid found on fundus exam and OCT.

Conclusions:

While full-field ERG analysis in patients with neuroretinitis may be within normal limits, multifocal ERG analysis is likely to show decreased waveform amplitudes and prolonged latencies. Multifocal ERG may contribute to a fuller understanding of the pathogenesis of neuroretinitis, and could potentially provide an avenue to earlier diagnosis and treatment of this rare condition.

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Keywords: Neuroretinitis, Multifocal Electroretinogram, Stellate Maculopathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 12

Neuromyelitis Optica Spectrum Disorder Presenting as Bilateral Anterior Optic Neuritis with Venous Stasis

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Introduction:

We present a case of bilateral anterior optic neuritis complicated with bilateral retinal vein stasis in the setting of neuromyelitis optica spectrum disorder.

Methods:

This is a descriptive case report based on clinical records, patient observation and analysis of diagnostic studies.

Results:

A 31 year-old man with no significant medical history presented with new onset of bilateral decreased vision and pain on eye movements. Vision in the left eye dramatically decreased a week prior to presentation and he started noticing blurry vision in the right eye 5 days thereafter. On examination, visual acuity was 20/30 OD and 20/1000 OS. He had a dense left afferent pupillary defect. Fundus examination showed crowded and swollen optic discs, dilated veins and numerous macular hemorrhages with pale center. There were ceco-central scotomas on visual field examination. Fluorescein angiogram disclosed delayed filling of the central retinal veins. An MRI of the brain and orbits showed enlarged enhancing optic nerves and no other abnormalities. AQP4 antibodies were positive in the blood and cerebro-spinal fluid. Patient was treated with a 3-day course of intravenous corticosteroids and underwent 5 plasma exchanges. Vision improved to 20/20 OD and 20/40 OS a week later. Optic disc swelling, dilation of the retinal veins and macular hemorrhages resolved within a month.

Conclusions:

Central retinal vein occlusions (CRVO) have been reported in severe papilledema, and optic disc swelling is a common feature of CRVO. However, venous stasis can also occur in mild optic disc swelling, especially when there is prominent enhancement of the optic nerves on the MRI. Retinal vein stasis with mild optic disc swelling should raise suspicion about a severe retrobulbar process impeding the venous outflow, especially when visual impairment is incommensurate with the fundus findings.

References: None.

Keywords: Neuromyelitis Optica, Anterior Optic Neuritis, Optic Disc Swelling, Venous Stasis, Central Retinal Vein Occlusion

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 13

Orbital Apex Syndrome Secondary to *Scedosporium boydii*

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Introduction:

Orbital Apex Syndrome (OAS) consists of any combination of 3rd, 4th or 6th nerve paresis, V1 distribution sensory loss, Horner's syndrome and visual loss due to optic nerve involvement. OAS secondary to mucormycosis in the immunocompromised patients is well described. Unlike *Aspergillus*, which is the most commonly reported, *Scedosporium boydii* has not been previously reported as a cause of OAS. *Scedosporium boydii* is now increasingly recognized as a cause of resistant life-threatening infections in immunocompromised patients.

Methods:

Case Report.

Results:

We report the case of an 89-year-old female with a remote history of lymphoma who presented with rapidly progressive infiltrative optic neuropathy. She also had a right OAS primarily manifested as a pupillary-involving right oculomotor palsy, right superior oblique palsy, and right abducens palsy. MRI of the brain showed a right intraconal orbital cellulitis with extension to the orbital apex. CT scan of the sinuses showed mucosal thickening or mass within the right sphenoid sinus extending into the right posterior ethmoid air cells. The patient underwent nasal endoscopy with a complete right ethmoidectomy and sphenoidectomy. She had a postoperative diagnosis of a right sphenoid mycetoma. H&E staining showed acute angled branching septate, compatible with *Aspergillus*. However, fungal cultures were positive for *Scedosporium boydii*.

Conclusions:

We present the first reported case of OAS secondary to *Scedosporium boydii*. Neuroimaging demonstrated a soft tissue right intracranial mass with extension to the right orbital apex. The biopsy and initial staining were consistent with *Aspergillus*, however additional fungal culture and additional staining were consistent with a final diagnosis of *Scedosporium boydii*. Diagnosis of *Scedosporium* infection is difficult, because clinical features and histopathology are similar to those of *Aspergillus*. The clinician should consider *Scedosporium boydii* in the differential diagnosis of an orbital apex syndrome.

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Keywords: Orbital Apex Syndrome, *Scedosporium*, Aspergillosis, Oculomotor Nerve Palsy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 14

Electrophysiologic Analysis of the Foster Kennedy Sign Due to a Pituitary Mass

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Introduction:

The Foster Kennedy sign is defined by unilateral optic nerve atrophy due to direct compression by an intracranial mass lesion with resultant contralateral papilledema. It varies in accompanied clinical presentation, and may include headaches or vision loss. Increased knowledge of disease progression and objective diagnostic options, including electrophysiologic tests, are needed to further address and monitor such pathologic conditions. This case is unique as it is due to a pituitary macro-adenoma, which is a rare precipitant of Foster Kennedy sign.

Methods:

A 44-year-old woman with a history of severe, post-partum pre-eclampsia experienced visual changes and was found on imaging to have a compressive pituitary macro-adenoma. She presented for neuro-ophthalmology evaluation where initial exam showed decreased visual acuity of the left eye, atrophy of the left optic nerve, and papilledema of the right optic disc without evidence of pupillary defects, nystagmus, or compromised gaze. Such presentation was consistent with the Foster Kennedy sign. Further diagnostic workup included visual field (VF) testing, ocular coherence tomography (OCT), visual evoked potential (VEP), full field electroretinogram (ERG).

Results:

30-2 VF indicated visually significant bilateral temporal hemianopsia. VEP and ERG resulted in subnormal amplitudes, which aided to objectify the pathogenesis behind the Foster Kennedy sign and its relationship to the patient's space-occupying pituitary mass.

Conclusions:

The Foster Kennedy sign is a rare finding resulting from different intracranial etiologies that compromise the integrity and function of the optic nerves, and thus, vision. In our case, the anterior visual pathway was directly affected, which supports the involvement of a direct pathogenic mechanism, specifically, pituitary macro-adenoma. Both clinical evaluation and quantifiable diagnostic testing proved valuable tools for the diagnosis and plan for future monitoring of this very rare case and hold promise for others with a similar mechanism.

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Keywords: Tumors, Visual Fields, Optic Neuropathy, Orbit/Ocular Pathology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 15

Pembrolizumab-Related Panuveitis/Choroiditis

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Introduction:

There have been several documented cases of Vogt-Koyanagi-Harada (VKH) like symptoms associated with interferon-alpha treatment in chronic hepatitis C patient. There has also been at least two reports of similar presentations with the use of ipilimumab, another monoclonal antibody used in the treatment of melanoma. We present a case of bilateral optic disc swelling and panuveitis with choroiditis and multifocal serous retinal detachments in a patient being treated with Pembrolizumab and Pegylated interferon alfa-2b for metastatic melanoma.

Methods:

A single case report.

Results:

A 68 year old male being treated with pembrolizumab and pegylated interferon alfa-2b for metastatic melanoma presented with a two week history of worsening headaches and progressive blurry vision. He was found to have bilateral disk edema, relative hypotony, panuveitis, and multifocal serous retinal detachments. Fluorescein angiography revealed bilateral optic disc leakage, diffuse leakage and pooling in the posterior pole consistent with active choroiditis and serous retinal detachments but no definite vasculitis. Optical coherence tomography imaging demonstrated significant optic disc swelling, diffuse retinal edema with multifocal pockets of sub-retinal fluid and choroidal thickening in both eyes. The decision was made in consultation with the patient's oncology team to stop his anti-cancer medications. The patient was then treated aggressively with posterior sub-Tenons triamcinolone injections in both eyes and oral prednisone on a slow taper. The patient made a rapid recovery with resolution of his iritis and vitritis within one week and almost complete resolution of his subretinal fluid and disc swelling within one month. His vision also improved significantly over this period of time.

Conclusions:

Our patient likely represents the first reported case of a VKH-like presentation in a patient being treated with pembrolizumab. His course was notable for rapid improvement of symptoms after the initiation of steroids and cessation of the concerning medications.

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Keywords: Pembrolizumab, Vogt-Koyanagi-Harada (VKH), Disc Swelling

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 16

“Here Kitty, Kitty, Kitty”: Optic Neuropathy in the Setting of Exposure to Bartonella Henselea

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Introduction:

Cat scratch disease caused by Bartonella henselea has traditionally been associated with unilateral neuroretinitis consisting of optic disc swelling and a macular star. Larger published case series show features such as bilaterality, retinal and choroid lesions, and enhancement of the optic nerve head on MRI are now being recognized as more common. We present a case with these features accompanied by high resolution OCT images and fundus photos documenting progression and resolution.

Methods:

Case report and review of literature.

Results:

A 16 year old female presented with complaint of 2 day history of fever and blurry vision in her right eye. Her past medical history was significant for recent exposure to stray kittens with fleas, barn yard animals, a close contact who recently returned from Moldova, and unprotected sexual activity. Her corrected visual acuity at near was 20/70 OD 20/20 OS with no afferent pupillary defect and full colors. Humphrey visual field 30-2 demonstrated enlarged blind spot in the right eye. Fundus exam showed bilateral optic disc swelling although the right disc was more prominent and atypical in appearance with an adjacent white retinal lesion. OCT confirmed disc swelling OU with circumpapillary NFL thickening and subretinal and intraretinal fluid tracking from the disc OD. The patient's vision rapidly declined to 20/200 OD and was therefore started on high-dose IV steroids and doxycycline which resulted in rapid improvement of retinal fluid and disc swelling. Extensive workup was conducted for both bilateral optic nerve swelling and neuroretinitis which eventually revealed infection with Bartonella henselea.

Conclusions:

Our case provides evidence to support a much less expected, but well documented ocular manifestation of cat-scratch disease, and anecdotally shows positive results for use of steroids and antibiotics in cases of worsening clinical presentation. It additionally provides detailed imaging of the progression and resolution of clinical findings.

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Keywords: Cat Scratch Disease, Bartonella Henselea, Neuroretinitis, Macular Star

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 17

Hemodialysis as a Possible Risk Factor for Ischemic Optic Neuropathy: Case Report

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Introduction:

Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) is presumed to result from circulatory insufficiency within the optic nerve head. NAION has been reported in association with many conditions that may predispose to decrease its perfusion. The hemodynamic compromise such as the one generated in systemic hypotension, blood loss and anemia may produce optic nerve ischemia. Hypotensive episodes in the setting of chronic anemia without blood loss, as in chronic hemodialysis, may result in Ischemic Optic Neuropathy (ION).

Methods:

Single Case Report

Results:

A 38 year-old caucasian male presented with painless visual loss OS. The patient reported chronic hemodialysis due to a past medical history of glomerulonephritis 18 years prior and hypertension. Laboratory evaluation revealed a low red blood cell count. In the neuro-ophthalmologic examination the best corrected visual acuity was OD 20/20 and OS 20/200 with a relative afferent papillary defect. Color vision was OD 5/8 and OS 0/8. The fundus examination revealed a pale optic disc edema with peripapillary retinal hemorrhage in OS. The OD disc was normal. Visual field evidenced a nasal depression with a centrocecal defect and the Optical Coherence Tomography showed a decrease average retinal nerve fiber layer thickness OS.

Conclusions:

Chronic hemodialysis can be considered as a risk factor for ION. Related to hypotension most often presents in patients with chronic renal failure and dialysis. The accelerated diffuse vasculopathy that occurs in this disease may predispose to the development of ION, as may previous chronic hypertension, with possible arteriosclerosis and impaired autoregulation of the optic disc vascular supply.

References: None.

Keywords: Ischemic Optic Neuropathy, Hemodialysis

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 18

Neuroretinitis After a Bee Sting

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Introduction:

To report and review a case of toxoplasma neuroretinitis after a bee sting

Methods:

This is a descriptive case report based on clinical records, patient observation and analysis of diagnostic studies.

Results:

A 17-year-old woman presented with 3-day history of decreased vision and pain on eye movement in the left eye. The patient had history of a bee sting about two weeks ago and had an epi pen injection for allergic skin reaction, otherwise she was healthy and had no recent vaccination or no contact with animals. On evaluation, 5 days after the development of symptom, the patient complained of eye pain and pain on eye movement in the left eye with seeing black spot. The examination showed clinical signs of optic neuropathy with decreased visual acuity (20/400), dyschromatopsia, visual field defect and relative afferent pupillary defect in the left eye and also showed swelling of inferior optic disc and papillomacular bundle in the left eye. MRI orbit with and without contrast with fat suppression showed slightly increased signal around the left optic disc with no enhancement of optic nerve or sheath. Further investigation with serologic test was considered. CBC, ESR, CRP, ANA, ANCA, ACE, Lyme, quantiferon gold, FTA-ABS, Bartonella were performed and they were unremarkable. Given the poor visual sensory function in the left, systemic corticosteroid was administered and showed minimal improvement of eye pain. Additional serologic test was considered for toxoplasmosis, HSV, histoplasmosis and toxoplasma IgG was positive and otherwise negative. Under the suspicion for activated toxoplasmosis neuroretinitis in the left eye, Bactrim with prednisone was started and in the four weeks with the treatment, her visual acuity has improved to 20/70 in the left eye.

Conclusions:

This is a rare case of toxoplasma neuroretinitis after a bee sting. The acquired ocular toxoplasmosis may be considered in clinical setting of optic neuritis or neuroretinitis after a bee sting.

References: None.

Keywords: Optic Neuropathy, Retina, Neuro-Ophth & Infectious Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 19

Analysis and Outcome of Ocular Syphilis Manifesting as Optic Neuritis – A Report of Five Cases From a Tertiary Referral Eye Care Centre

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Introduction:

Syphilis is a sexually transmitted disease caused by the spirochete *treponema pallidum* with protean manifestations. Ocular syphilis can masquerade as anterior uveitis, panuveitis, retinitis, retinal vasculitis, vitritis or papillitis. We aim to describe clinical features and outcome of patients with ocular syphilis who presented with disc swelling at a tertiary referral eye care centre.

Methods:

Retrospective cohort study of 8 eyes of 5 patients from 2004-2012.

Results:

All 5 patients were male, with mean age of 42 years (range 35-50). 3 patients had bilateral disc swelling. There were no other retinal or choroidal lesions. Neuroimaging was performed in all patients to rule out space occupying lesions. Laboratory diagnosis was supported with two serological tests – a positive venereal disease laboratory test (VDRL) or rapid plasma reagin (RPR) as well as either *treponema pallidum* particle agglutination (TP-PA) or syphilis immunoglobulin G (IgG). Three of them had positive retrovirus. Lumbar puncture was performed in all patients, with cerebrospinal fluid (CSF) VDRL positive in 3 (60%) patients. All patients received 14 days of intravenous benzylpenicillin with 4 (80%) patients receiving concurrent systemic steroids. Average time from presentation till initiation of penicillin treatment was 5.2 ± 3.7 days. Mean logmar visual acuity at presentation was 0.68 with improvement to mean logmar VA of 0.04 at 1 year post presentation.

Conclusions:

Ocular syphilis can present with papillitis that may be unilateral or bilateral. Although life threatening diseases should be ruled out first, one must not forget infection as an important differential – particularly in patients with an atypical presentation. In this series of patients with syphilitic optic neuritis, appropriate prompt treatment together with judicious use of systemic steroids tends to produce good visual outcomes.

References: None.

Keywords: Optic Neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 20

Retinal Hyper-excitability and Ischemic Optic Neuropathy Following Oxaliplatin and Capecitabine Chemotherapy for Carcinoma of the Appendix

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Introduction:

Oxaliplatin and capecitabine together are a primary therapy for advanced colorectal cancer. The combination is relatively new but increasingly common without fully delineated side effect profiles, though there have been case reports of ocular toxicities including optic disc edema, transient vision blurring and blepharoptosis.

Methods:

Case report and literature review of a 64 year old man undergoing adjuvant oxaliplatin and capecitabine therapy for locally advanced appendiceal carcinoma who experienced episodic peripheral whitening of his vision ("white tunnel vision") lasting 5-30 seconds triggered by light following an oxaliplatin infusion.

Results:

The white tunnel vision episodes decreased in frequency over time following his oxaliplatin infusion. The patient demonstrated anatomically crowded optic discs with disc edema bilaterally, but no other observable fundus pathology. Fluorescein angiography and temporal artery biopsies were not consistent with temporal arteritis, and MRI of the brain and orbits was unremarkable. His symptoms and optic disc edema entirely dissipated after eight weeks without further chemotherapy. Given the timing and negative work-up his optic disc edema and his white tunnel vision are thought to be chemotherapy toxicities.

Conclusions:

Oxaliplatin's dose-limiting neurotoxicity is characterized by hyper-excitability of peripheral pain receptors. This patient's episodic white tunnel vision may reflect a similar retinal hyper-excitability toxicity preferentially involving rods versus cones or magnocellular versus parvocellular ganglia. The optic disc edema could be from axonal edema in an already small anatomic disc secondary to oxaliplatin (axonal swelling seen in lab studies), or due to short posterior ciliary artery vasospasm secondary to capecitabine which exhibits vasospastic side effects like 5-fluorouracil. The optic disc pathology could conceivably have caused breakdown in the retinal-blood barrier allowing oxaliplatin to induce the retinal hyper-excitability toxicity. This is the first report of this phenomenon, and it is important to alert oncologists to this possible side effect given the regimen's expanding usage.

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Keywords: Chemotherapy and Radiation Injury, Optic Neuropathy, Retina

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 21

Phenotypic Spectrum of Optic Neuropathy Associated with Primary Sjögren's Syndrome

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Introduction:

Optic neuropathy associated with primary Sjögren's syndrome (SS) is seldom reported and little is known of its variable spectrum of clinical presentations.

Methods:

We described 3 different cases of optic neuropathy associated with primary SS.

Results:

Case 1: A 50-year-old woman was referred for incidentally found bilateral optic atrophy. She had dry eye symptoms for a month without subjective visual decline. Visual acuities (V/A) were 20/30 in both eyes. Color vision and visual field defects were found. Brain MRI was normal. Schirmer's test was below 5 mm, anti-Ro/SSA and anti-La/SSB antibodies were positive, whereas anti-aquaporin-4 (AQP4) antibody was negative. Salivary gland biopsy showed lymphoplasmacytic infiltration. Chronic optic neuropathy associated with primary SS was diagnosed. Plasmapheresis with immunosuppressants improved V/A up to 20/20, as well as color vision and visual fields. Case 2: A 67-year-old woman showed acute monocular V/A decrease with optic disc edema. MRI showed optic nerve enhancement. Schirmer's test was 5-10 mm bilaterally without sicca symptoms. Anti-Ro/SSA was positive and salivary gland biopsy revealed primary SS. Due to steroid dependence after high dose treatment, immunosuppressants were added. Case 3: A 43-year-old woman was newly diagnosed with SS- associated encephalitis. One month later, acute visual loss to counting fingers occurred in the right eye with pain. Based on positive serum anti-Ro/SSA, antinuclear and AQP4 antibodies and enhancement of the optic nerve on MRI, neuromyelitis optica spectrum disorders (NMOSD) associated with SS was diagnosed. Plasmapheresis fully recovered visual functions, which was maintained with immunosuppressants.

Conclusions:

Optic neuropathy associated with primary SS can present as acute optic neuritis, insidious progression of chronic optic atrophy, or in the context of NMOSD. Optic neuropathy may present initially without sicca symptoms, which makes the diagnosis difficult. Specific antibodies are supportive for the diagnosis and treatment in atypical cases of optic neuropathy.

References: None.

Keywords: Optic Neuropathy, Sjögren's Syndrome

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 22

Syphilitic Perineuritis with Preserved Visual Function

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Introduction:

Syphilis has reemerged since the past 20 years. Designated as great masquerader, it can have multiple clinical manifestations in the eye: anterior uveitis, chorioretinitis, exudative retinal detachments and papillitis, to name a few. We report a case of syphilitic optic perineuritis, rare presentation of the disease.

Methods:

Retrospective case report.

Results:

58 year-old man presented with four weeks history of intermittent blurry vision in the right eye. He also reported having a recent history of skin rash on the upper arms and trunk as well as recurrent tinnitus. His past medical history was significant for well-controlled type 2 diabetes and hyperthyroidism. Best corrected visual acuity was 20/20 in each eye. There was very subtle right relative afferent pupillary defect. Biomicroscopic exam was normal in each eye. Posterior segment exam revealed few vitreous cells and a florid optic nerve edema with multiple peripapillary flame hemorrhages in the right eye. Fundoscopy was normal on the left. Formal visual field testing (Humphrey 24-2 algorithm) was normal in each eye. Optical coherence tomography (OCT) of the peripapillary retinal nerve fiber layer (RNFL) demonstrated marked elevation of the peripapillary RNFL on the right. MRI of the brain and orbits was normal. CBC, ESR, CRP, ANA, ACE were normal, HIV testing was negative. The rapid plasma reagin (RPR) test though was strongly positive (titer 1:512) and Treponema pallidum particle agglutination (TP-PA) testing was positive as well.

Conclusions:

Optic perineuritis, an unusual presentation of syphilis, is a form of inflammation of optic nerve sheath with sparing of axons comprising the optic nerve itself and thus, preserved visual function. This case is unique in that optic nerve head edema was quite pronounced with multiple peripapillary hemorrhages yet the patient was completely asymptomatic with normal visual function. It underscores the importance of including syphilis serologies in the work up of patients with optic nerve head edema.

References: None.

Keywords: Syphilis, Perineuritis

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 23

Diagnosis of Optic Nerve Sheath Meningioma by Optic Nerve Sheath Decompression

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Introduction:

Optic nerve sheath meningioma (ONSM) is typically diagnosed based on clinical suspicion and imaging characteristics, and is most often treated with radiation. Historically, biopsy, optic nerve sheath decompression, and debulking surgeries have been avoided for fear of optic nerve vascular disruption and tumor spread into the orbit. Recently, however, a limited number of case reports have reexamined the utility of optic nerve sheath decompression (ONSD) with biopsy for suspected ONSM.

Methods:

We present a patient with unilateral optic disc edema and initial questionable findings of enhancement on MRI orbit. Clinical, neuroradiologic, and histopathologic findings will be presented confirming the diagnosis of ONSM.

Results:

A 48-year-old man presented with unilateral optic disc edema (ODE) and an enlarged blind spot. Initial imaging demonstrated questionable right optic nerve sheath enhancement vs. motion artifact. Subsequently, a lumbar puncture demonstrated an elevated opening pressure of 25 cm H₂O and he was diagnosed with idiopathic intracranial hypertension (IIH). The unilateral ODE initially resolved with acetazolamide. Following weight reduction and acetazolamide discontinuation, the ODE recurred and his vision subsequently worsened to 20/30. Repeat imaging 11 months after initial presentation demonstrated clear right optic nerve sheath enhancement. Optic nerve sheath decompression (ONSD) with biopsy was performed, simultaneously to decompress the nerve and secure a pathologic diagnosis, which confirmed ONSM. He was treated with radiation, but the visual acuity and fields improved after ONSD alone.

Conclusions:

The utility of optic nerve sheath decompression with biopsy should be reconsidered in cases of suspected ONSM with a complicated differential diagnosis, both for restoration of vision through relief of axoplasmic stasis and for definitive pathologic diagnosis.

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Keywords: Optic Nerve Sheath Meningioma, Optic Nerve Sheath Decompression, Optic Disc Edema

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 24

Isolated Optic Disc Metastasis as the Presenting Sign of Adenocarcinoma of the Lung

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Introduction:

The optic disc is an uncommon location for metastasis and rarely the presenting sign of an underlying malignancy. There were 13 previous cases reported in the literature of lung carcinoma metastatic to the optic disc, however no cases of documented adenocarcinoma of the lung were found with an extensive literature review.^{1,2} Most cases were a result of small cell lung cancer and others lacked pathological details on the type of lung cancer.¹

Methods:

Clinical examination and biopsy of lung lesion.

Results:

A 67-year old woman noticed decreased vision in the right eye (OD) for 3 weeks. She was treated for presumed giant cell arteritis after an optometrist noted disc edema and an elevated ESR of 80mm/h; however, subsequent temporal artery biopsy was negative and she was referred to neuro-ophthalmology. On exam, her visual acuity was 20/40 in each eye with a right relative afferent pupillary defect. Visual field testing revealed an enlarged blind spot and infero-nasal defect OD (MD -7.22dB). Fundoscopy revealed a well-circumscribed white mass with fine blood vessels on its surface originating from the optic nerve head. MRI of the brain demonstrated 4 small enhancing lesions in the parietal lobes and cerebellum. A quest for underlying primary neoplasm was initiated and a CT of the chest revealed a left hilar mass measuring 6cm. A subsequent biopsy of the lesion demonstrated adenocarcinoma of the lung. The patient underwent stereotactic radiotherapy for the brain metastases and systemic therapy with premetrexed-cisplatin. Her vision was closely monitored and at her 6 month follow up she had a decline in her vision to 20/60 with a worsening of her visual field defect (MD -9.18dB). She underwent low-dose stereotactic radiotherapy to the right optic nerve.

Conclusions:

Familiarity with the clinical features of optic disc metastasis can lead to the search for an underlying malignancy and allow for the rapid initiation of treatment at an earlier stage.

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Keywords: Metastasis, Optic Disc, Lung Cancer, Neoplasm, Radiotherapy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 25

Purkinje Cell Antibody (PCA)-2 Positive, Collapsin Response-Mediating Protein-Associated (CRMP)-5 Negative Paraneoplastic Optic Neuropathy

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Introduction:

Purkinje cell antibody (PCA)-2 is a marker of neurological autoimmunity related to cancer that has not been previously associated with visual pathway dysfunction.¹

Methods:

Clinical examination and biopsy of lung lesion.

Results:

A 57-year old female presented to the emergency room with bilateral sequential vision loss. Examination by an ophthalmologist demonstrated bilateral optic disc edema and panuveitis. MRI of the brain revealed several small FLAIR and T2-hyperintensities within the subcortical, deep and periventricular white matter, and corpus callosum. MRI of the spine performed because of suspicion of demyelinating disease was normal but revealed a lung lesion that a subsequent biopsy confirmed as small cell lung cancer. Further workup did not demonstrate any evidence of metastatic disease. The patient underwent 4 rounds of chemotherapy with cisplatin and etoposide, 15 sessions of radiotherapy to the lung area, and 10 sessions of radiotherapy to the brain. She was then referred to neuro-ophthalmology where her examination revealed a visual acuity of 20/25 with superior optic nerve pallor and corresponding inferior altitudinal visual field defects in both eyes. A paraneoplastic panel revealed positive PCA-2 antibody titers (1:64,550) and negative CRMP-5 titers confirmed with western blotting. Extensive workup for other autoimmune, inflammatory and infectious causes of optic neuropathy were negative. The patient continued to do well and was stable 8 months after diagnosis.

Conclusions:

Previous patients positive for PCA-2 presented with limbic encephalitis, cerebellar ataxia, Lambert-Eaton myasthenic syndrome, motor or autonomic neuropathy associated with small cell lung cancer.¹ Although PCA-2 often coexists with CRMP-5, the latter antibody was negative in our patient after she underwent treatment.² Discovery of the PCA-2 antibody in patients with optic disc edema and vitritis may suggest an underlying malignancy, which would allow for early detection and initiation of treatment.

References:

1. Vernino S, Lennon VA. New Purkinje cell antibody (PCA-2): marker of lung cancer-related neurological autoimmunity. *Ann Neurol* 2000;47:297-305.
2. Pittock SJ, Kryzer TJ, Lennon VA. Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. *Ann Neurol* 2004;56:715-719.

Keywords: Paraneoplastic, Optic Neuropathy, Uveitis, Lung Cancer, Autoantibodies

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

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Introduction:

When injury to the optic nerve canal according Rajinikanth MG, 2003, causing compression of blood vessels, which leads to the cessation of nerve impulses, causing blindness. This explains the usefulness of decompression surgery with a combination of conservative and surgical methods. It is believed that decompressive surgery is most advisable to use up to 7 days from date of injury and methylprednisolone injection should be started as soon as was first diagnosed tone. Also showing dekompreyvnnyh to endoscopic operations is the lack of a positive effect from the use of methylprednisolone over 72 hours, during the progressive reduction of corticosteroids or confirmed by CT or MRI signs of compression of the optic nerve blindness

Methods:

We examined 6 patients with compressive lesions of the optic nerve. The most effective was the use of neuroprotective support before, during surgery and in the early postoperative period.

Results:

So the patient, despite the heavy multiple fracture of the lower and outer walls of the orbit with displacement, the crack in the apex of the orbit, low preoperative visual acuity (within 0.04 on the affected side and 0.6 on the opposite side), 3 months after injury visual acuity in both eyes is 1.0.

Conclusions:

Consequently, the use of neuroprotective support for compression of traumatic optic neuropathy caused by fractures of the orbit will help protect the optic nerve from the possibility of re-injury, and improving ways to use it will improve the effectiveness of the treatment as a whole.

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Andrew G. Lee. Clinical Pathways in Neuro-Ophthalmology An Evidence-Based Approach, Second Edition / [Andrew G. Lee, Paul W. Brazis]. – New-York-Stuttgart: Thieme, 2003. – 486 p. Dojcinovic I. O 8-8 complications majeures d'un traumatisme maxillo-facial: neuropathie optique traumatique et mucormycose / Dojcinovic I., Broome M., Richter M. // Revue de Stomatologie et de Chirurgie Maxillo-Faciale. – 2005. - Vol 106 - № SUP4. – P. 33-33. Kountakis S.E. Endoscopic optic nerve decompression for traumatic blindness. / [Kountakis S.E., Maillard A.A., El-Harizi S.M., Longhini L., Urso R.G.] // Otolaryngol. Head Neck Surg. - 2000. – Vol. 123 – P. 34-37. Nau H.E, Gerhard L. Optic nerve trauma: Clinical, electrophysiological and histological remarks. / [Nau H.E, Gerhard L., Foerster M.] // Acta. Neurochir. – Wien, 1987. – 22p. Rajiniganth M. G. Traumatic Optic Neuropathy. Visual Outcome Following Combined Therapy Protocol [Ashley Anne Weaver. Computational Modeling of Eye Trauma for different orbit Anthropometries and Different Projectile Impacts.: Thesis ... Master of science. Biomedical Engineering / Ashley Anne Weaver ; Virginia tech – wake forest university school of biomedical engineering & sciences. - Winston-Salem, North Carolina. – 2010. – 96 p.; Rajiniganth M. G., Ashok K. Gupta, Amod Gupta, Jayapalli Rajiv Bapuraj] / Arch. Otolaryngol., head., neck surg. – Vol. 129. – 2003. – P. 1203-1206.

Keywords: Traumatic Impairment, Optic Nerve, Neuroprotective Therapy, Methylprednisolone, Compression Optic Neuropathy

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 27

A Case of Bilateral Optic Neuritis Due to NMO in the Setting of HIV

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Introduction:

NMO is an autoimmune disorder that causes ON and LETM. HIV is one of the most common causes of acquired immunodeficiency but is not commonly associated with ON. This case highlights a rare HIV patient with acute bilateral optic neuritis due to NMO IgG antibodies.

Methods:

A case study report.

Results:

A 52 year old AA female with HIV presented with sudden acute bilateral vision loss. She first noted sudden vision loss in her left eye and two days later it involved the right eye. The vision loss was associated with left eye pain that was worse with movement. She was hospitalized after she was seen by an ophthalmologist and found to have swollen optic nerves OU. She was treated with three days of IV solumedrol 1000mg with no improvement. One week later, visual acuities were CF OD and HM OS. Pupils were 5mm with no APD. Dilated funduscopic exam still showed mildly swollen ON OU. The patient was readmitted and treated with plasmapheresis. An MRI brain showed diffuse T2 signal abnormality involving the bilateral optic nerves throughout their extension as well as the optic chiasm associated with abnormal enhancement. A spinal tap showed an opening pressure of 18 cm of water. The CSF cultures were negative. PCR for CMV, HSV and VZC were negative. Cryptococcal antigen was negative. Toxoplasmosis IgG antibody was negative. The CSF had 14 white cells (94% lymphocytes), 0 red cells, glucose 48 and protein 79. The IgG synthesis rate was elevated and there were oligoclonal bands present in the CSF that were absent in the serum. HIV RNA PCR was 124 and CD4 count was 736. Serum NMO IgG was 59.4 (normal <1.6). After treatment with plasma exchange and rituximab her vision improved to CF OD and OS.

Conclusions:

This is the fifth reported case of NMO occurring in the setting of HIV. Treatment in these cases is challenging due to the immunosuppressed status of the patients.

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2. Salazar, Cerghet, Shad, Markowitz. NMO-IgG positive relapsing longitudinally extensive transverse myelitis (LETM) in a seropositive HIV patient. Clinical Neurology and Neurosurgery, Volume 115, Pages 1873-1875, 2013.
3. Feyissa, Singh, Smith. Neuromyelitis optica in patients with coexisting human immunodeficiency virus infections. Mult Scler. volume 19. pages1363-6. 2013

Keywords: Neuromyelitis Optica, Optic Neuritis, HIV, Demyelinating Disease, Infectious Disease

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 28

Acute Optic Neuritis Associated with Subdural Hematoma

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Introduction:

A 70-year old man was referred to neuro-ophthalmology for subacute right monocular vision loss. One week prior to evaluation, he developed a dull right peri-orbital headache, which was followed 3-days later by progressive monocular vision loss. A few days before the onset of his headache, a fifth wheel trailer hitch had struck the top of his head without loss of consciousness. He had also traveled the Western United States in the months before presentation, however, he denied any location-specific infectious symptoms. He denied any history of demyelinating disease. Review of systems was positive for stable idiopathic left hearing loss of several years duration.

Methods:

Case report.

Results:

Visual acuity was counts fingers right eye (OD) and 20/25 left eye (OS). Color vision was 0/10 OD and 9/10 OS with a right relative afferent pupillary defect. Extra-ocular movements were full without evidence of nystagmus. Fundus examination of both eyes revealed flat, orange discs with sharp margins and C/D ratio of 0.3. The right eye demonstrated arteriole attenuation with superior arcade venous sheathing without leakage on fluorescein angiogram. Neurologic exam confirmed left hearing loss and wide based gait without cerebellar dysmetria. Contrasted MRI of the brain and orbits was significant for right optic nerve enhancement and subacute bilateral subdural hematomas up to 1.1-centimeters in thickness on the right. Cerebrospinal fluid studies showed a leukocytosis of 5/mm³ (53% lymphocytes) and elevated protein at 92 mg/dL. Serum evaluation for infectious and inflammatory markers was negative. Three weeks after receiving intravenous steroids, visual acuity OD improved to 20/30.

Conclusions:

Subdural hematoma associated optic *neuropathy* has been previously described, but to the authors' knowledge, this is the first reported case of a subdural hematoma associated optic *neuritis*. The exact pathophysiologic mechanism remains elusive, but we postulate that subdural hematomas may trigger a reactive, immune-mediated T-cell response, which may rarely result in optic neuritis.

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Keywords: Optic Neuritis, Subdural Hematoma

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 29
NAION, BRAO, Tumor or All!

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Introduction:

Capillary hemangiomas of the optic disc are vascular hamartomas that may rarely arise from the optic nerve.

Methods:

Case report and review of literature.

Results:

A 61-year-old male presented in August of 2014 for evaluation of persistent right optic nerve swelling. He reported noticing distortion in the superior field of his right eye in October of 2012. He was diagnosed locally with an epiretinal membrane (ERM), and subsequently underwent vitrectomy with ERM membrane peel in May 2013. Post-operative vision did not improve, and exam revealed optic nerve head edema. Humphrey visual field testing revealed a superior altitudinal defect in the right eye, and a normal left field. His local ophthalmologist administered multiple courses of oral prednisone over the course of a year, without improvement in his optic nerve edema and unchanged visual field defect. He underwent multiple neuroimaging studies that were normal. He eventually referred to Neuro-Ophthalmology consultation. Examination revealed 20/25 acuity in the right eye compared to 20/20 in the left. Color perception was normal in each eye, with subtle early release of the right pupil. Dilated ophthalmoscopy revealed a vascular growth of the right optic nerve nasally, with associated inferior pallor and gliosis. Optical Coherence Tomography (OCT) of the right eye exhibited relative inferior altitudinal macular thinning and mild inferior temporal RNFL loss. Fundus fluorescein angiography revealed a vascular optic nerve mass consistent with a capillary hemangioma, with delayed filling of the inferior temporal arterial and venous vasculature.

Conclusions:

Capillary hemangioma of the optic nerve is a rare entity. The hemangioma may cause vision loss by axonal compression, or compromise of the optic nerve and/or retinal vasculature. This case illustrates visual field loss secondary to a combination of these 3 mechanisms. Optic nerve hemangioma should not be confused with other optic nerve pathology such as NAION to avoid unnecessary intervention.

References: None.

Keywords: Hemangioma, NAION, BRAO

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 30**Documented Progression of "Impending NAION" to Permanent Visual Loss**

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Introduction:

The primary risk factor for NAION appears to be a small, crowded optic disc. Asymptomatic disc swelling in patients with this disc appearance has been observed and called "impending NAION" but progression to full-blown disease has not been described. We present 3 cases of documented asymptomatic disc swelling with progression to NAION and permanent vision loss.

Methods:

Retrospective clinical case series

Results:

Case 1: A 69 year-old man with presented with sudden OS vision loss. Visual acuity was 20/20 OD and 20/40 OS with an inferior altitudinal scotoma OS, and normal perimetry OD. Bilateral optic disc swelling with peripapillary hemorrhage was noted. Right optic disc swelling improved slightly 5 weeks later with normal right eye vision, but 6 days later new visual field loss OD and recurrent optic disc swelling OD occurred. Case 2: 7 years after NAION OD, a 52 year-old man presented with transient visual obscuration OS. Visual acuity and perimetry were normal OS with left optic disc swelling and peripapillary hemorrhage. Several days later, he presented with new visual field loss and reduced visual acuity OS and worse optic disc swelling. Within 8 weeks he had permanent visual field defects and optic disc pallor OU. Case 3: A 69 year-old woman had temporal right optic disc swelling with normal visual acuity and visual fields. Fellow eye had "disc at risk." She had sudden onset of vision loss 1 month later, and subsequent exam showed pallor at the site of prior swelling. The left eye now has similar swelling with normal visual function.

Conclusions:

The pathogenesis of non-arteritic anterior ischemic optic neuropathy (NAION) remains uncertain; our case series demonstrates how optic disc swelling without visual acuity or field loss may precede NAION onset by days or weeks. Patients with this presentation may benefit from early intervention once therapeutic agents are available.

References: None.

Keywords: Optic Neuropathy, Visual Fields, Vascular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 31

Leber's Hereditary Optic Neuropathy?

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Introduction:

Leber's hereditary optic neuropathy (LHON) is a mitochondrial disease primarily affecting the optic nerve. Pattern electroretinogram characteristics of LHON include prominent reduction of N95 with a normal P50 component (1). Optical coherence tomography (OCT) typically shows thickening of the retinal nerve fiber layer (RNFL) (2). Here we present a case of LHON with unusual OCT and ERG findings.

Methods:

Review of medical chart.

Results:

An 11 year old girl with normal developmental history presented with decreased vision in the left eye (OS) for 3 months that began after a fainting episode. She denied head trauma, pain, or progression of visual loss. Visual acuity was 20/20 in the right eye (OD) and 4/200 OS. A 3+ afferent pupillary defect and loss of gross colors to 2/4 were seen OS. Intraocular pressures, extraocular motility, and slit lamp exam were normal. Fundus exam showed a 0.6 cup-to-disc ratio with 1+ optic atrophy OS, and a 0.4 cup-to-disc ratio with a pink appearing rim OD. MRI of the orbits, ACE, ANA, NMO-IgG, Lyme, and syphilis testing were negative. LHON teseting revealed a 14484 mutation. She was started on Idebenone 900 mg daily. Follow-up exam 3 years later showed progression of visual loss to counting fingers and temporal pallor of the optic disc OS. OCT showed decreased macular volume wihtout optic atrophy. Inner RNFL thinning was seen and the outer RNFL was intact. Electroretinography showed normal rod function bilaterally but did reveal photoreceptor loss and inner retinal dysfunction, indicative of cone system dysfunction. Pattern electroretinography showed severe reduction of P50 and N95.

Conclusions:

The mixed genetic, OCT, and ERG findings make it unclear whether a retinal or optic nerve pathology is responsible for vision loss in this patient. Among patients with LHON who do not develop RNFL thinning, one should consider macular OCT and ERG testing to evaluate alternative diagnoses.

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Keywords: Leber's Hereditary Optic Neuropathy, LHON, Retinal Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 33

Chiasmal Neuritis in Seropositive Neuromyelitis Optica Spectrum Disease

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Introduction:

Inflammation of the visual pathways affects most commonly the optic nerves, in association with multiple sclerosis, infections and other autoimmune disorders. The aim of this study was to determine the frequency of chiasmal involvement in patients with neuromyelitis optica spectrum disorder (NMOSD).

Methods:

Retrospective study, including patients with chiasmal involvement on clinical and neuroimaging criteria, in a seropositive NMOSD population, seen at our institution between January 2012 and April 2015.

Results:

Among 83 patients with optic neuritis who underwent aquaporin 4 (AQP4) antibody testing, 18 patients were seropositive. Of these, 3 patients (16.7%) showed radiologic and clinical signs of optic chiasm involvement. All 3 patients presented with severe bilateral visual loss of counting fingers or worse visual acuity. Contrast-enhanced magnetic resonance imaging showed enhancement of the optic chiasm in all three patients and contiguous involvement of both optic nerves in two of the patients. In none of the remaining 65 patients who tested negative for AQP4 antibody was optic chiasmal involvement noted, either clinically or on neuroimaging.

Conclusions:

Chiasmal involvement is not uncommon in patients with afferent pathway inflammation associated with seropositive NMOSD. An acute inflammatory chiasmal syndrome may be the presenting sign of NMOSD, prompting specific management.

References: None.

Keywords: Neuro-Ophth and Systemic Disease, Optic Chiasmitis, Neuro-Imaging, Visual Fields, Demyelinating Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 34

CSF-JC Virus PCR-Negative Progressive Multifocal Leukoencephalopathy presenting with Visual Loss

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Introduction:

Progressive Multifocal Leukoencephalopathy (PML) is an infectious demyelinating disease of the brain caused by JC virus.¹ Typically, the diagnosis of PML is established when JC virus DNA is detected in the cerebrospinal fluid (CSF) of a susceptible individual with characteristic clinical and radiological findings. However, CSF-JC virus PCR testing^{1,2} can result in false negatives.

Methods:

A 63-year-old man presented with two months of painless visual loss in both eyes. Just over one year prior to presentation, he was diagnosed with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), and underwent six cycles of chemotherapy with bendamustine and rituximab, ending seven months prior to presentation. His visual acuity was finger counting at 2 feet in the right eye and hand motion in the left eye. His pupils were briskly reactive with no relative afferent pupillary defect. There was very mild optic disc pallor bilaterally. The remainder of his exam was normal.

Results:

A contrasted brain MRI revealed nearly symmetric, bilateral parieto-occipital white matter T2 hyperintensities without mass effect and with mild, mostly peripheral enhancement. There were several small scattered areas of T2 hyperintensity and enhancement in the frontal white matter. CSF analysis showed 0 white blood cells, 69 mg/dL total protein, and 49 mg/dL glucose. By PCR, no DNA was detected in the spinal fluid for JC virus or other viruses. A brain biopsy revealed gliotic areas of brain parenchyma with scattered lymphocytes. SV-40 staining demonstrated nuclear positivity in scattered cells, confirming the presence of JC virus and the diagnosis of PML.

Conclusions:

CSF PCR for JC virus is often considered to be the principal diagnostic test for PML, however it can be negative in the disease^{1,2}. Caution should be taken when excluding the diagnosis on the basis of this test.

References:

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Keywords: Neuro-Ophth and Infectious Disease, Demyelinating Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 35

Left Homonymous Quadrantanopia Due to an Aggressive Culprit

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Introduction:

To report the case of an otherwise healthy 38 year-old male presenting with left homonymous quadrantanopia due to an unusual culprit.

Methods:

This is a case report of a patient presenting to the Ophthalmology emergency room with one month of headaches and subjective blurry vision. The patient denied nausea, vomiting, seizures, or gait imbalances. Vision was 20/25 OU without APD or gaze limitations. The patient was found to have a left homonymous quadrantanopia. Anterior segment examination was unremarkable while the posterior segment was notable for Grade 2 papilledema.

Results:

Imaging demonstrated a large, avidly enhancing, dural based, 5.3 cm x 7.1 cm x 7.0 cm right temporo-parieto-occipital lobe mass, with 1 cm of right-to-left midline shift and transtentorial herniation with mass effect on the brainstem. The patient underwent preoperative embolization of the lesion. He then underwent a craniotomy for presumed meningioma. Pathology, however, showed a WHO grade II hemangiopericytoma. Metastatic workup was significant for a heterogeneously enhancing 1.4 cm liver mass and a 0.9 cm aortocaval lymph node. There were no postoperative complications.

Conclusions:

We report a 38 year old man who presented with left quadrantanopia due to hemangiopericytoma, a relatively rare intracranial soft-tissue sarcoma clinically and radiographically indistinguishable from meningioma. This diagnostic determination can only be made through immunohistochemical study. It is important to distinguish these two entities as hemangiopericytomas tend to recur aggressively and have a high metastatic potential. Hemangiopericytomas are best treated with total resection and adjuvant radiotherapy. These tumors require diligent follow-up by neurosurgery and ophthalmology because of their recurrence potential.

References: None.

Keywords: Tumors, Visual Fields, Neuroimaging, Neuropathology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 36

Pourfour du Petit Precipitated by Neosynephrine Drops

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Introduction:

Reverse Horner's (RHs) or Pourfour du Petit syndrome (PdPs) is a rare. The most common clinical presentations include mydriasis, eyelid retraction, exophthalmos and hyperhidrosis. The pathophysiology of this disorder is not well explained; it is suggested to be secondary to cervical sympathetic chain hyperexcitability, or oculosympathetic spasm.

Methods:

This is a case report and review articles

Results:

A 38 year-old female with no PMH was presented with a 10-year history of intermittent right lid retraction. These events occur once a month with a recent increase in frequency. During this event she gets a tightening sensation of periorbital muscles and significant lid retraction. She is not aware of any pupil enlargement, excessive sweating. Neuro-Ophthalmologic examination was positive for RUL crease was higher OD 11 mm and OS 8 mm. MRD 1 OD 2.0, OS 1.75 mm, MRD 2 OD 8 OS 7. 10 minutes after 2.5 % neosynephrine MRD 1 OD 7 OS 2.5. Pupils were in light OD 2.5mm OS 3.0mm and in dark OD 4.5 mm OS 4.75- 05.0mm. There was no dilation lag and no APD. 30 minutes after 2.5 % neosynephrine pupils OD 5.0 mm and OS 4.0 mm. CTA of neck and brain and MRI of brain and cervical spine to T4 were normal. We reviewed 18 cases with RHs. RHs have been reported following penetrating and non-penetration trauma and in conjunction with mass lesions such as tumors or vascular abnormalities.

Conclusions:

RHs can be precipitated by neosynephrine which might be due to longstanding preganglionic 2nd order neuron dysfunction with transsynaptic degeneration of the 3rd order neuron, leading to denervation supersensitivity or due to a 3rd neuron dysfunction resulting in denervation supersensitivity resulting in a severe lid retraction on the affected side. However there is dysfunction of the sympathetic on the right side the baseline function of the sympathetic nervous system remain intact.

References:

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- 3: Balik V, Kolembus P, Svajdler M, Sulla I, Vaverka M, Hrabalek L. A case report of rapid spontaneous redistribution of acute supratentorial subdural hematoma to the entire spinal subdural space presenting as a Pourfour du Petit syndrome and review of the literature. Clin Neurol Neurosurg. 2013 Jul;115(7):849-52.
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Keywords: Eyelid & Adnexal Disease, Pupils, Neuroimaging, Orbit/Ocular Pathology, Vascular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 37
Seizing to See

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Introduction:

Epilepsy is a spectrum disease with wide variety of neurologic manifestations. We report a case of multifocal epilepsy whose initial manifestation was homonymous hemianopia.

Methods:

Case Report

Results:

We present a 12-year-old boy who initially presented with transient left homonymous hemianopia. His symptoms progressed to complex partial seizures. His MRI brain was normal. After failing numerous anti-epileptic drugs and VNS placement, he had a pre surgical evaluation which showed left temporal lobe seizures. He eventually underwent inferior temporal corticectomy. Complex partial seizures continued even after corticectomy. At 26, he had an evaluation for revision surgery, and was found to have a persistent homonymous visual field defect with seizures. At the epilepsy monitoring unit, he had a focal seizure with bilateral arm posturing and postictal left homonymous defect that lasted 20 minutes. This was confirmed by confrontational testing but not by Humphrey visual field (HVF). Unfortunately, the transient nature of his visual field defect made HVF testing difficult. On EEG, seizures were seen in the right frontal hemisphere, which spread to the right posterior quadrant specifically the occipital lobe followed by attenuation. This precluded him from surgery due to the multifocal sources of his seizures.

Conclusions:

This is a unique case of epilepsy where the seizures are characterized by homonymous hemianopia in addition to complex partial seizures. The semiologic and electrographic features localized the seizures spread to the right posterior quadrant. This case supports the localization value of visual changes in correlation with ictal patterns.

References: None.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 38

Homonymous Ganglion Cell Layer Thinning following Temporal Lobectomy Demonstrating Retrograde Transsynaptic Retinal Degeneration in an Adult Patient with Refractory Seizures

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Introduction:

Optical coherence tomography (OCT) is a non-invasive imaging technique which provides transpupillarily cross-sectional scans of the retina and the optic disc. With the improvement of the resolution of optical coherence tomography, the ganglion cell complex (GCC) has also become routinely accessible in the clinic. Retrograde trans-synaptic degeneration of retinal GCC may result from post-synaptic lesions of the visual pathway.

Methods:

Case report, and review of literature.

Results:

A 53-year-old female reports right superior homonomous field defect sustained during traumatic brain injury with resultant epidural hematoma and left temporal lobectomy 32 years prior to presentation. Her examination revealed visual acuity of 20/20 in each eye with normal color vision and pupillary reactions. Dilated funduscopy revealed healthy appearing optic disks, without frank pallor. Humphrey visual field testing revealed right superior homonomous visual field loss.

Conclusions:

In our case, the damage to the post-synaptic temporal lobe visual axons resulted in a left inferior homonomous GCC thinning noticed on OCT through trans-synaptic retrograde retinal degeneration. The pattern of GCC loss matches with the right superior homonomous visual field loss. This finding supports the use of GCC thickness as an imaging marker of trans-synaptic degeneration in the visual pathway secondary to brain lesions that can help localize the lesion.

References: None.

Keywords: Ganglion, Retina, Seizures

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 39

Bilateral Vision Loss and Optic Tract Edema on MRI after Bilateral Internal Carotid Artery Coil Embolization

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Introduction:

Delayed visual loss after paraophthalmic internal carotid artery (ICA) aneurysm coil embolization has been documented. The putative cause is coil-induced perianeurysmal inflammation affecting the visual pathway^{1,2,3,4}. We present the first case of subacute binocular visual loss associated with striking bilateral optic tract T2/FLAIR hyperintensity.

Methods:

Case Report

Results:

A 41 year-old woman presented with progressive bilateral vision loss starting 2 weeks after right ICA aneurysm coil embolization. Fourteen months earlier, she had undergone left ICA aneurysm coil embolization and placement of a flow-diverting stent without any damage to vision. Previous brain MRI had disclosed no abnormality of the visual pathway. But after right aneurysm coiling, visual acuity dropped to 20/100 OD and 20/80 OS with Humphrey perimetry suggesting bilateral optic tract damage. Brain MRI disclosed coiled suprasellar aneurysms displacing the distal optic chiasm and proximal optic tracts and marked T2/FLAIR hyperintensity of both optic tracts. After high-dose corticosteroid treatment, visual acuity improved to 20/30 OD and 20/25 OS.

Conclusions:

This case adds to the small reported series of visual pathway damage after coil embolization. Our case is unusual in showing T2 signal hyperintensity of both optic tracts. Other reports have described high T2 signal in the optic tract¹, optic nerves², and chiasm². Perianeurysmal inflammation as the cause is suggested by visual improvement after corticosteroid treatment^{1,2,3}. Coated bioactive coils have been implicated, but a similar phenomenon occurs after coiling with bare platinum coils. Vision loss may also be caused by mass effect from enlargement of the aneurysm or coil compaction causing a water hammer effect. Recognition that vision loss is a potential risk of coil embolization is important. Prompt corticosteroid treatment may be critical in reversing it. Alternative approaches include repeat coiling, surgical coil mass extraction, and carotid artery occlusion.

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Keywords: Interventional Neuroradiology, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 40

A Rare Case of Contrast-Related Transient Cortical Blindness

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Introduction:

Neurotoxicity from contrast agents is a rare complication of angiographic procedures. Reported clinical effects include transient cortical blindness, encephalopathy, seizures, and focal neurologic deficits. Imaging may show enhancement in the occipital lobes of patients with cortical blindness due to contrast deposition in the tissue. Most cases return to baseline visual function within a few days.

Methods:

Case report and review of the literature.

Results:

A 50 year old woman presented to the emergency department with worsening headaches, where imaging revealed a large basilar artery tip aneurysm. She underwent dual crossing-Y stent construct and embolic coiling with neurosurgery. The morning after the procedure she reported bilateral vision loss. Initial ophthalmologic exam found generally depressed visual fields and light perception vision. CT brain, MRI brain, and repeat angiogram showed scattered embolic changes throughout both cerebral hemispheres, but did not identify a lesion that explained the severe visual deficits. Vision rapidly improved over the next four days with intravenous fluids and dexamethasone, but visual fields continued to show checkerboard defect. At four-week follow-up, visual acuity was 20/25 OU and visual fields were full.

Conclusions:

We present a case of transient cortical blindness following endovascular basilar aneurysm repair. Posterior circulation intervention has the highest risk of this rare complication. This case was unique due to a lack of imaging changes that correlated with the vision loss, either due to ischemia or the reversible encephalopathy syndrome related to contrast deposition. Hyperosmotic contrast agents may cause fluid shifts that disrupt the blood-brain barrier and allow contrast deposition in the brain tissue, leading to cerebral edema. Our patient's procedure was performed with an isosmolar agent (iodixanol) diluted with saline. Other etiologies leading to a disrupted blood-brain barrier must be considered, such as a reperfusion syndrome due to redirected blood flow from the large aneurysm.

References:

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Keywords: Interventional Neuroradiology, Higher Visual Cortical Functions, Vascular Disorders, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 41

Cilioretinal Artery Occlusion: A Rare Complication of Severe Papilledema

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Introduction:

Central vision loss in the setting of papilledema can result from optic neuropathy, macular pathology (e.g., subretinal fluid, choroidal folds), or a combination of optic neuropathy and macular pathology.¹ The central vision loss is largely reversible when due to macular pathology, whereas it is not reversible when due to optic neuropathy.¹ We report 3 patients who developed irreversible central vision loss due to cilioretinal artery occlusion associated with severe papilledema in the setting of idiopathic intracranial hypertension (IIH).

Methods:

A retrospective review of our database of patients with IIH identified 3 patients with central vision loss in one eye due to cilioretinal artery occlusion. All patients were assessed with kinetic or static perimetry, fundus photography, optical coherence tomography (OCT) of the optic disc and macula, and fluorescein angiography. One patient was also studied with laser speckle blood flowgraphy imaging.

Results:

All three patients had an arcuate visual field defect corresponding to the distribution of the cilioretinal artery in the affected eye. In all cases, the cilioretinal artery occlusion occurred in the setting of severe papilledema (modified Frisen grade III or higher). In all cases, the visual field defect was permanent.

Conclusions:

Cilioretinal artery occlusion is rarely reported as a complication of papilledema.^{2,3} Approximately 20% of the population has a cilioretinal artery, which arises from the short posterior ciliary arteries rather than the central retinal artery.³ We propose that cilioretinal artery occlusion might result from compression of the cilioretinal artery by the edematous retinal nerve fiber layer or decreased perfusion of blood from the cilioretinal artery due to increased venous pressure^{2,3}, similar to the mechanism in venous stasis retinopathy⁵.

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Keywords: High Intracranial Pressure, Pseudotumor Cerebri, Vascular Disorders

Financial Disclosures: Dr. Randy Kardon's Grant Support includes: Veterans Administration (Rehab R&D):C9251-C, 1I01RX000889-01A1, PT120517-56 Department of Defense (DOD): W81XWH-10-1-0736, W18XWH-10-1-0561 NIH: 1R01EY023279-01 Novartis: OCTiMS. No other authors have any financial disclosures

Grant Support: Veterans Administration (Rehab R&D):C9251-C, 1I01RX000889-01A1, PT120517-56, Department of Defense (DOD): W81XWH-10-1-0736, W18XWH-10-1-0561, NIH: 1R01EY023279-01, Novartis: OCTiMS

Poster 42**To Be or Not To Be, IIH is the Question**

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Introduction:

Idiopathic intracranial hypertension (IIH) is mainly characterized by headaches and elevated intracranial pressure with normal cerebrospinal fluid (CSF) content. Moreover, brain and orbit magnetic resonance imaging studies image are invariably unremarkable. Typically, patients with IIH present clinical signs and symptoms that differ from conditions that mimic disc edema or other secondary cause of nerve swelling. However, in patients lacking definite clinical criteria this may be a difficult task; particularly cases were absence of true optic nerve edema is a differential diagnosis. Optic nerve head drusen (ONHD) can pose a diagnostic challenge in cases of suspected disc edema without symptoms. Nonetheless, despite similarities in optic nerve head appearance, etiology and visual outcome of these two conditions is quite different.

Methods:

A 37 year old obese female with hypertension and hypothyroidism presents for a routine eye examination. Although mainly asymptomatic, she does report occasional frontal headaches. She has a pre-existing diagnosis of pseudopapilledema secondary to ONHD. Examination is unremarkable except for tilted discs along with superior and inferior blur disc margins, but without evidence of ONHD. Bilateral optic disc elevation is observed with optical coherence tomography (OCT), but presence of ONHD is not clearly delineated. Given patient's profile and clinical findings the diagnosis of IIH cannot be disregarded and further diagnostic work up is warranted.

Results:

No abnormalities on brain MRI, with and without contrast. Bilateral scleral flattening is noted in axial T2 weighted images (WI) of orbits. MRV is normal. Opening pressure of 35 cm H₂O with normal CSF composition is obtained. Diagnosis of IIH is recognized and oral acetazolamide treatment is started.

Conclusions:

The case accentuates the importance of a detailed history and thorough examination before consenting to the diagnosis of pseudopapilledema, which led to the suspicion of IIH.

References: None.

Keywords: Neuroimaging, Pseudotumor Cerebri, OCT, High Intracranial Pressure, Headache

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 43

Pseudo-Susac Syndrome Due to Elevated Intracranial Pressure

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Introduction:

We present a complicated case of autonomic instability, quadriplegia and encephalopathy followed by vision loss and hearing loss to illustrate the potential morbidity of secondary elevations of intracranial pressure (ICP).

Methods:

Case report and review of the literature

Results:

A previously healthy 44-year-old male acutely developed tachycardia, hypertension, headaches, confusion, hallucinations, flaccid quadriplegia, bowel and bladder incontinence. Within one month he had acute bilateral visual loss, followed by acute bilateral hearing loss. Outside work-up included unrevealing brain MRI, C-spine MRI, bland CSF and extensive normal blood work. EMG showed axonal degeneration. He was treated with plasma exchange for presumed auto-immune etiology with moderate improvement of both mental status and quadriplegia, but neither vision nor hearing. Upon presentation to our institution four months later visual acuity was NLP in both eyes with exam findings of bilateral central retinal vein occlusions (CRVO) and chronic atrophic papilledema. MRI showed non-enhancing T2 signal in both optic nerves, increased optic nerve sheath width, and bilateral meningoceles in the tegmen tympani extending into the petrous apices and inner ear cavities. MR venography showed narrowing of multiple dural venous sinuses. Lumbar puncture opening pressure was 42 cm H₂O and CSF was bland. He was treated with intravenous immunoglobulin and methylprednisolone for presumed ongoing autoimmune contribution to his illness. He underwent ventriculoperitoneal shunt (VPS) placement with rapid mild improvement of hearing, but not vision. Digital subtraction angiogram showed complete reconstitution of flow in cerebral veins and normalization of their diameters. One week after VPS placement optic disc swelling had resolved and audiometry testing had improved.

Conclusions:

Elevated intracranial pressure presumed secondary to neuro-inflammatory disease accounts for sensorineural hearing loss, papilledema, CRVO and dural venous sinus narrowing in our patient. It is important for physicians to be aware that elevated ICP can cause both hearing and vision loss.

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Keywords: Idiopathic Intracranial Hypertension, Central Retinal Vein Occlusion, Hearing Loss, Papilledema, Meningocele

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 44

Acquired Tonsillar Ectopia in a Case of Pseudotumor Cerebri

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Introduction:

The development of tonsillar descent is a rare but reported complication after lumboperitoneal shunting in pseudotumor cerebri. Fatal tonsillar herniation following lumbar puncture(LP) has also been rarely reported in pseudotumor cerebri. We report a case of pseudotumor cerebri with a minor tonsillar descent who developed worsening of the descent after repeated lumbar punctures.

Methods:

A single case report and review of literature.

Results:

41 year old Caucasian woman with headache and papilledema was diagnosed with pseudotumor cerebri when she had unremarkable brain MRI (except minor tonsillar ectopia <4 mm), unremarkable MR venogram and an opening pressure of 29 cm H₂O on LP with normal CSF contents. She had stable visual functions following medical management with acetazolamide- visual acuity 20/20 OU, grade 1 papilledema OU and scattered peripheral defects on perimetry with MD <3 db. However she had mild metabolic acidosis. Attempts to wean acetazolamide led to return of headaches. Repeat LPs performed as temporizing measures showed opening pressures above 30 cm of H₂O but with normal CSF contents.

4 years later when she reported occipital headache worsening with cough and an unsteady gait repeat brain MRI showed worsened tonsillar descent 8 mm below the foramen magnum. Repeat MR venogram showed severe right mid transverse sinus focal stenosis and long segment of pronounced stenosis in the left transverse sinus. She underwent suboccipital craniectomy and C1 laminectomy which stabilized her symptoms.

Conclusions:

This report highlights an unusual and rare presentation of acquired tonsillar descent in pseudotumor cerebri. Metabolic acidosis has led to fatal tonsillar herniation following LP in pseudotumor cerebri. We believe that repeated LPs and metabolic acidosis with a contribution from intracranial hypertension might have led to the tonsillar descent. Fortunately this was recognized before it became fatal

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Keywords: Tonsillar Ectopia, Pseudotumor Cerebri, Lumbar Puncture, Papilledema

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 45

A Case of Perineural Invasion from Squamous Cell Carcinoma

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Introduction:

Squamous cell carcinoma (SCC) is the second most common cutaneous malignancy, accounting for 5% to 10% of periocular cutaneous tumors (1). Literature on SCC with perineural invasion (PNI) is scarce (2). Incidence ranges from 2.6 to 43.4% (3,4). Typical features for SCC with PNI are older patients, with recurrent and/or multiple incompletely excised SCC. Two groups of patients with PNI have been described: one without neurological symptoms (incidental finding on histological examination) and a second group with clinical symptoms of damaged nerves, which has an increased risk of local recurrence and regional and distant metastases (2,5). MRI provides the most sensitive radiographic methodology to detect PNI (6). Management guidelines for PNI are evolving. Radiotherapy for the potential proximal and distal extent of involvement is the mainstay of treatment. Combined chemo-radiotherapy has shown improved outcome in bulky disease. Role of surgery is mostly diagnostic (biopsy) and palliative (7).

Methods:

Single Case Report

Results:

A 65 year-old man presented with 45 day long permanent diplopia. He brought a previous orbital MRI which showed a supraorbital tumor that involved orbital soft tissues. Examination revealed left hemicranial anesthesia, a supraciliary tumor, and an abduction restriction in the left eye. A new MRI was ordered. It showed a left supratroclear tumor, with perineural dissemination through the supraorbital nerve that reached Meckel's cavum, and involvement of the cavernous sinus lateral wall. Left lateral muscle was atrophic. Biopsy revealed SCC infiltration. Chemotherapy and radiotherapy were provided.

Conclusions:

PNI from SCC should be considered in the presence of an orbital tumor in association with sensory deficit and diplopia. Even though MRI provides the most sensitive radiographic methodology to detect it, PNI may still be present without neuroimaging evidence. The importance of such diagnosis relies on poorer prognosis PNI implies.

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Keywords: Perineural, Invasion, Squamous, Cell, Carcinoma

Financial Disclosures: The authors had no disclosures.

Grant Support: None

Poster 46**Juvenile Nasopharyngeal Angiofibroma with Intracranial Extension**

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Introduction:

Juvenile nasopharyngeal angiofibroma (JNA), the most common benign tumor of the nasopharynx, accounts for 0.5% of all head and neck neoplasms. This vascular tumor is found in adolescent males. Its aggressive local growth may lead to paranasal sinus, orbital and intracranial extension, even without detectable clinical signs and symptoms (1). Ocular findings are uncommon (2). Exophthalmos (14%), decreased vision (5%) partial ophthalmoplegia (2%), and facial deformities were reported (1). Diagnosis is based on clinical findings and neuroimaging (3). Pre-operative angiography should be routinely performed, and tumor feeder vessels embolized before tumor resection (4). Treatment of choice is surgical excision, combined with radiotherapy in large tumors. Cure ranges between 70 and 100%. (2,4). Follow-up is mandatory due to high relapse rate (3, 4).

Methods:

Single Case Report

Results:

A 20 year old man presented with a 6 year vision loss of the left eye after the second embolization prior to resection of JNA. Ocular evaluation revealed a normal right eye, and light perception with an afferent pupillary defect on left eye. On external examination prominence of the nose and left cheek, and monocular exophthalmos were observed. Fundus of left eye showed a pale disc. OCT of left eye showed a peripapillary retinal nerve fiber layer thickness significantly decreased. MRI showed injury centered in the left pterygopalatine fossa, and extended infiltrating the extraconal orbital space (proptosis of the eyeball), and ipsilateral masticatory parapharyngeal space, cavum, both nostrils and skull base. It also extended to the endocranium in the suprasellar cistern, with compression of the optic chiasm and affection of both carotid cavernous sinuses.

Conclusions:

JNA may produce significant ocular complications due to orbital or intracranial extension, including exophthalmos, optic atrophy and ocular motor palsy. Early diagnosis, interdisciplinary evaluation and treatment are needed in order to improve prognosis.

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Keywords: Juvenile, Nasopharyngeal, Angiofibroma, Intracranial, Extension

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 47**Choroidal Folds Secondary to Cavernous Hemangioma**

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Introduction:

Choroidal folds are associated with papilledema, hypotony, thyroid disease, and inflammation of the orbit. However, little is known about its association with orbital tumors and its prognosis after tumor resection. Our purpose is to describe a case of choroidal folds and its associated findings caused by an orbital cavernous hemangioma.

Methods:

We followed a patient diagnosed with an intraconal cavernous hemangioma of the left orbit and conducted diagnostic studies including multifocal ERG, OCT, visual fields, and fundus photography. The patient underwent surgical resection of the hemangioma, and the same studies were conducted post-operatively to compare the results.

Results:Pre-operative:

Visual acuity was 20/25 OD, 20/250 and 20/80 with pinhole OS. OCT of the left eye showed thickening of the macula and choroidal folds, which appeared as light and dark parallel lines in the temporal retina and macula. Multifocal ERG showed decreased amplitudes in the left eye. Post-operative:

Visual acuity was 20/40 and 20/20 with pinhole OD, and 20/200 and 20/25 with pinhole OS. OCT of the left eye showed choroidal folds and improvement of macular thickening. Multifocal ERG showed a 46% improvement in the average amplitudes.

Conclusions:

In this patient, an orbital cavernous hemangioma led to the development of choroidal folds, which resulted in vision loss likely due to the effect of choroidal folds on the neurosensory retina. Additionally, the vision was almost certainly affected by hyperopic shift as a result of the intraconal location of the tumor. However, the difference in pre- and post-operative pinhole acuity demonstrates a difference in potential acuity which is not fully explained by resolution of a hyperopic shift. Resection of the tumor via anterior orbitotomy showed improvement in vision, but the choroidal folds remained and the vision was not restored completely at one month follow-up.

References: None.

Keywords: Diagnostic Tests, Mferg, Retina, Tumors, Orbit, Orbit/Ocular Pathology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 48**High Definition Fiber Tractography of a Giant Macroadenoma**

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Introduction:

High-definition fiber tracking (HDFT) is a novel method of neuroimaging post-processing that allows precise delineation of white matter fibers in the anterior and posterior visual pathway. This technique contributes to pre-operative planning for resection of large sellar lesions.

Methods:

Case report and review of literature.

Results:

A previously healthy 37 year old man presented with three months of progressive loss of peripheral vision and headaches which persisted despite wisdom teeth extraction. He presented for urgent Ophthalmology examination complaining of two days of horizontal binocular diplopia. Examination revealed acuity of 20/30- in each eye, with a prominent right afferent pupillary defect (APD). Motility exam revealed decreased abduction bilaterally. Dilated ophthalmoscopy revealed bilateral optic disk pallor. Formal visual fields revealed a complete bitemporal hemianopsia. MRI of the skull base identified a large, 6.4 cm sellar and suprasellar mass with enlarged sella turcica, invasion of the sphenoid sinus and complete encasement of both parasellar internal carotid arteries. HDFT was performed and imaging reviewed prior to endoscopic endonasal approach to anterior, posterior, and bilateral middle skull base and bilateral cavernous sinus tumor removal with reconstruction and vascularized nasal flap, using stereotactic image guidance. Biopsy revealed a sparsely granulated growth hormone producing pituitary macroadenoma, with characteristic keratin staining pattern. Visual fields 12 days post op revealed significant improvement in bitemporal field loss.

Conclusions:

High-definition fiber tracking (HDFT) delineates white matter fibers in the anterior and posterior visual pathway. The identification of disruption of optic nerve, tract, and chiasmal fibers by sellar tumors contributes to significant post-operative improvement in visual fields and visual function.

References:

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Keywords: NeuroImaging, Skull Base, Tumors, Optic Neuropathy, Visual Fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 49**Double Vision Followed By Oscillopsia**

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Introduction:

To report and review MRI and a case presented with double vision followed by oscillopsia

Methods:

This is a descriptive case report based on clinical records, patient observation and analysis of diagnostic studies.

Results:

A 35-year-old right handed man presented to Neuro-Ophthalmology clinic with double vision after the recent brain surgery. The patient had medical history of von Hippel-Lindau disease, cerebellar hemangioblastoma and surgical history of two resections of cerebellar hemangioblastoma and ventriculoperitoneal shunt placement. On examination at 3 months after the last surgery, the patient had good visual sensory function in both eyes and the finding showed limitation of infraduction (about 30% of normal) on adduction in the right eye and 4 prism diopter hypertropia which followed three steps test with excyclotorsion on Double Maddox Rod test, which were suggestive of fourth cranial nerve palsy in the right eye. On seven months after the surgery, MRI T2/FLAIR showed increased signal in the left pons which was suggestive of hypertrophic olivary nucleus in the left. On twelve months after the surgery, the patient complained of oscillopsia and examination showed vertical pendular nystagmus with palatal myoclonus.

Conclusions:

This is a case of fourth cranial nerve palsy followed by oculopalatal myoclonus. The patient developed oscillopsia and palatal myoclonus after the latent period of about 12 months. The signal change in MRI suggesting hypertrophic olivary nucleus was observed prior the clinical symptoms and signs. The development of oculopalatal myoclonus should not be mistaken for recurrence of tumor or stroke.

References: None.

Keywords: Neuroimaging, Nystagmus, Ocular Motility

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 50

Transcranial Orbitotomy After Superselective Coil Embolization Sacrifice of Intracranial Ophthalmic Artery Preserves Vision in Resection of Recurrent Large Orbital Apex Solitary Fibrous Tumor, Via Collateral Retrograde Orbital Circulation

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Introduction:

We report the case details of a 51-year-old male with a recurrent, progressive solitary fibrous tumor (SFT), engulfing proximal ophthalmic artery, and the pre-operative endovascular and surgical methods that promoted preservation of vision despite sacrifice of the ophthalmic artery.

Methods:

A retrospective and radiographic chart review

Results:

The SFT (1.7cm X 1.2 cm X 1.1 cm), originally resected via Kronlein orbitotomy, recurred 39 months after resection (9.9 mm X 6.8 mm X 7.9mm) growing over 26 months (2.9cm X 2.0cm X 1.65 cm). Super-selective endovascular coil embolization occluded the intracranial ophthalmic artery immediately distal to its C6 intracranial origin, and resulted in retrograde ophthalmic artery filling through ECA and ICA collateral vessels, maintaining CRA filling. Post-angiographic neuro-ophthalmic examination revealed no change in ocular motility, vision and visual field. One week later, the tumor was excised via right frontal pterional craniotomy with lateral orbitotomy, extended transfacial muscle (temporalis) dissection, and transcranial orbital dissection. The approach provided excellent direct visualization of the tumor from orbital apex to globe, minimized the difficulty of operating in the previously scarred lateral operative bed, and allowed gross total resection. Despite intraoperative sacrifice of the tumor-encased proximal orbital segment of ophthalmic artery and meningo-lacrimal branch, CRA filling was maintained via other ECA and ICA collaterals despite sacrifice of the major lateral collaterals and the patient retained normal vision and visual field. Transient abduction deficit was readily explained by post-operative muscle edema, and a partial frontal branch facial nerve palsy was transient and continues to improve.

Conclusions:

Extended transcranial orbitotomy and super-selective angio-embolization are valuable techniques that may promote favorable outcomes in deep orbital surgery of lesions affecting the orbital apex, by relying on collateral circulation than may maintain retrograde ophthalmic artery and thereby CRA flow.

References: None.

Keywords: Solitary Fibrous Tumor, Transcranial Orbitotomy, Ophthalmic Artery, Retrograde Filling, Collateral Circulation

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 51

An Unusual Orbital Foreign Body

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Introduction:

Needlefish are slender fish with pointy beaklike jaws. In this report we describe a patient in whom a needle fish lodged the tip of its jaw in his optic canal.

Methods:

Case report.

Results:

A 53 year-old male, scuba diving off the coast of the United Arab Emirates (UAE), surfaced and removed his mask. A needlefish jumped out of the water, piercing his left medial canthus and upper eyelid. He immediately lost his vision. Computed tomography obtained at a local emergency room demonstrated a bony foreign body within the orbit apex. He underwent emergent "cleaning out". No foreign material was noted to have been found. He was given a three week course of prophylactic antibiotics and presented to our institute one month following injury. At that time he reported no light perception OS. There was a scar extending from the medial canthus to the upper eyelid margin. Ocular motility was abnormal with reduction in supraduction (50%) and adduction (25%). Exophthalmometry measurements were symmetric at 21 OU. IOP was normal and symmetric. Slit lamp evaluation was unremarkable. Funduscopy evaluation was notable for optic atrophy OS, and otherwise normal (Figure 1). Magnetic resonance imaging (MRI) indistinctly demonstrated the fish jaw extending through the left optic canal into the prechiasmatic suprasellar cistern with the left optic nerve displaced inferomedially. No other abnormality was identified. Due to the location of the jaw with intracranial extension, and improbability of visual recovery no further intervention was recommended. The patient remained in stable condition when last contacted three months following injury.

Conclusions:

This case demonstrates the radiographic appearance (MRI and CT) of an unusual injury: a needle fish jaw lodged in the optic canal. This case is also important in that it demonstrates that such cases can be managed without removal of the foreign body.

References: None.

Keywords: Orbital Foreign Body, Trauma, Fish, Optic Nerve, Imaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 52

Multifocal ERG in MEWDS and BRAO

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Introduction:

Spectral domain optical coherence tomography (SD-OCT) has become the most widely available and easily accessible retinal imaging technique in ophthalmology. In the era of SD-OCT, multifocal electroretinogram (mERG) still has value especially in cases where the retina appears normal or cannot be well visualized.

Methods:

Case series.

Results:

Case 1. 31-year-old woman with acute, painless, visual loss in the right eye (OD) associated with photopsias and nyctalopia. She has no medical history and takes no medications. Her examination shows an acuity of 20/40 OD and 20/20 in the left eye (OS), normal color vision in both eyes (OU). The visual field shows a temporal superior scotoma OS. Pupils are normally reactive without an RAPD. Ocular motility is normal. The fundus appears normal, and a mERG shows a defect which corresponds to the visual field abnormality OS in keeping with multiple evanescent white dot syndrome (MEWDS). Case 2. 69-year-old woman experiences positive visual phenomena OS for 2 days with a resultant scotoma OS. Her medical history includes a uveal melanoma OD with an ocular prosthesis in that eye, AMD, renal failure and dyslipidemia. Her examination shows normal acuity and color vision OS. The visual field exhibits a nasal superior scotoma OS. The left pupil is normally reactive. Ocular motility is normal OS. The fundus shows dry AMD changes with numerous small and intermediate sized drusen intermixed with an area of retinal whitening inferiorly. The mERG shows a defect which corresponds to the visual field and the area of retinal whitening, in keeping with a branch retinal artery occlusion (BRAO).

Conclusions:

In addition to SD-OCT, mERG remains an important technique in detecting retinal pathology particularly in its ability to specifically localize and correlate the retinal defect with the visual field.

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Keywords: mERG, SD-OCT, BRAO, MEWDS, Scotoma

Financial Disclosures: The authors had no disclosures.

Grant Support: This work is supported in part by an unrestricted grant from the Research to Prevent Blindness, Inc. N.Y., N.Y.

Poster 53

Myocarditis and Arteritic Anterior Ischemic Optic Neuropathy Secondary to Giant Cell Arteritis

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Introduction:

Giant cell arteritis (GCA) is a primary vasculitis of medium and large vessels with a broad range of clinical presentations. Myocarditis is a rare known manifestation of GCA. We present a case of a 67 year old man who presented with acute systolic heart failure of unknown etiology. Development of arteritic anterior ischemic optic neuropathy lead to the diagnosis of myocarditis secondary to GCA.

Methods:

Case Report

Results:

A 67 year old man with a history of asthma, migraine, post-polio syndrome, and hepatitis B complained of new dizziness and fatigue after sustaining a tick bite. After empiric treatment with doxycycline for tick borne illness he developed an intractable headache with intermittent vertical binocular diplopia. Outside CSF studies, brain MRI, tick borne illness laboratory investigation, and ophthalmological examination were reportedly normal. One month later he developed acute chest pain and was found to be in atrial fibrillation with rapid ventricular response with elevated troponins. His initial transthoracic echocardiogram was normal, but two days later repeat exam revealed marked systolic heart failure. CT chest revealed mediastinal and hilar adenopathy. He was transferred to our institution for evaluation for presumed myocarditis. A cardiac MRI did not show signs of myocarditis so alternative diagnoses were pursued. Bronchoscopy was non-diagnostic. He developed sudden painless loss of vision in his left eye with elevated platelets, ESR, and CRP and was started on systemic steroids with improvement of his vision. Temporal artery biopsy revealed findings consistent with GCA. Cardiac PET revealed diffuse FDG uptake consistent with myocarditis and a diagnosis of myocarditis secondary to GCA was made.

Conclusions:

Myocarditis is a rare manifestation of giant cell arteritis. In this case, the cause of acute systolic heart failure was determined based on neuro-ophthalmologic findings.

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Keywords: Giant Cell Arteritis, Arteritic Ischemic Optic Neuropathy, Myocarditis, Headache

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 54**Creutzfeldt-Jakob Disease an Important Differential Diagnosis of Progressive Supranuclear Palsy**

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Introduction:

Creutzfeldt–Jakob disease (CJD) is a prion disorder characterized by rapidly progressive dementia, myoclonus, ataxia, visual disorientation, and motor dysfunction. Criteria for diagnosis of CJD include CSF markers, 14-3-3 and tau, EEG and MRI.

Methods:

Single case report

Results:

A 71 year-old man presented with left veering ambulation and mild left leg weakness. Lumbar spine MRI and EMG were unremarkable. One month later he noticed intermittent horizontal diplopia, a 10-pound weight loss, worsening handwriting and worsening left sided weakness. There were no behavioral changes. Visual acuity was 20/25 OU, HVF 24-2 revealed superior arcuate defects consistent with symmetric thinning of the optic disc OU. He had normal anterior segments, pupillary reactions, IOP and fundi OU. He had convergence insufficiency, reduced vertical more than horizontal saccades. Strength was 5/5 throughout with 4/5 quadriceps on the left. Reflexes were decreased throughout. There was dysmetria. His gait was shuffling. He had mild memory impairment and no disinhibition. Myoclonic jerks were noted when he was asleep. Antibodies to gm1, gd1a and gd1b in the CSF were positive and paraneoplastic panel was negative. EEG showed bitemporal slowing. He was treated with 5 days of IV methylprednisolone followed by 60mg prednisone for concern of encephalitis. He developed worsening memory and was treated with IVIG for 5 days. The patient continued to decline and developed visual hallucinations. MRI revealed DWI positivity in the bilateral basal ganglia, thalamus and anterior gray matter. CSF 14-3-3 and tau were highly elevated. He was given a likely diagnosis of CJD. The family declined brain biopsy. He passed away three weeks.

Conclusions:

CJD has been misdiagnosed as Progressive Supranuclear Palsy. Diplopia is a common complaint in early CJD, most commonly due to abnormalities of vertical gaze. Given the rapid decline of these patients it is essential to diagnosis CJD as early as possible to provide the family and patient with the time required to absorb this diagnosis.

References: None.

Keywords: Creutzfeldt-Jakob, Progressive Supranuclear Palsy, Diplopia

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 55

A Case of HSV-2 Presenting with Encephalomyelitis and Diffuse White Matter Lesions

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Introduction:

Disseminated HSV-2 presenting with a relapsing, protracted, encephalomyelitis has not been well described.

Methods:

Case report from a tertiary medical center.

Results:

A 39 year-old woman, 8 months post-partum, presented with 3 weeks of progressive leg numbness. Exam showed bilateral mild iliopsoas weakness and patchy leg numbness. She had also noted mild hearing loss. MRI revealed scattered periventricular white matter lesions and enhancing spinal cord lesions. She was treated with IV steroids. A week later she developed right-sided hearing loss and vertigo, a positive head impulse test, and right cochlear enhancement on repeat MRI. Days later, she developed a diffuse morbiliform and vesicular rash, and was treated with one week of IV acyclovir. CSF revealed a lymphocytic pleocytosis with elevated protein, PCR was negative for HSV-1 and VZV and positive for HSV-2 with elevated IgM (1.15 IV) and IGG titers (27.91 IV, reference range <0.8 IV). She then developed leg numbness, worsening vertigo and gait imbalance. Repeat MRI showed new atypical appearing subcortical, pontine and cerebellar T2 lesions. She was treated with 6 weeks of IV acyclovir, plasmapheresis and IVIG. She was found to have low natural killer (NK) cells (47 cells/uL, reference range 59-401) that later returned to normal. Clinically, she has become less ataxic, and CSF studies have demonstrated declining HSV-2 antibody titers.

Conclusions:

An unexplained relapsing course of atypical white matter brain and spinal cord lesions may rarely complicate HSV-2 encephalomyelitis, and is exceedingly rare in immunocompetent adults.¹ Steroids may suppress NK cell levels,² which are known for their innate defense against herpesvirus infections.³ It is likely that the combination of transient steroid-induced immunosuppression as well as the post-partum state allowed the virus to flourish and widely disseminate.^{4,5}

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Keywords: HSV-2, Encephalomyelitis, Head-Impulse Test, Immunodeficiency, Natural Killer

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Relapsing Polychondritis Causing Inflammatory Optic Neuropathy, a Case Report

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Introduction:

Relapsing Polychondritis (RP) is a severe, episodic, and progressive systemic inflammatory condition involving cartilaginous structures of the eyes, ears, nose, and laryngotracheobronchial tree.^{1,2} It is potentially fatal disease, that often goes misdiagnosed and mismanaged, that can cause wide-spread systemic manifestations including irreversible vision loss.^{1,2} Our goal is to elucidate this rare condition as it relates to the ophthalmic care of patients and provide a clinic vignette illustrating the clinical presentation, diagnosis and management of a patient with RP.

Methods:

A 62-year-old man with no significant ocular history presented with painful and itchy eyes as well as flashes and floaters in both eyes for 2 days. He had also noted red, swollen ears over the same time frame. He had recently suffered from a bout of pneumonia, which was treated with oral antibiotics and steroids. His visual acuity and color vision were normal, but automated perimetry revealed bilateral visual field constriction. He had trace conjunctival injection, 1+ anterior chamber inflammation, and bilateral optic disc edema.

Results:

Cranial MRI and MRV were unremarkable, including no stigmata of increased intracranial pressure. His serologic workup was unremarkable except for an elevated sedimentation rate, C-reactive protein, and positive rheumatoid factor. He was started on high dose oral steroids, which resulted in significantly improved vision, discomfort, and redness of the eyes and ears. He was then started on methotrexate and the prednisone was tapered accordingly.

Conclusions:

In review articles of patients with RP, the average elapsed time from patient presentation to correct diagnosis was 2.9 years, with one third of patients being evaluated by 5 or more physicians before receiving appropriate treatment.^{1,3,4} Despite these challenges, prompt diagnosis is of the utmost importance as treatment with systemic steroids and immunomodulators can preserve vision and prevent potentially fatal damage to major organ systems.

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Keywords: Relapsing Polychondritis, Optic Disc Edema, Uveitis, Red Ears, Episcleritis/Scleritis

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 57
Double Take

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Introduction:

A 13 year old Afghani boy was referred with an apparent isolated optic nerve sheath meningioma. The outside imaging report stated that “intracranial contents appear normal”. A careful dilated fundus exam, however, uncovered an epiretinal membrane in the left eye and lesions resembling retinal astrocytic hamartomas in the right eye. These associated findings alerted us to a possible underlying systemic diagnosis of neurofibromatosis type 2 (NF2) and prompted a review of the original MRI images. Upon re-reading by a neuro-radiologist, bilateral trigeminal and vestibular schwannomas were identified, establishing a provisional diagnosis of NF2 by the Manchester Criteria (1).

Methods:

Subsequent investigations included an audiogram, imaging of the entire CNS, and genetic testing. The audiogram was normal. The MRI spine revealed a very large paraspinal mass (70 mm x 65 mm x 87 mm) with intradural extension into the spinal canal. An biopsy was done, and the paraspinal mass was pathologically confirmed as a WHO grade I schwannoma. Genetic testing identified a truncating mutation in exon 1 of the NF2 gene. The patient has since been enrolled in a multi-disciplinary surveillance program headed by neuro-oncology.

Results:

This case represents a ‘near miss’ for delayed diagnosis of NF2. The original MRI report was falsely reassuring, identifying only the orbital tumour, and missing multiple intracranial tumours pathognomonic for NF2. Furthermore, our patient lacked the most common ophthalmic association of NF2 (cataract), and exhibited findings that were either non-specific (epiretinal membrane), or very subtle (retinal astrocytic hamartomas). Finally, despite harbouring multiple intracranial tumours and a large paraspinal tumour, he was neurologically intact.

Conclusions:

Young patients diagnosed with primary optic nerve sheath meningioma have a high likelihood of comorbid NF2; knowledge of this association may minimize time to diagnosis.

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Keywords: Pediatric Neuro-Ophthalmology, Genetic Disease, Neuro-Ophth & Systemic Disease, Orbit

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 58**A Brain on Fire! A Case of Neuromyelitis Optica Mimicking Progressive Multifocal Leukoencephalopathy**

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Introduction:

Neuromyelitis optica is an aggressive form of demyelination that typically causes recurrent optic neuritis and transverse myelitis. Atypical presentations can be difficult to diagnose.

Methods:

Case report and review of literature.

Results:

A 66-year-old woman with history of longstanding rheumatoid arthritis (currently on methotrexate and infliximab) presented with acute imbalance, fever and left-sided weakness. She underwent head CT that showed a hyperdense lesion within right corona radiata (CR) and basal ganglia (BG) with possible involvement of R. thalamus. It was suspected that she had an acute stroke. Few hours later she developed an episode of involuntary, non rhythmic jerking of left upper and lower limbs that lasted a few minutes. Her mental status started to wax and wane the next morning. Serological testing including Lyme, SPEP, ANCA, RPR, and FTA ABS were negative. IGG level in CSF was remarkably elevated at 13.20 mg/dL with an IGG index of 0.70. Her paraneoplastic panel was positive for AChR Ganglionic Neuronal Abs. MRI revealed T2 signal abnormalities with mild mass effect at right temporal lobe, white matter changes of right frontal parietal lobe, with involvement of R. thalamus and posterior limb of Internal capsule(IC), also signal abnormalities of right pons and midbrain. There was no diffusion restriction and minimal patchy enhancement was noticed. MRI-guided brain biopsy showed parenchymal inflammation without signs of infection. A large, T2 hyperintense, non-enhancing mass with some mild associated internal reduced diffusion and associated expansion of the right temporal stem was again noted. A repeat LP was still suggestive of an inflammatory process, however, CSF HSV-2 IgM positive from encephalitis panel. Infectious disease medicine recommended restarting acyclovir. PCR was negative for HSV. Aquaporin-4 antibodies were positive in serum and CSF. Patient was put on 5 day course of IV solumedrol with improvement in her mental status and muscle strength. Patient was started on Rituximab.

Conclusions:

NMO can mimic progressive multifocal leukoencephalopathy (PML) and acute disseminated encephalomyelitis (ADEM).

References: None.

Keywords: Neuromyelitis Optica, Aquaporin-4, Demyelination

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Langerhan's Cell Histiocytosis Masquerading as Optic Glioma

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Introduction:

Langerhans cell histiocytosis (LCH) is a rare disease of uncertain etiology. LCH possibly related to clonal proliferation of CD1a-positive langerhans cells forming a pseudotumoral growth. LCH may present as unifocal, multifocal with a benign or fatal course. LCH disorders are classified into 3 groups: eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease. The incidence of LCH ranges from 1 to 9 cases per million/ year. Of all cases of LCH, temporal bone involvement has been reported in 20% to 30%. Herein we present an unusual case of LCH masquerading as optic glioma. The clinical, radiological and histopathological results are discussed.

Methods:

This is a case report with retrospective chart review including radiographic and histopathological studies. The literature search was performed using the following search terms: langerhans' cell histiocytosis of optic chiasm, central nervous system and langerhans' cell histiocytosis.

Results:

A 21-year-old male with no significant past medical history presented with progressive hypersomnolence, headache, blurred vision, and 20 pounds weight gain. Neuro-ophthalmological examination revealed a VA of 20/50 on the right and 20/25 on the left. Pupils were equal, and there was no RAPD. EOM was full. Humphrey visual field showed bitemporal hemianopsia. MRI of the brain revealed hypothalamic- suprasellar mass with impingement on both optic nerves and the pituitary stalk consistent with an optic glioma. Due to the associated risks biopsy was deferred. Three weeks later he presented with left otorrhea and CT scan of the temporal bone showed destruction of the mastoid process. Surgical exploration revealed fragile, fleshy grape-like cluster lesions. The diagnosis of LCH was confirmed by *histopathological* and immunohistochemical *staining*. Chemotherapy was subsequently initiated.

Conclusions:

This report describes an unusual mode of presentation masking the presence of LCH thereby delaying diagnosis and management. Although LCH is uncommon in this location it should be considered in the differential diagnosis of a suprasellar mass.

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Grois N, Barkovich AJ, Rosenau W, Ablin AR. Central nervous system disease associated with Langerhans' cell histiocytosis. *Am J Pediatr Hematol Oncol*. 1993 ;15(2):245-54.

Keywords: Optic Neuropathy, Neuroimaging, Tumor, Neuro-Ophth & Systemic Disease, Visual Field

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 60

Profound Bilateral Optic Disc Edema One Month Post-Partum: A Rare Etiology

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Introduction:

Intracranial subdural hematoma formation is a rare, yet potentially fatal complication of spinal anesthesia, as well as inadvertent dural puncture of various iatrogenic etiologies.¹⁻¹⁶ The proposed pathophysiologic mechanism involves significant cerebrospinal fluid loss with resultant caudal displacement of the brain and rupture of bridging cerebral vessels. We present a case of profound bilateral optic disc edema secondary to intracranial subdural hematomas, presumably due to unintentional dural penetration during epidural anesthesia for labor.

Methods:

CASE REPORT: A 27-year-old Ethiopian female, with no significant past medical history, was referred for neuro-ophthalmic evaluation of bilateral disc edema. Patient reported intractable periorbital and frontal headaches, with accompanying photophobia, since vaginal delivery four weeks prior. Childbirth was uncomplicated, though epidural anesthesia required two attempts for correct catheter placement. Upon initial examination, visual acuity was 20/20 OU, with no rAPD. Dilated fundoscopic examination revealed Grade IV disc edema with numerous peripapillary hemorrhages bilaterally. Humphrey visual field testing indicated an enlarged blind spot OU, and RNFL OCT substantiated significant disc edema, with average thicknesses of 381 μ m OD and 452 μ m OS. Emergent MRI imaging revealed bilateral complex intracranial subdural hematomas. Consequently, the patient underwent successful burr-hole evacuation of the largest right frontoparietal component, which measured 7.7 cm in AP diameter and 2 cm in transverse thickness. Though headaches temporarily recurred 10 days post-operatively, repeat MRI at that time indicated a considerable decrease in the size of the subdural hematomas and no significant new hemorrhaging. The patient began treatment with oral acetazolamide for headache control. Vision remains at 20/20 OU, now with marked reduction in the degree of papilledema (Grade 1 OU).

Conclusions:

Intracranial subdural hemorrhaging status post inadvertent dural puncture may occur within the obstetric population. This clinical entity has not been sufficiently reported in neuro-ophthalmic literature to date, thus improved awareness of this potentially life-threatening complication is critical.

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Newrisk P and Read D. Subdural haematoma as a complication of spinal anaesthetic. *British Medical Journal* 1982; 285: 341-342. Cohen JE, Godes J and Morales B. Postpartum bilateral subdural hematomas following spinal anesthesia: case report. *Surg Neurol* 1997; 47: 6-8. Davies JM, Murphy A, Smith M and O'Sullivan G. Subdural haematoma after dural puncture headache treated by epidural blood patch. *British Journal of Anaesthesia* 2001; 86 (5): 720-723. Kayacan N, Arici G, Karsh B and Erman M. Acute subdural haematoma after accidental dural puncture during epidural anaesthesia. *International Journal of Obstetric Anesthesia* 2004; 13: 47-49. Ozdemir N, Ari MK, Gelal MF and Bezircioglu H. Intracranial chronic subdural haematoma as a complication of epidural anesthesia. *Turkish Neurosurgery* 2009; 19 (3): 285-287. Aziz F. A fatal case of subdural hematoma: a complication of epidural analgesia. *The New York Medical Journal* 2010; 5 (2): 1-3. Demetriades AK, Sheikh MF and Minhas PS. Fatal bilateral subdural haematoma after epidural anaesthesia for pregnancy. *Arch Gynecol Obstet* 2011; 284: 1597-1598. Gomez-Rios MA and Nieto-Serradilla L. Bilateral interhemispheric subdural hematoma after accidental lumbar puncture and epidural blood patch. *Arch Gynecol Obstet* 2012; 286: 531-532. Fiala A, Furgler G, Baumgartner E and Paal P. Delayed subdural haematoma complicated by abducens nerve palsy and cortical vein thrombosis after obstetric epidural anaesthesia. *Br J Anaesth* 2012; 108 (4): 705-706. Lopez Soler EC, Villalba Garcia JM, Fernandez Madruga R, Fernandez Rodrigo M, Mirallas Mezquita M and Minguez Sorio P. Subdural haematoma secondary to epidural anesthesia; a rare complication. *Neurologia* 2013; 28: 380-382. Bakar B, Ozer E and Hakki Tekkok I. Life-threatening acute subdural haematoma after combined spinal-epidural anaesthesia in labour. *Rev Bras Anestesiol* 2015; 65 (5): 417-420. Richa F, Chalhoub V, El-Hage C, Dagher C and Yazbeck P. Subdural hematoma with cranial nerve palsies after obstetric epidural analgesia. *International Journal of Obstetric Anesthesia* 2015; article in press. Narouze SN, Casanova J, El-Jaberi M, Farag E and Tetxclaff JE. Inadvertent dural puncture during attempted thoracic epidural catheter placement complicated by cerebral and spinal subdural hematoma. *Journal of Clinical Anesthesia* 2006; 18: 132-134. Lage Duarte W, de Souza Araujo F, Almeida MF, Geber DG and Viana de Castro CH. Subdural hematoma after inadvertent dura mater puncture: case report. *Rev Bras Anestesiol* 2008; 58 (4): 387-390. Rocchi R, Lombardi C, Marradi I, Di Paolo M and Cerase A. Intracranial and intraspinal hemorrhage following spinal anesthesia. *Neurol Sci* 2009; 30: 393-396. Zeidan A, Farhat O, Maaliki H and Baraka A. Does postdural puncture headache left untreated lead to subdural hematoma? Case report and review of literature. *International Journal of Obstetric Anesthesia* 2006; 15: 50-58. Kim M and Park K-S. Intracranial chronic subdural hematoma presenting with intractable headache after cervical epidural steroid injection. *J Korean Neurosurg Soc* 2015; 58 (2): 144-146. Lee S-J, Lin Y-Y, Hsu C-W, Chu S-J and Tsai S-H. Intraventricular hematoma, subarachnoid hematoma and spinal epidural hematoma caused by lumbar puncture: an unusual complication. *The American Journal of the Medical Sciences* 2009; 337 (2): 143-145. Subramanian B, Panzica PJ, Pawlowski JB, Ramanavarapu V, Pomposelli FB, De La Torre R and Lerner AB. Epidural blood patch for acute subdural hematoma after spinal catheter drainage during hybrid thoracoabdominal aneurysm repair. *Journal of Cardiothoracic and Vascular Anesthesia* 2007; 21 (5): 704-708. Pumberger M, Memtsoudia SG, Stunder O, Herzog R, Boettner F, Gausden E and Hughes AP. An analysis of the safety of epidural and spinal neuraxial anesthesia in more than 100,000 consecutive major lower extremity joint replacements. *Regional Anesthesia and Pain Medicine* 2013; 38 (6): 515-519. Ruppen W, Derry S, McQuay H and Moore MA. Incidence of epidural hematoma, infection, and neurologic injury in obstetric patients with epidural analgesia/anesthesia. *Anesthesiology* 2006; 105: 394-399.

Keywords: High Intracranial Pressure, Headache, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 61

Supranuclear Palsy and Ataxia Related to Anti-Ma2 Paraneoplastic Syndrome: a Diagnostic and Therapeutic Dilemma

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Introduction:

Anti-Ma2 paraneoplastic syndrome is characterized by limbic, diencephalic or brainstem encephalitis, alone or in combination, with oculomotor deficits in 92% of patients with brainstem dysfunction. In young males, this syndrome is highly associated with germ cell tumors, and commonly presents with MRI abnormalities as well as abnormal CSF and EEG studies.² The recommended management approach includes treatment of the underlying malignancy as well as immunotherapy,³ with neurologic stabilization or improvement in approximately 54% of patients.¹

Methods:

Case report and literature review.

Results:

A 29 year old male presented with several weeks of difficulty looking down, head tremor and gait instability. Neuro-ophthalmic examination was significant for absent vertical saccades with preserved smooth pursuit on oculocephalic and optokinetic maneuvers. MRI brain with and without contrast revealed no intracranial abnormalities. Routine EEG was also normal. CSF examination was normal except for the presence of oligoclonal bands. Testicular exam revealed a mass later identified as a mature teratoma with metastasis to one paraaortic lymph node. The patient was treated with 5 cycles of plasma exchange as well as high-dose corticosteroids and orchiectomy, followed by two cycles of bleomycin/etoposide/cisplatin. Initial serum test for Anti-Ma1/Ma2 was indeterminate, but was felt to represent a positive result in the setting of recent plasma exchange. However, repeat testing at 3 and 9 months was negative. Despite treatment of the underlying malignancy and negative whole-body PET-CT scan, the patient's symptoms continued to worsen, and repeat brain MRI 9 months following symptom onset showed new midbrain atrophy and enlargement of the 3rd ventricle.

Conclusions:

This is an unusual presentation of Anti-Ma2 paraneoplastic syndrome, with normal initial brain MRI and negative repeat serologies for Anti-Ma2 antibodies, as well as worsening symptoms despite treatment of the underlying malignancy. These characteristics make definitive diagnosis and successful treatment particularly challenging, and highlight a need for further investigation into therapeutic interventions earlier in the disease course.

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Keywords: Paraneoplastic, Supranuclear, Brainstem, Autoimmune, Malignancy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 62

Painful Ophthalmoplegia Due to Burkitt's Lymphoma (BL) in an HIV-Patient

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Introduction:

To raise awareness on an uncommon etiology of cavernous sinus syndrome, although more frequent in an HIV population, but poorly taken under consideration. The diagnosis was established with certainty by means of surgical biopsy.

Methods:

Clinical report of an HIV-patient who consulted with complete and sudden painful ophthalmoplegia in his left eye that developed in 10 days, associated with lymphadenopathy and increased liver and spleen's size. He has been diagnosed of HIV in 2012, and was undergoing retroviral treatment. 2 months prior his symptoms: CD 4+173 cells/mm³. Normal VA 20/20 OU and normal fundus oculi. His etiological investigation aroused BL after biopsy of the cavernous sinus and anatomopathological analysis. A brief summary of the patient will be presented, and also the studies carried out to diagnose this rare etiology.

Results:

Our patient underwent the basic neuroophthalmologic examination, brain MRI that revealed an occupying mass in left cavernous sinus, interconsultations with Neurology and Neurosurgery department. The decision of surgical biopsy was conclusive of BL, and intratecal chemotherapy was performed. After treatment, the patient referred diplopia only in extreme abduction of his left eye, and a persistent mydriasis could be noticed.

Conclusions:

Although BL affects the central nervous system very rarely, BL should be considered in any immunosuppressed patient presenting with diplopia or ophthalmoparesis.

References: None.

Keywords: Tumors, Ocular Motility, Neuroimaging, Neuro-Ophth & Infectious Disease, Neuro-Ophth & Systemic Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 63

Cut From the Same Cloth

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Introduction:

We describe a patient with both HLA-B27 positive anterior uveitis and idiopathic CNS inflammatory syndrome responsive to steroids.

Methods:

Case report.

Results:

A previously healthy 15 year-old African-American boy was diagnosed with bilateral HLA-B27 positive anterior uveitis, successfully controlled with topical difluprednate and oral prednisone. Eight months later, he experienced the acute onset of headaches, left eyelid ptosis, and binocular diplopia. Visual acuity was 20/20 bilaterally. Pupils were reactive without relative afferent pupillary defect. There was trace cell in both anterior chambers and intraocular pressure was normal. Extraocular motility was full with small esodeviation on balance testing. He had mild left upper eyelid ptosis. Brain MRI showed enhancing and T2 hyperintense lesions in the right midbrain, superior colliculus, cerebellar peduncles, cerebellar vermis, and leptomeningeal enhancement along the vermal folia. CSF showed a mild lymphohistiocytic pleocytosis with negative cytology and ACE. Serum ACE, ferritin, TSH, FT4, TPO, TSI, Lysozyme, ESR, CRP, complement factors, aquaporin-4, PPD, ANA, anti-ds DNA, anti-Sm, anti-RNP, anti-SSA, anti-SSB, cystercercus, and HIV labs were within normal limits or negative. Chest X-ray was negative. He received 5 days of 1g IV methylprednisolone without symptomatic improvement; however, repeat MRI showed reduced enhancement of his CNS lesions. He was discharged on 20mg of oral prednisone daily. His symptoms resolved in one month. Repeat MRI two months after presentation showed almost complete resolution of his CNS lesions.

Conclusions:

This is a novel case of idiopathic CNS inflammatory disease in the rare setting of bilateral HLA-B27 positive anterior uveitis.^{1,2,3} Given his lesion distribution and response to steroids, a presumed diagnosis of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) was made.^{4,5} While not previously reported with CLIPPERS, HLA-B27 positivity may represent a novel association with this new and still incompletely defined CNS disease.

References:

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Keywords: CLIPPERS, Uveitis, Neuroinflammation, HLA-B27, Brainstem

Financial Disclosures: The authors had no disclosures.

Grant Support: This study was supported in part by National Eye Institute Vision Core Grant P30EY010608, a Challenge Grant to The University of Texas Medical School at Houston from Research to Prevent Blindness, and the Hermann Eye Fund.

Poster 64**Diffuse Large B-Cell Lymphoma Mimicking the Presentation of a Carotid-Cavernous Fistula**

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Introduction:

To report an alternative cause of subacute progressive unilateral proptosis with dilated conjunctival vessels suggestive of a carotid-cavernous fistula.

Methods:

Background: Carotid-cavernous fistula (CCF) symptoms typically include unilateral proptosis and dilated conjunctival vessels. While these symptoms may also portend thyroid eye disease, orbital neoplasm or inflammation, dilated vessels point toward a vascular origin. We report a case of an orbital lymphoma initially presenting with signs suggestive of a CCF.

Results:

A 70-year-old male presented with subacute progressive dilated episcleral vessels with subsequent periorbital edema OD, followed by binocular vertical diplopia. Neuro-ophthalmologic examination revealed visual acuity of 20/30 OD and 20/20 OS and normal color vision with 6/6 HRR plates OU. Pupils were 5mm with normal reaction without RAPD OU. Conjunctival injection with corkscrew episcleral blood vessels were noted at the limbus OD. Intraocular pressure was 16 mmHg OD and 19 mmHg OS, and proptosis of 3mm OD was observed. Visual field testing was unreliable with non-specific changes OU. The motility exam revealed decreased supraduction OU, along with a 3-4 diopter left hypertropia with upgaze that converted to a 10-12 diopter right hypertropia with downgaze, suggestive of a partial oculomotor nerve palsy OD. Ophthalmoscopy showed venous distention OD. Cerebral angiography showed no carotid-cavernous fistula. MRI revealed several enhancing cerebral lesions in left cingulate gyrus, right parietooccipital lobes, and superior right orbit with superior rectus involvement. Inferior displacement of the globe was noted, likely impinging venous outflow from right orbit. An orbital biopsy revealed an aggressive diffuse large B-cell lymphoma.

Conclusions:

This case illustrates an alternative diagnosis to explain limited orbital venous outflow in the absence of a CCF. Increased venous pressure occurred secondary to mass effect from the neoplasm on the orbital venous channels. Motility defects may be neuropathic in etiology, with mechanical components possibly related to the superior orbital mass.

References: None.

Keywords: Orbit/Ocular Pathology, Tumors, Vascular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 65

Optic Nerve Head Features of a Multiple Sclerosis Patient Masquerading as Glaucomatous Cupping

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Introduction:

The purpose of this abstract is to illustrate a case of Multiple Sclerosis with bilateral temporal pallor of optic nerve heads and Cup/Disc ratio of 0.6 that was initially diagnosed and managed as glaucomatous cupping

Methods:

A case report of a 16 year old female patient who presented with a one month history of ocular pain on eye movement associated with photopsias. Ophthalmic and Neurological evaluation, Automated Perimetry, OCT (ONH and RNFL), MRI (Brain and Cervical spine), VEP, Colored Fundus Photographs and Laboratory Investigations (CBC, CRP, ESR, ALT,AST, Creatinine, Potassium, Sodium,Urea, Anticardiolipin, Lupus anticoagulant, Rheumatoid Factor, TORCH, ACE, CSF examination, TB-DNA, NMO (Aqua Purin - 4Abs)Oligoclonal bands in Serum and CSF) were performed for the patient

Results:

Fundus examination revealed bilateral temporal pallor of optic nerve heads and enlarged cup/disc ratio of 0.6. Average Intraocular pressure was 20mmHg in both eyes on repeated measurements. Automated Perimetry revealed bilateral paracentral defects. OCT revealed bilateral enlarged cup/disc ratio of 0.6 and reduced thickness of RNFL and Ganglion Cell complex MRI (Brain and Cervical Spine) reported bilateral cerebral, callosal and cerebellar as well as pontine foci and patches of altered signal intensity, likely Multiple Sclerosis with one active lesion at the left parietal region .VEP reported bilateral optic nerve dysfunction and impaired retinocortical transmission mostly attributed to Multiple Sclerosis . Laboratory investigations confirmed the clinical and radiological diagnosis of Multiple Sclerosis

Conclusions:

The presence of optic nerve head pallor, particularly temporal pallor, in the presence of suspicious glaucomatous cupping should be investigated for the possibility of Multiple Sclerosis

References: None.

Keywords: Temporal Pallor of Optic Nerve Head, Glaucomatous Cupping, Multiple Sclerosis

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 66

Transcalvarial Spread of Lymphoma Causing Venous Sinus Congestion, Papilledema, and a Scalp Lump

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Introduction:

The bony cranial vault usually prevents intracranial tumors from spreading extracranially. Transcalvarial extension of a tumor without significant destruction of skull bone is rare.

Methods:

A 46 year old man had five months of worsening blurry vision, transient visual obscurations, and pulsatile tinnitus. A CT head was unremarkable. Subsequent neuro-ophthalmic examination was notable only for decreased visual acuity in the left eye (20/40 left eye versus 20/20 right eye), and moderately severe bilateral papilledema. Visual fields showed blind spot enlargement, left eye more than right. Opening pressure on lumbar puncture was elevated at 38 cm of water. Routine CSF studies (not including cytology) were unremarkable. He was started on acetazolamide. An MRI/MRV head showed an unusual intracranial enhancing mass overlying the right parietal convexity and invading the superior sagittal sinus and incompletely occluding it. This mass extended through the skull into the extracranial scalp, where it formed a right parietal soft tissue scalp mass. Abnormal marrow signal was focally evident between the extracranial and intracranial components of the tumor, but no definite bony destruction of the calvarium was seen. Radiological differential diagnosis included meningioma and lymphoma. The patient carefully palpated his scalp and, indeed, discovered a new right scalp lump (photograph).

Results:

Two consecutive ultrasound-guided needle biopsies of the scalp mass were nondiagnostic; therefore, a right parietal craniotomy was undertaken, and lesional tissue was sent to pathology. Histopathologic examination established a diagnosis of diffuse large B cell lymphoma (80%) arising from a follicular lymphoma (20%). Our patient had a complete response to treatment with five cycles of CHOP-R chemotherapy and declined radiation treatment. His symptoms resolved, and follow-up neuro-ophthalmic examinations and visual fields were normal.

Conclusions:

Intracranial lymphoma may sometimes breach the bony confines of the calvarium and have extracranial extension without significant bony erosion of intervening skull.

References: None.

Keywords: High Intracranial Pressure/Headache, Neuro-Ophth & Systemic Disease, Neuroimaging, Pseudotumor Cerebri, Tumors

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 67

Clinical Variability in Wolfram Syndrome: Report of a Sample of 16 Patients

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Introduction:

Wolfram syndrome is an autosomal recessive disease characterized by the presence of diabetes mellitus (DM), optic atrophy (AO), central diabetes insipidus, hearing loss and neurological disorders such as cerebellar ataxia and psychiatric manifestations. It is caused by mutations in the WFS1 gene. The aim of this study is to present a sample of 16 patients with Wolfram syndrome.

Methods:

We present a sample of 16 patients with Wolfram syndrome, analyzing mutations in the WFS1 gene and describing the clinical manifestations. We performed a complete neurological and ophthalmological examination of these patients, including visual perimetry, fundus and OCT (optical coherence tomography) of optic nerve, when the age of the patients allowed a proper cooperation.

Results:

All individuals in the sample have mutations in the WFS1 gene, communicating in this work at least 5 new mutations not described in the scientific literature. All patients have optic atrophy and ceco-central visual defects in perimetry. However, other typical clinical manifestations present in Wolfram syndrome varies greatly in its clinical expression. In this manner in this sample are presented in one hand patients with mild visual disturbances secondary to optic atrophy, without any other clinical alteration; and patients with severe optic atrophy, diabetes mellitus, diabetes insipidus, deafness and severe ataxia.

Conclusions:

The sample presented here shows that the spectrum of clinical expression of this syndrome is very variable, without an adequate phenotype-genotype correlation.

References: None.

Keywords: Wolfram Syndrome, Congenital Optic Neuropathy, Diabetes Mellitus, Diabetes Insipidus, Hearing Loss

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 68

The Elusive Embolus: Hiding in Plain Sight

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Introduction:

Branch retinal artery occlusion, BRAO is a vision threatening condition caused by occlusion of one or more of the major arteries in the retina, frequently caused by an embolus. Identification of an embolus has important implications to identifying a cause, determining a treatment, and preventing other end-organ damage. Proximal emboli on the optic nerve head are more difficult to visualize compared to distal emboli, which are more easily seen against the contrast of the pigmentary retina.

Methods:

We present 4 cases of patients referred to our clinic with BRAO who had proximal emboli on the optic nerve head. Emboli were invisible or overlooked by biomicroscopy, but easily visualized by red-free and autofluorescence imaging.

Results:

Provided fundus images show emboli that are imperceptible or nearly so on optic nerve heads, but easily visualized with red-free and/or autofluorescence imaging.

Conclusions:

We encourage clinicians to use red-free and autofluorescence imaging when there is suspicion of BRAO but no embolus visualized upon biomicroscopy. Further investigation is warranted and necessary to determine the sensitivity of this relatively inexpensive, noninvasive, and often readily available tool to diagnose proximal embolic BRAO on the optic nerve head.

References: None.

Keywords: Branch Retinal Artery Occlusion, Elusive Embolus, Cilioretinal Artery Occlusion

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 69

Aortic Aneurysm is Common in Treated Giant Cell Arteritis

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Introduction:

Giant Cell Arteritis (GCA) typically affects the vasa vasorum supplying the cranial-cervical arteries. However, any medium to large vessel can be involved. Aortic aneurysm secondary to aortitis may be an unexpected complication of GCA. Corticosteroid related weakening of an already widened aortic wall is also a possibility. We review underlying mechanisms and screening guidelines for aneurysms in GCA.

Methods:

Single case report and literature review

Results:

A 72 year old female complained of a sharp unilateral headache, intermittent fever, and scalp tenderness. Physical Examination revealed visual acuities of 20/20 OU, visual fields full to confrontation. Funduscopic exam was unremarkable. Serologic panel revealed elevated CRP and SED rates. The patient began high dose steroid therapy and temporal artery biopsy confirmed the diagnosis of GCA. CRP and platelets normalized and prednisone was tapered over the next year. After one year, thoracoabdominal contrast enhanced MRA revealed an aneurysm of the ascending aorta 3.6 cm in diameter.

Conclusions:

Investigators report patients with GCA are up to 17.3 times more likely to develop thoracic aortic aneurysms and up to 2.4 times more likely to develop an isolated abdominal aneurysm. Pathologic examination of ruptured aneurysm generally reveals active arteritis. Long term treatment with glucocorticoids may potentially add to the risk of aneurysm development. The present case emphasizes even patients with well controlled GCA may have silent aortic involvement. All patients need to be screened for the presence of aortic pathology.

References: None.

Keywords: Vascular Disorders, Neuro-Ophth & Systemic Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 70

Chiasmal Tract Neuritis Secondary to Neuromyelitis Optica

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Introduction:

Both neuromyelitis optica (NMO) and multiple sclerosis (MS) can present as acute optic neuritis. The involvement of more posterior structures of the optic nerve, including the chiasm tends to be more indicative of NMO. Distinguishing between NMO and MS is of great importance in guiding treatment.

Methods:

Case Report.

Results:

A 37-year-old female presented with the sudden onset of bilateral visual loss, headache, and pain with extraocular movement. Initial examination on 9/15/15 showed visual acuity of 20/30 OD and 20/20 OS, color vision was markedly diminished, 0 of 6 HRR plates, flicker-fusion was decreased bilaterally, measuring 17 hz OD and 21 hz OS. Humphrey visual field OD showed a dense central scotoma. HVF OS showed a preponderant temporal hemifield defect. Initially, the fundoscopic examination was normal. Neuroimaging studies demonstrated enhancement of the right optic chiasm and also edema involving the right optic tract. Laboratory studies showed a markedly elevated NMO- IgG antibody at 27.9, (positive range > 5.1). The patient was aggressively treated with high dose intravenous Solu-Medrol followed by an oral steroid taper, six treatments of plasmapheresis and four doses of Rituxan. The patient was reevaluated two weeks later. VA improved to 20/20 OU, HRR plates 0.5/6 OD and 1/6 OS. Repeat fundoscopic examination showed bilateral optic nerve pallor. Flicker-fusion improved to 21 hz OD and 24 hz OS. Visual field dramatically improved with resolution of the central scotoma OD and clinically improved left temporal hemifield defect OS.

Conclusions:

Consideration of NMO was given at the initial evaluation, which was confirmed with the serology. It is noteworthy that in this patient the diagnosis of NMO was established within 48 hours after presentation. We instituted aggressive management with steroids, plasmapheresis and Rituxan, which greatly improved the outcome. Delay in the diagnosis of NMO would have protended a poorer prognosis for full recovery.

References:

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Keywords: Neuromyelitis Optica, Chiasm, Chiasmatic Neuritis

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 71

A Report and Electrophysiologic Analysis of an Isolated Case of Bilateral Optic Atrophy Due to Ocular Graft-Versus-Host Disease

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Introduction:

Hematopoietic stem cell transplantation (HSCT) is a successful treatment for many hematologic malignancies. Despite successes, its known risks include graft-versus-host disease (GVHD). Ocular manifestations occur in up to 90% of patients with chronic GVHD, most commonly affecting the ocular surface, though some cases involve the posterior segment. This unique case reveals a sole clinical exam finding of bilateral optic nerve atrophy in a patient not treated with cyclosporine A. This presentation is completely unique. Furthermore, this study provides objective data from electrophysiologic studies.

Methods:

A 41 year old female with acute myeloid leukemia (AML) in full remission status-post HSCT and chronic GVHD presented with 5 months of deteriorating, blurry vision in both eyes, 1 year after HSCT. She did not receive cyclosporine A for immunosuppression. Visual acuities fluctuated throughout evaluations and posterior exams showed only bilateral optic nerve pallor.

Results:

Visual field testing fluctuated, ultimately resulting in bilateral central deficits. She had poor color vision with color plate testing. Ocular coherence tomography (OCT) of both maculas showed no edema. OCT of the optic nerves showed diffuse nerve fiber layer thinning bilaterally. OCT of the retina showed generalized retinal thinning bilaterally with nasal sparing of the right eye. Conventional VEP showed decreased amplitudes with normal latencies bilaterally.

Conclusions:

Due to the patient's onset of symptoms following HSCT, the GVHD chronicity and repeatedly negative infectious and malignancy workups, optic atrophy secondary to GVHD was ultimately favored over other proposed etiologies. This unique case highlights the clinical course of a patient who presented with bilateral optic atrophy alone in an atypical diagnosis of surface-sparing ocular GVHD. Clinical evaluation and quantifiable diagnostic testing proved valuable to diagnose and plan for future monitoring of this very rare case and hold promise for others with a similar mechanism.

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Walter, Bertz, Gerling, Bilateral optic neuropathy after bone marrow transplantation and cyclosporin A therapy, *Graefes Archives of Clinical and Experimental*, 238, 472-476, 2000.

Keywords: Graft-Versus-Host-Disease, Acute Myeloid Leukemia, Hematopoietic Stem Cell Therapy, Optic Atrophy, Visual Evoked Potential

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 72**IV Bevacizumab: Friend or Foe of the Optic Nerve?**

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Introduction:

I present a woman who suffered unilateral blindness from optic neuropathy, after radiation and IV bevacizumab for glioblastoma of the temporal lobe

Methods:

observational/case report

Results:

A 57 y.o. female received a diagnosis of grade 3 astrocytoma of the the right temporal lobe. She completed radiation to the tumor bed after gross total tumor resection two and a half months after the surgery for a total of 59.4 Gy. Temodar was given once but tumor recurrence led to further surgery 5 months after the initial surgery and now pathology showed grade 4 malignant glioblastoma. She underwent q 2 weeks IV bevacizumab, supplemented by NOVO-TFF therapy for a total of 6 bevacizumab treatments. Eight months after completing radiation therapy and after the six bevacizumab treatments she noted blindness in her right eye. She was NLP right eye and 20/20 left eye with a left superior quadrant defect compatible with the prior tumor location and surgeries. The right optic nerve was pale and the right pupil was amaurotic. MRI showed enlargement of the right pre-chiasmal optic nerve with T2 hyperintensity and trace enhancement. Bevacizumab related optic neuropathy was diagnosed and treatment was stopped. Bevacizumab is used to treat choroidal neovascularization, diabetic macular edema and even radiation related retinopathy. Could this adverse event occur because of radiation sensitizing the optic nerve to vaso-occlusive events? Is it purely an anti-VEGF complication we all need to be aware of? How should we treat this?

Conclusions:

Rarely bevicizumab has been reported to cause optic neuropathy after radiation for CNS tumors. I will discuss the literature and suggest possible etiologies and possible treatment options.

References: None.

Keywords: Optic Neuropathy, Chemotherapy and Radiation Injury

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 73**Autoimmune Optic Neuropathy, Case Series**

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Introduction:

Auto-immune optic neuropathy represents a heterogeneous group of conditions, some with recognized systemic autoimmune disease and various autoimmune markers in serologic testing including NMO Abs. Others may present with recurrent visual loss and steroids dependency, but lack any evidence of other systemic inflammatory disease. The aim of this study is to characterize the clinical course of patients with recurrent and/or progressive autoimmune optic neuropathy.

Methods:

Retrospective chart review. Patients who were subsequently defined as MS or NMO positive were excluded.

Results:

There were 4 males and 2 females. The mean age of presentation was 47 (range 35-58y). Mean follow up was 4.9 years (range 1-12y). Two patients had simultaneous bilateral onset, 3 had sequential involvement of the second eye, and 1 had pure unilateral disease. All patients had normal brain and cervical imaging (except isolated optic nerve enhancement), and normal lumbar puncture content. Comprehensive inflammatory work up was negative in all of them. Two patients had few episodes of recurrent optic neuritis and could be weaned of steroid after several months. Both had good final visual acuity. 4 patients had chronic relapsing course (fulfilling CRION criteria) and required prolonged treatment with steroid sparing agent.

Conclusions:

Autoimmune optic neuropathy might be a distinct variety of optic nerve inflammation which is not secondary to one of the described demyelinating syndromes. A thorough investigation is necessary to exclude other systemic autoimmune disease and comorbidities. Early recognition of patients is important because they require aggressive and long-term immunosuppressive therapy in order to prevent substantial visual impairment.

References: None.

Keywords: Optic Neuropathy, Inflammatory, NMO, Steroid, CRION

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 74**Sneeze-Induced Amaurosis**

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Introduction:

We present the first case of a patient with recurrent amaurosis fugax (AF) induced by sneezing. He was found to have a flow limiting stenosis in the ipsilateral ophthalmic artery.

Methods:

A 74 year old man with a history of hypertension and hyperlipidemia presented to the ER with a temporary loss of vision in his left eye. His CT head had no abnormalities and he was discharged home on Aspirin. He had another spell of transient vision loss in his left eye a few days later and Clopidogrel was added. After this second ER visit he continued to have four to five additional spells. All but one spell were preceded by a sneeze. The first spell was described as a central darkness but for all others he noted a diffuse darkness and blurred vision. None had any altitudinal quality. Fundoscopic examination was unremarkable with no vascular changes suggestive of embolic disease vascular insufficiency.

Results:

Carotid ultrasound, MRI and MRA brain were normal. After another episode he was switched to Aspirin/Extended-Release Dipyridamole and since then has not noted any further events. A diagnostic cerebral angiogram revealed a short segment flow-limiting stenosis in the distal left ophthalmic artery, just proximal to the origin of the central retinal artery. He continues on the medication with no further spells.

Conclusions:

We suspect that the abrupt changes in blood pressure and distal blood flow due to the Valsalva effects of a sneeze resulted in symptomatic retinal ischemia. A transient increase in intraocular pressure with a secondary decrease in retinal perfusion pressure may be another contributing factor in this situation. It is likely that these improved due to mainly the vasodilatory effect of Dipyridamole.

References: None.

Keywords: Amaurosis Fugax, Interventional Neuroradiology, Intracranial atherosclerosis, Retina

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 75

Morbidity and Mortality in Patients After Skull Base Osteomyelitis. A Report of 3 Cases and Review of the Literature.

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Introduction:

Skull base osteomyelitis (SBO) is an uncommon but life threatening condition, most commonly secondary to otitis externa ⁽¹⁾. We report 3 cases of SBO which presented with neuro-ophthalmic manifestations without aural pathology. Knowledge of SBO by the neuro-ophthalmologist is essential.

Methods:

Retrospective case series and review of literature.

Results:

Three cases of non-otogenic SBO are presented. All presented with neuro-ophthalmic features. Detailed history revealed an insidious onset over several months. Initial radiological abnormalities were subtle and easily overlooked. The neuro-ophthalmologist is essential in monitoring the efficacy of treatment. One patient had a fatal outcome whereas the other 2 recovered after an extended course of antibiotics.

Conclusions:

It is important that neuro-ophthalmologists are familiar with the presentation as well as the subtle radiological features in central or non-otogenic SBO. These patients are usually elderly and immuno-compromised ⁽²⁾, present with optic neuropathy and/or cranial nerve palsies and commonly have a prior history of headache⁽²⁾ or neck pain. The onset is insidious and a high index of suspicion is required.

References:

- 1) Johnson AK, Batra PS. Central Skull Base Osteomyelitis: An Emerging Clinical Entity. Laryngoscope; 124:1084-1088, May 2014.
- 2) Pang A, Chong K. Skull base osteomyelitis originating in the middle ear or mastoid: A review of 3 cases. Ear, Nose and Throat Journal;90(3):121-4, March 2011.

Keywords: Skull Base Osteomyelitis, Optic Neuropathy, Sinusitis, Cavernous Sinus Syndrome, Orbital Apex Syndrome

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 76

Anti-Phospholipid Syndrome and Neurofibromatosis 1- New Association or Coincidence?

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Introduction:

Structural vascular anomalies and ischemia associated with neurofibromatosis 1 (NF1) are well reported and are thought to result from neurofibromin dysfunction. Documented cases of associated anti-phospholipid syndrome (APS) that fulfill the accepted diagnostic criteria for APS are exceptionally rare.

Methods:

We present a patient with NF1 and asymptomatic cavernous meningioma and contralateral optic atrophy who also had clinical and laboratory evidence of APS.

Results:

A 40 year old woman with known NF1 presented with sudden painless right vision loss and was diagnosed with central retinal vein occlusion. MRI of the brain revealed a left cavernous sinus meningioma. Past history was significant for three spontaneous abortions. Two of her three children had dermatologic stigmata of NF1. Examination revealed multiple café au lait spots and visual acuities of 20/300 OD and 20/25 OS. Color vision was 1/15 OD and 15/15 OS. The pupils were reactive with right relative afferent papillary defect. The anterior segments were normal with one Lisch nodule OS. Ophthalmoscopy revealed right optic atrophy and a normal left nerve. Octopus VF was not possible OD but showed mild constriction OS. OCT measured average retinal nerve fiber layer thickness of 52µm (right) and 97µm (left). Positive lab results include increased anti-β₂ glycoprotein 1 IgA and anti-β₂ glycoprotein 1 IgM antibodies, C4 and ESR (51mm). Repeat tests at 3 months revealed persistently elevated ESR and anti-β₂ glycoprotein 1 IgA. She fulfilled Sydney Criteria for diagnosis of APS with a least one clinical and laboratory evidence of APS: frequent abortions, a vascular occlusive episode and persistently elevated anti-β₂ glycoprotein 1 IgA antibodies.

Conclusions:

The association of NF1 and APS has been reported previously and this case, to our knowledge, documents the first ophthalmic manifestation. Although the concurrence of these disorders, both with wide phenotypic spectra, might be coincidental, it might represent a new unrecognized association.

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Keywords: Neurofibromatosis 1, Anti-Phospholipid Syndrome, Anti-Glycoprotein 1, Optic Atrophy, Meningioma

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 77

Headache in Multiple Sclerosis May Be Due to Idiopathic Intracranial Hypertension

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Introduction:

Headache is common in individuals with proven MS and generally considered either migraine or muscle tension type. Idiopathic Intracranial Hypertension (IIH) with Multiple Sclerosis (MS) is rarely reported. We examined three patients with IIH. In two cases papilledema was absent, confounding the correct diagnosis.

Methods:

Case series of women with IIH and MS and literature review.

Results:

Three women with definite relapsing remitting MS complained of generalized headaches. None experienced visual obscurations, tinnitus, nor diplopia. Visual acuity was preserved, and visual fields showed only big blind spots. Papilledema was absent in two out of three cases. Spinal fluid pressures were significantly elevated in all cases. In one individual, headache and associated positive MRI scans preceded by one year the development of the first clinical sign of MS, a left hemi-paresis. Two patients responded to conventional treatment; one required ventriculoperitoneal shunt for headache control.

Conclusions:

More than 50% of patients with MS complain of frequent headaches, typically classified as migraine or tension type. 3 patients previously reported present with unremitting headaches. Each case demonstrated disc head swelling. In two of our three patients, fundus findings were consistently normal, confirmed by optical coherence tomography and fundus photos. The cause of IIH in our patients is uncertain. IIH reportedly occurs with other autoimmune conditions, including Systemic Lupus Erythematosus (SLE), Sjogren's syndrome, Crohn's disease, Guillain-Barre syndrome, and Ankylosing Spondylitis. Similar to our patients, several SLE patients with IIH reportedly had no papilledema. Also, most reported cases had no additional predisposing risk factors. Although, most reports were not case controlled for co-morbidities. Recently investigators demonstrated elevated inflammatory markers and cytokines in patients with IIH. It seems plausible inflammatory states caused by autoimmune conditions like MS and SLE cause dysfunction of the arachnoid villi. IIH is a consideration in patients with MS and headache.

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Keywords: High Intracranial Pressure/Headache, Neuro-Ophth & Systemic Disease (Eg. MS, MG, Thyroid), Demyelinating Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 78**Multifocal Electroretinography and Visual Evoked Potential Findings in a Case of Optic Disc Pit**

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Introduction:

To present multifocal electroretinography (mfERG) and visual evoked potential (VEP) findings in a case of a unilateral optic disc pit.

Methods:

ISCEV guidelines were followed while performing mfERG and VEP. Color fundus photography, SITA-standard Humphrey Visual Field (HVF), and spectral-domain Optical Coherence Tomography (OCT) were also obtained.

Results:

A 34 year-old woman complaining of decreased vision was found to have a left optic disc pit. Visual acuity was 20/80 in the right eye and 20/100 in the left eye. Vision improved with pinhole to 20/25 in the right eye and 20/30 in left eye. Intraocular pressures and anterior segment examination were unexceptional. Dilated fundus examination revealed mild temporal optic disc pallor, and a localized oval depression at the temporal border of optic disc in the left eye. No macular abnormalities were observed. OCT supported the clinical findings with mild temporal thinning of the nerve fiber layer in the region of the optic disc pit. HVF 30-2 findings showed a superior arcuate defect. HVF 10-2 revealed a trace subtle defect. MfERG findings revealed differences in voltage amplitude and waveform latencies in the specific region of the optic disc pit when compared with corresponding regions in the right eye. VEP findings were abnormal in both eyes, with poorly defined n135 waveforms at 15 minutes check size of stimulation. Latencies and amplitudes of n75 and p100 waveforms in the left eye were slightly prolonged and reduced, respectively.

Conclusions:

Optic disc pit is a rare congenital condition, first reported by Weithe in 1882.¹ Although OCT is commonly used to describe the morphology of optic disc pits,² few studies have reported mfERG and VEP findings. Both mfERG and VEP appear to have a role in defining the electrophysiology characteristics of optic disc pits.

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Keywords: Optic Disc Pit, Electroretinography, Visual Evoked Potentials

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 79
Right in Front of Your Face

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Introduction:

Neurosarcoidosis is a rare but well documented cause of vision loss and should be considered when neuroimaging shows multiple enhancing intracranial masses.

Methods:

Case report

Results:

A 54-year-old African American woman with diabetes and hypertension presented with a 2-week history of painless left-sided vision loss and a 6-month history of a red-brown cutaneous lesion at the right nasal bridge. Best-corrected visual acuity was 20/25 on the right and counting fingers on the left with a left relative afferent pupillary defect. Anterior segment and dilated fundus examinations were unremarkable. MRI with contrast showed irregular, nodular enhancement of both optic nerve sheaths with a 4x4x2 mm-nodular enhancing mass abutting the medial aspect of the left optic nerve just posterior to the orbital apex. There were an additional 3 extra-axial enhancing lesions along the superior margin of the left tentorium, the medial aspect of the right middle cranial fossa, and the vertex. Workup revealed normal CBC, ANA, ACE level, and lysozyme. CSF analysis showed a mild lymphocytic pleocytosis with normal glucose and negative cytology. Punch biopsy of the cutaneous lesion revealed non-caseating granulomas consistent with sarcoidosis. CT of the chest showed hilar adenopathy. A diagnosis of neurosarcoidosis was made. Treatment with 60 mg of oral prednisone led to rapid improvement of visual acuity to 20/30 in the left eye, reduction in the size of all of the intracranial masses, and complete resolution of the orbital apex mass compressing the left optic nerve. She is now stable on azathioprine and a slow steroid taper.

Conclusions:

Neurosarcoidosis can cause vision loss via direct optic nerve sheath involvement, and is important to consider in the differential diagnosis of enhancing CNS lesions. Prompt identification of systemic manifestations and biopsy of a skin nodule characteristic of cutaneous sarcoidosis aided in this patient's prompt diagnosis and successful treatment.

References: None.

Keywords: Neuro-Ophth & Systemic Disease, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 80

Visual Evoked Potential Findings in a Case of Posterior Ischemic Optic Neuropathy Following NSAID-Induced Gastrointestinal Hemorrhage

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Introduction:

This case report aims to add to the paucity of clinical data on posterior ischemic optic neuropathy (PION) by presenting the electrophysiological findings in an unusual case of PION following NSAID-induced gastrointestinal (GI) hemorrhage.

Methods:

ISCEV guidelines were followed to record single channel VEP (visual evoked potential) findings. Results of SITA-standard Humphrey visual field (HVF) and spectral-domain OCT were also obtained.

Results:

A 56-year-old male presented with history of decreased vision in left eye for 3 years following an acute episode of GI hemorrhage secondary to NSAID use for chronic shoulder pain. Upon initial examination, visual acuity was 20/20 in the right eye (OD) and hand motion in left (OS). Intraocular pressures and anterior segment exam were unexceptional. A dilated fundus exam revealed bilateral disc pallor, 1+ in OD and 2+ in OS. HVF results revealed an inferior arcuate defect in OD, and non-specific peripheral visual field loss, with infrotemporal preservation in OS. OCT of optic nerves showed bilateral temporal thinning of the nerve fiber layer and other regions consistent with areas of visual field loss. VEP findings were abnormal, with prolonged latencies and decreased amplitudes observed bilaterally.

Conclusions:

With anterior etiologies accounting for 90% of cases of ischemic optic neuropathy, little has been reported about PION[1]. Unlike anterior ischemic optic neuropathy, PION is difficult to recognize due to its rarity and relatively subtle clinical exam findings. Additionally, the vast majority of PION cases occur perioperatively [1] rather than in association with medication use as in our patient. To the best of our knowledge, this is the first reported use of VEP findings to assess PION in NSAID induced GI hemorrhage. [1] (Biousse & Newman, NEJM, June 2015)

References:

Biousse, Newman, Ischemic Optic Neuropathies, New England Journal of Medicine, Vol. 372, pages 2428-2436, June 2015

Keywords: Posterior Ischemic Optic Neuropathy, Visual Evoked Potentials, Ischemic Optic Neuropathy, Optic Neuropathy, Electrophysiology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 81

Neuro-Ophthalmologic Manifestations of Cholangiocarcinoma: A Case Series

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Introduction:

Cholangiocarcinoma is a rare liver malignancy originating in the biliary epithelium. Patients may present with signs and symptoms of biliary obstruction, or nonspecific complaints such as malaise, weight loss, and night sweats. It is uncommon for this malignancy to spread distally and our review of the literature identified only 16 cases of brain metastasis from cholangiocarcinoma none of which presented neuro-ophthalmologic manifestations. Metastasis to the brain and orbit can result in neuro-ophthalmologic deficits such as diplopia, proptosis, and decreased vision. We present the first and largest series of the neuro-ophthalmologic manifestations of cholangiocarcinoma.

Methods:

We completed a retrospective chart review of recent cholangiocarcinoma patients presenting to ophthalmology clinics within two tertiary care centers in the Texas Medical Center.

Results:

Chart review identified four patients with neuro-ophthalmologic symptoms related to cholangiocarcinoma. One patient presented with diplopia due to metastasis to the left medial rectus, two had involvement of the brain resulting in sixth nerve palsy and hemianopsia, and one presented a hypercoagulable state that predisposed the patient to a stroke causing homonymous hemianopsia and visual hallucinations. The clinical presentation of these patients included symptoms of partial to complete vision loss, diplopia, and visual hallucinations.

Conclusions:

Neuro-ophthalmic manifestations of cholangiocarcinoma depend upon both mechanism and localization. We report 4 cases of cholangiocarcinoma with neuro-ophthalmologic findings. To our knowledge, this is the largest such series reported in the English-language ophthalmic literature.

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Keywords: Tumors, Optic Neuropathy, Visual Fields, Neuro-Ophth & Systemic Diseases

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 82**Tacrolimus Optic Neuropathy: A Case Series and Review of the Literature**

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Introduction:

Tacrolimus is a potent immunosuppressant that inhibits cytokine synthesis and blocks T-cell development. Optic neuropathy from tacrolimus toxicity is very uncommon with only a few case reports in the literature. We report three cases of tacrolimus optic neuropathy following bone marrow transplant complicated by graft versus host disease. These three cases demonstrate differing clinical and radiologic presentations of tacrolimus optic neuropathy.

Methods:

Case series and review of the literature

Results:

The first case presented with unilateral optic nerve head swelling and peripapillary hemorrhages similar in appearance to NAION with a normal appearing MRI. The second case demonstrated bilateral optic nerve head edema with flame shaped hemorrhages and the MRI demonstrated subtle enhancement of both optic nerves. The third case had normal appearing optic nerves with a clinical presentation of bilateral optic neuropathy, however the MRI demonstrated profuse T2 hyper intensity throughout the anterior medulla, pons, midbrain and internal capsule in addition to T2 hyper intensity of the optic nerves. This patient's marked clinical and radiographic findings were noted to improve following cessation of the medication

Conclusions:

Tacrolimus optic neuropathy can present as a unilateral, bilateral, anterior or posterior optic neuropathy. Enhancement of the optic nerve may or may not be present and additional radiologic findings can include diffuse intracerebral lesions. Lastly, all of our patients had graft versus host disease which raises the suspicion of whether patients with GVHD have a higher propensity to develop optic neuropathy from tacrolimus. Being aware of the spectrum of clinical presentation will help the neuro-ophthalmologist to detect this vision threatening toxicity.

References: None.

Keywords: Tacrolimus Toxicity, Optic Neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 83**Intraocular-Orbital-Cerebral Toxoplasmosis as an Initial Presentation of AIDS**

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Introduction:

To Demonstrate Clinical Manifestations and Treatment Outcome of Intraocular-Orbital-Cerebral Toxoplasmosis in Newly Diagnosed HIV-Infected Patient

Methods:

Case report

Results:

A 67-year-old Thai man presented with acute painful visual loss of his right eye for 5 days. External examination of right eye showed visual acuity of no light perception (NLP), complete ptosis, generalized chemosis, axial proptosis and severe ocular motility restriction. External examination of left eye was unremarkable. Slit-lamp bio-microscopy of right eye revealed active panuveitis with large area of infiltration involving entire posterior segment, particularly in the posterior pole. Slit-lamp bio-microscopy of left eye was significant only for senile cataract. MRI of the brain and orbit showed profound right optic nerve sheath enhancement, right orbital inflammation and multiple targetoid lesions in the brain. He was subsequently diagnosed with HIV infection according to the presence of anti-HIV antibody in his serum. Lumbar puncture was not performed regarding high risk of brain herniation. PCR for *toxoplasma sp.* was positive from aqueous humor of right eye. After treatment with oral Trimethoprim/Sulfamethoxazole for 6 days, the patient demonstrated clinical improvement except for NLP of his right eye. This was confirmed by MRI which showed marked decrease enhancement of right optic nerve sheath and numbers of targetoid lesions.

Conclusions:

Concurrent intraocular-orbital-cerebral involvement is a rare clinical presentation of toxoplasmosis. Patient with new-diagnosed HIV infection can present with this uncommon manifestation. In our case, the diagnosis was confirmed by positive PCR for *toxoplasma sp.* from aqueous humor and significant improvement after treatment.

References: None.

Keywords: Neuro-Ophth & Infectious Disease, Neuroimaging, Optic Neuropathy, Orbit/Ocular Pathology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 84**Total Absence of Conjugate Horizontal Eye Movements and Facial Paresis as the First Presentation of Multiple Sclerosis**

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Introduction:

Eye movement abnormalities are a common manifestation of Multiple sclerosis (MS). Here we report a patient with total absence of conjugate horizontal eye movements, and facial diparesis, as an initial presentation of MS.

Methods:

Case report and review of literature.

Results:

An 18 year old girl presented with a two-month history of blurry vision, diplopia and new left facial droop involving the upper and lower face. She had right facial droop one month before this admission that improved after receiving steroid treatment for presumed Bell's palsy. On exam, she had absent horizontal saccades, pursuit, VOR, and OKN, but spared convergence. Upper eyelids, pupils and vertical eye movements were intact. The initial differential diagnosis included a vascular or inflammatory etiology and Miller-Fisher syndrome. MRI showed a pontine, paramedian T2 hyper-intense lesion, with subtle post-contrast enhancement, involving bilateral sixth nerve nuclei and facial colliculi. In addition, multiple other T2 hyper-intense lesions were also observed, some enhancing, indicating dissemination in time and space satisfying MS diagnostic criteria. CSF studies revealed multiple oligoclonal bands. She was treated with five days of steroids, and Interferon Beta-1a. On follow up three weeks later, she regained horizontal ductions of the right eye. The abduction of the left eye was still impaired. Pursuit and VOR failed to improve left abduction.

Conclusions:

The abducens nucleus is the final common pathway for all horizontal conjugate eye movements. A complete bilateral conjugate gaze paralysis associated with preceding peripheral facial diparesis suggests a demyelinating lesion affecting the facial colliculi with secondary inflammation of the immediately adjacent bilateral abducens nuclei. To our knowledge, absent conjugate horizontal eye movements complicating acute bilateral facial colliculi demyelination have not been previously reported in MS.

References: None.

Keywords: Demyelinating Disease, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 85

Bilateral Vision Loss Due to Chiasmal Neuropathy Secondary to Muslinoma

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Introduction:

Intracranial aneurysms are surgically managed by microsurgical clipping of the aneurysm neck, endovascular coiling of the aneurysm sac or balloon occlusion of the parent vessel. Cases with broad-based aneurysms may not be amenable to these techniques. Microsurgical wrapping of the aneurysm wall with muslin may be applied.

Methods:

Case report, and review of literature.

Results:

We report a case of 59-year-old female who initially presented with the incidental finding of multiple intracranial aneurysms on MRI. She underwent elective clipping of the right MCA bifurcation aneurysm and wrapping of a small anterior communicating artery aneurysm with muslin. After 40 months, she experienced progressive, bilateral visual loss, facial pain and retrobulbar headache. On examination, best corrected visual acuity was 20/25 in the right eye and counting fingers in the left eye, with color vision of 10/13 in the right eye and 0.5/13 in the left and a 0.6 log APD in the left eye. Visual field testing revealed a junctional scotoma, with dense central vision loss in the left eye. Cranial magnetic resonance imaging revealed multiple enhancing lesions surrounding both aneurysms and involving the optic chiasm. Intravenous methylprednisolone (1g/day) was administered over for 5 days, with significant improvement in acuity and fields within 36 hours. After 1 month, visual acuity improved to 20/20 in the right eye and 20/30 in the left with near-complete resolution of the visual field defect.

Conclusions:

A muslin-induced optic neuropathy is a rare but serious complication of a chronic inflammatory reaction in response to muslin wrapping. Treatment options include surgery, steroids and cyclophosphamide, but recovery of the vision is unpredictable. Muslin should only be utilized with caution in neurovascular repairs in close proximity to the anterior visual pathway. Patients with muslin in close proximity to the visual pathway need to be warned about and screened for vision loss.

References: None.

Keywords: Muslinoma, Aneurysm, Chiasmal, Neuritis

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 86**Horner Syndrome in a Patient with Marfan Syndrome and Carotid Artery Tortuosity**

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Introduction:

Marfan syndrome (MFS) is an autosomal dominant disorder of the connective tissue characterized by early development of thoracic aortic aneurysms and/or dissections. The presence of MYH-11 mutation has been associated with Familial thoracic aortic aneurysm and dissection (TAAD). Horner syndrome in a patient with MFS indicates carotid dissection until proven otherwise.

Methods:

Case report, and review of literature.

Results:

A 15-year-old male with a Marfanoid habitus presented for outpatient ophthalmic evaluation. His ocular examination revealed distance uncorrected visual acuity of 20/20 in each eye. He had no classical ocular signs of MFS with normal lenses and reasonable keratometry. However, he did have some retinal arterial tortuosity more obvious in right eye than the left. He was found to have a variance of both the Fibrillin 1 (FBN1) and the Myosin-11 (MYH11) genes. Echocardiography revealed aortic root dilatation (38mm) but no other abnormalities. Four months later, he presented for an urgent evaluation of a droopy right eyelid and asymmetric pupils noticed by the parents. He was found to have 2mm ptosis and anisocoria in the pattern of right Horner syndrome. The diagnosis was confirmed pharmacologically using apraclonidine with reversal of anisocoria. He was referred for an urgent neurological evaluation and neuro-vascular imaging that revealed bilateral carotid and vertebral artery tortuosity with no signs of dissection.

Conclusions:

Horner syndrome is one of the presenting neurologic findings in patients with carotid dissection (present in about 50% of patients). Early recognition of Horner syndrome, allows early diagnosis and prompt management of carotid artery dissection to prevent its neurovascular complications. Our case did not have any radiological findings of dissection. However, we theorize that oculosympathetic neurotmesis may have resulted from the repeated trauma of the carotid pulsations and daily head movements given the weak connective tissue support of the sympathetic chain.

References: None.

Keywords: Horner, Marfan, Taad, Aneurysm

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 87

Leukemic Infiltration of the Optic Nerve

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Introduction:

Leukemic infiltration of the optic nerve is rare and optic neuropathy as presenting symptom of relapse in patients with leukemia is rarer still. We report a patient with acute myelogenous leukemia (AML) who was in remission yet relapsed with an acute optic neuropathy in the left eye.

Methods:

A 30-year-old woman presented with a 1 month history of painless progressive visual loss in her left eye (OS). She denied any previous ocular history. She had a medical history of acute myelogenous leukemia (AML) for which she received induction chemotherapy and 4 cycles of consolidation chemotherapy resulting in complete remission 9 months ago. Examination showed a visual acuity of 20/25 in the right eye (OD) and count fingers OS. She had a relative afferent pupillary defect OS. Confrontation visual field was normal OD and severely constricted OS. Ocular motility was normal and there was no ptosis or proptosis. Anterior segment and posterior segment examinations were unremarkable including a sharp, pink, and healthy optic nerves.

Results:

Pattern VEP was normal OD and non-recordable OS. With the flash VEP, the P-100 was delayed at 120 ms OS. A gadolinium enhanced, fat-suppressed cranial and orbital MRI showed focal enlargement and enhancement of the intracranial segment of left optic nerve consistent with leukemic infiltration. The patient was admitted, prescribed high dose IV methylprednisolone and received systemic and intrathecal chemotherapy. Allogeneic transplantation and radiotherapy to the left optic nerve are being discussed at the time of submission of this case.

Conclusions:

In a patient with a history of leukemia and acute optic neuropathy, leukemic infiltration of the optic nerve is the main differential diagnosis. Contrasted fat-suppressed cranial and orbital MRI imaging is very helpful in the detection of the leukemic optic nerve infiltrate with the infiltrated optic nerve characteristically enlarged and enhancing. A variety of therapies have been proposed for leukemic infiltration of the optic nerve including intrathecal chemotherapy and radiotherapy. The optimal therapy for our patient remains to be seen.

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Keywords: Optic Neuropathy, Chemotherapy and Radiation, Neuroimaging, Leukemia

Financial Disclosures: The authors had no disclosures.

Grant Support: Unrestricted Grant from Research to Prevent Blindness (New York, NY).

Poster 88**Malingering and Secondary Gain in the Afghanistan and Iraq Conflicts**

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Introduction:

Functional or non-organic visual loss (NOVL) is defined as a loss or decrease in visual acuity or visual field range with no identifiable organic cause. NOVL can be a difficult diagnosis to make and requires a high index of suspicion. This can be especially difficult in the setting of true organic pathology, as was the experience with several patients presenting to an Ophthalmology clinic after sustaining either ocular or non-ocular injuries. This case series examines several such patients with NOVL that were either injured or developed an ocular condition while serving in Iraq or Afghanistan. The aim of this series is to provide a review of several possible presentations of NOVL and the various modalities that the ophthalmologist can use to arrive at a diagnosis of NOVL.

Methods:

A retrospective chart review was conducted of patients with NOVL presenting to an Ophthalmology department after sustaining either ocular or non-ocular injuries during operations in Iraq or Afghanistan.

Results:

Seven patients were diagnosed with NOVL after sustaining either ocular or non-ocular injuries during operations in Iraq or Afghanistan. A variety of useful techniques are available, including binocular visual fields, 4 PD prism test, and refractive fogging, to better assess for a possible functional overlay.

Conclusions:

The process of diagnosing NOVL begins with a detailed history and a high index of suspicion. The exam and work-up must be thorough to exclude any possible organic pathology that could be contributing to the patient's symptoms. Once NOVL is suspected, the ophthalmologist has several simple examination techniques at their disposal to properly identify these patients in a timely fashion that may eliminate or reduce the need for additional and more costly testing. The early recognition and diagnosis NOVL, though often a tedious task for the clinician, is essential for the appropriate care and proper disposition of these patients.

References: None.

Keywords: Non-organic visual loss, Functional Visual loss, Malingering

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 89

Congenital Hereditary Idiopathic Horner Syndrome in an Upstate New York Family

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Introduction:

Congenital hereditary idiopathic Horner syndrome has been rarely described in the literature, herein we present three affected first-degree relatives.

Methods:

Case series and literature review.

Results:

A 44-year-old woman was referred for possible pseudotumor cerebri. She incidentally reported a left “eye droop” present from birth. Pupils measured 4 mm OD, 3.5 mm OS in light, and 5 mm OD, 4.5 mm OS in dark. Marginal reflex distance (MRD) was 6 mm OD, 3 mm OS. Her palpebral fissure height was 8 mm OD, 6 mm OS. After the instillation of 0.5% apraclonidine, pupils measured 3.5 mm OD, 3.5 mm OS in light, and 4 mm OD, 4.5 mm OS in dark. MRD was 7 mm, 5 mm, respectively. Palpebral fissure height measured 10 mm, 11 mm, respectively. A CTA head and neck were normal with no carotid dissection. At a subsequent visit, her 10-year-old son and 76-year-old mother were examined and found to have ptosis and miosis, without heterochromia iridum or anhidrosis. The son exhibited reversal of ptosis and the mother exhibited reversal of ptosis and anisocoria to apraclonidine. In all cases, ptosis was noted since birth, and there was no history of birth trauma. A post-ganglionic lesion is surmised in all three cases. The patient reports that her sister, maternal grandmother, and a maternal first-cousin also exhibit ptosis. A review of literature identified five case reports of hereditary congenital Horner syndrome (1918 - 1992). They described an autosomal dominant inheritance with variable penetrance, consistent with the family we studied.

Conclusions:

Congenital hereditary idiopathic Horner syndrome is an autosomal dominant condition with incomplete penetrance. We report three first-degree relatives with ptosis and miosis. Further exploration including a genome wide association study of this family could improve our understanding of the developing sympathetic nervous system.

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Keywords: Congenital, Hereditary, Idiopathic, Horner Syndrome

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 90

Rhinocerebral Mucormycosis in an HIV/AIDS Patient Presenting as Isolated Unilateral Sixth Nerve Palsy: Case Report and Literature Review

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Introduction:

Mucorales causes a rare but serious and potentially life-threatening fungal infection. Mucorales is invasive and angiotrophic. It causes significant vascular changes including thrombus, arteritis and aneurysm.¹ It occurs primarily in immunocompromised individuals with compromised neutrophil function. The occurrence in HIV/AIDS patients is rare since T cell is not the main defensive mechanism and neutrophil function is relatively preserved with those patients.^{2 3 4} In this report, we have a case of rhinocerebral mucormycosis that presented as isolated sixth nerve palsy without Horner's syndrome due to intracavernous internal carotid artery (ICA) mycotic aneurysm in an HIV/AIDS patient. The case is unique due to the clinical presentation, location of the pathology and the uncommon risk factor.

Methods:

This is a case report

Results:

Rhinocerebral mucormycosis can be one of the causes of the isolated sixth nerve palsy without Horner's syndrome.

Conclusions:

As practitioners, we need to be vigilant for the presentation of mucormycosis in HIV/AIDS patient since prompt diagnosis and treatment can potentially significantly impact the outcome of mucormycosis.

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4. Ibrahim, A. S., Spellberg, B., Walsh, T. J. & Kontoyiannis, D. P. Pathogenesis of mucormycosis. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 54 Suppl 1, S16–22 (2012).
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Keywords: Abducen, Mucor, HIV

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 91

A Jaw Dropping Case

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Introduction:

A 78-year-old woman presented with two months of intermittent diplopia associated with headaches and jaw pain that worsened with chewing.

Methods:

Case Report.

Results:

Her medical history was significant for hypertension, hyperlipidemia and breast cancer (s/p lumpectomy and chemotherapy 24 years prior). On initial presentation, she had normal visual acuity and full ductions. She had a small right hypertropia that worsened in left gaze and right head tilt. ESR and CRP were normal. A head CT and brain MRI were unremarkable. A left temporal artery biopsy revealed no vasculitis. EMG with repetitive stimulation was normal. Serum acetylcholine receptor, MuSK, and voltage-gated calcium channel antibodies were normal. One month later she presented with worsening headaches and diplopia. She also experienced jaw weakness so severe she had to use her hand to close her jaw in order to chew solid foods. On examination she had ptosis, exotropia, left adduction deficit, left hypertropia, inability to close her jaw, and weak eyelid closure. She had lower extremity ataxia and reduced deep tendon reflexes (absent in the lower extremities). Anti-GQ1B antibodies were not present, and a repeat brain MRI with contrast was unchanged. A lumbar puncture was performed. CSF analysis revealed WBC 91 (15% segs), RBC 3000, protein 160, glucose 13. Cytology was positive for metastatic carcinoma. Chest CT revealed a 0.5 cm pulmonary nodule and a right breast soft tissue mass.

Conclusions:

This elderly patient presented with fluctuating diplopia, headache and jaw pain. When GCA and a myasthenic syndrome had been ruled out, it was assumed she had a microvascular cranial nerve palsy. Instead of improving, however, she developed multiple cranial nerve palsies, ataxia and areflexia. Two MRI brain studies were non-diagnostic. Although the Miller Fisher variant of GBS was considered, lumbar puncture revealed a pleocytosis and hypoglycorrhachia, and CSF cytology confirmed the correct diagnosis. Final diagnosis: Meningeal carcinomatosis (primary breast cancer with metastatic disease).

References:

1. Iqbal Z, Michael BD, Pomeroy I, Ali R, Wilson M, Wiesmann U. Multiple cranial neuropathies: One diagnostic difficulty. *Practical Neurology*; 12:195-198, 2012.
2. Nakatsuji Y, Sadahiro S, Watanabe S, et al. Leptomeningeal signet-ring cell carcinomatosis presenting with ophthalmoplegia, areflexia and ataxia. *Clin Neuropathol*. 20, 272-5, 2001.

Keywords: Diplopia, Neuro-Ophth & Systemic Disease, Multiple Cranial Neuropathies, Meningeal Carcinomatosis

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 92
Slowly Eye Turned

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Introduction:

In the setting of an otherwise isolated sixth nerve palsy without vascular risk factors, it is important to evaluate reflex tearing with a Schirmer test as the presence of ipsilateral decreased tearing can localize the lesion to the petrous apex.

Methods:

Case report.

Results:

A 63-year-old healthy man presented with three months of painless horizontal diplopia. He denied weakness, ptosis, trouble swallowing or difficulty breathing. His previous MRI brain was reportedly normal. Edrophonium testing reportedly improved his right abduction deficit, although the patient denied improvement. A single fiber EMG was supportive of the diagnosis of myasthenia gravis. His diplopia improved but did not resolve with 100 mg prednisone every other day. On examination, his vision was 20/20 bilaterally. 24-2 Humphrey automated SITA-fast perimetry was normal. His pupils were 3mm OU briskly reactive without RAPD with palpebral fissures of 8mm OU. He had visibly slowed and limited abduction OD with 2.5mm abduction OD compared to 9mm abduction OS. There was no nystagmus, lightening saccades, lid twitch or fatigue and no evidence of proptosis or retraction. He had a large esotropia in primary gaze that increased in right gaze. Slit lamp examination and dilated fundus evaluation were unremarkable. V1-V3 sensation was intact. A Schirmer test with anesthetic and intranasal tickle was performed with 2mm OD and 19mm OS. Review of previous MRI revealed a destructive right petrous apex mass, which was resected and found to be a chondroma. On evaluation six months later, his saccadic velocity and abduction normalized, but his tearing deficit persisted.

Conclusions:

Identification of an ipsilateral reflex tearing deficit in the setting of an otherwise isolated sixth nerve palsy localizes the lesion to the petrous apex. Furthermore, it is important to differentiate the supranormal saccadic velocity in myasthenia gravis from the slowed saccadic velocity in sixth nerve palsies.

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Keywords: Ocular Motility, Neuroimaging, Skull Base, Tumors, Myasthenia

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 93

A Difficult Day with Double Trouble

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Introduction:

A 59 year old woman with a history of hypothyroidism, an inner ear implant and lupus (complicated by autoimmune hemolytic anemia and raynaud's disease) presented with 1 week of intermittent horizontal binocular diplopia. She denied headache and giant cell arteritis symptomatology. Examination demonstrated normal afferent function, full ductions and an incomitant esotropia worse in right gaze. She was diagnosed with a subtle microvascular right sixth nerve palsy. Two weeks later, she developed intractable bifrontal headaches and photosensitivity. On neuro-ophthalmic evaluation she had bilateral limitation of abduction, left greater than right, and slight limitation of elevation of both eyes. A head CT with enhancement demonstrated slightly enlarged extraocular muscles and crowding of the orbital apex bilaterally. Bloodwork was significant for a slightly elevated WBC count with a longstanding microcytic anemia (Hb 10.4) and thrombocytosis. Thyroid function studies and myasthenia gravis work-up was normal. However, antithyroglobulin antibody was elevated at 59 (N<2). Thyroid orbitopathy was considered a probable diagnosis at this time. However, the patient's complaint of relentless headaches prompted pursuing an MRI brain and orbits with contrast that demonstrated diffuse pachymeningeal enhancement, abnormal enhancing soft tissues in the orbital apices bilaterally particularly surrounding the intercanalicular segments of the optic nerves and enlarged enhancing extraocular muscles. Lumbar puncture demonstrated an opening pressure of 24 cm H2O with normal constituents. Blood ACE, lysozyme, RPR, VDRL, ANCA, complement level and inflammatory markers were unremarkable. The patient improved significantly upon solumedrol although diagnosis was unclear. An immunoglobulin and IgG4 level was ordered and the serum IgG4 level was significantly elevated. A pachymeningeal/leptomeningeal biopsy demonstrated multifocal lymphoplasmacytic infiltrate containing elevated numbers of IgG4 plasma cells in keeping with IgG4 related disease hypertrophic pachymeningitis. The patient responded significantly to solumedrol with resolution of her headache and diplopia and is currently on Rituximab therapy.

Methods:

Case report.

Results:

This patient suffered from IgG4 related hypertrophic pachymeningitis and orbital disease. Her restriction of ductions, extraocular muscle enlargement and elevated antithyroglobulin antibody were most in keeping with thyroid orbitopathy. However, the patient's major complaint of severe headaches and atypical disease course raised suspicion for a more central etiology. Hypertrophic pachymeningitis was first described by Charcot and Joffrey as a condition in which "the neighboring leptomeninges always suffer as well becoming opaque and thick." [i] The disorder can present in a myriad of ways including chronic headache, hypopituitarism, cranial nerve palsies, papilledema, cerebellar ataxia and motor or sensory compromise. It can result from infectious, inflammatory and infiltrative disorders and at times may be idiopathic. [ii][iii] Recognition of IgG4 related disease (IgG4RD) occurred in 2001 in sclerosing autoimmune pancreatitis. [iv] Since then, the spectrum of the disease has significantly expanded to include involvement of multiple organ systems. Effects on the central nervous system by IgG4 occur secondary to hypertrophic pachymeningitis, hypophysitis and infiltration of cranial nerves. The clinical presentation of IgG4RD hypertrophic pachymeningitis is similar to other etiologies pachymeningitis; however, involvement of other organs may provide clues to the diagnosis. In our case, the presence of diffuse pachymeningeal enhancement in addition to diffuse enlargement of the extraocular muscles and orbital soft tissue involvement led to the consideration of this disease in the differential which was later confirmed with pathologic diagnosis.

Conclusions:

The patient's inner ear implant limited initial neuro-imaging to a CT scan that demonstrated enlargement of the extraocular muscles with an elevated antithyroglobulin antibody, which many would consider compatible with thyroid orbitopathy. However the history of the patient's relentless headache did not fit the clinical picture and prompted ordering of an MRI demonstrating diffuse hypertrophic pachymeningitis. The orbital and pachymeningeal findings ultimately led to the consideration of a number of diagnoses, most importantly IgG4 disease. Final Diagnosis: IgG4 related disease presenting as hypertrophic pachymeningitis with orbital involvement

References: None.

References:

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[iv] Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med*. 344(10):732-738. 2001

Keywords: None.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 94**Resolution of Sixth Nerve Palsies Following Treatment with Primary Fractionated Stereotactic Conformal Radiotherapy of Petroclival Meningiomas**

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Introduction:

Petroclival meningiomas are a recognised cause of sixth nerve palsy. Despite their benign pathology, petroclival meningiomas remain a surgical challenge due to the complex anatomy, close association with critical neurovascular structures and difficult exposure of this region. Fractionated Stereotactic Conformal Radiotherapy (FSCRT) is a process whereby radiotherapy is delivered via a fractionated schedule utilizing nonrigid immobilization, thereby providing the precision of stereotaxy while allowing adjacent normal structures to repair sublethal damage. To our knowledge there are no studies on the role of FSCRT on petroclival meningiomas.

Methods:

A review of the case notes of three patients presenting with unilateral (n=2) and bilateral (n=1) sixth nerve palsies secondary to radiologically diagnosed petroclival meningiomas treated with primary FSCRT, was undertaken.

Results:

All three patients were treated with FSCRT and received 50Gy in 30 fractions with 6MV Photons over a period of six weeks. MRI scans were performed at diagnosis, 3 months post treatment and annually thereafter. All three patients achieved a marked symptomatic and clinical improvement following treatment and this persisted throughout the five year follow-up period, obviating the need for Fresnel prisms. The mean percentage reduction in the distance angle of the esotropia was 99% (range 97%-100%). None of the patients experienced side-effects related to the treatment.

Conclusions:

Stereotactic radiosurgery (SRS) is considered a good first-line treatment for small tumours. FSCRT, however, is helpful in cases in which SRS has limitations, such as with tumours arising near critical neurovascular structures. The results of FSCRT in skull base tumours, with respect to tumour control and improvement of neurological deficits have been comparable to SRS. FSCRT shows promising results for the management of symptomatic sixth nerve palsies secondary to petroclival meningiomas and should be offered as first line therapy.

References: None.

Keywords: Adult Strabismus with a Focus on Diplopia, Ocular Motility, Neuroimaging, Tumors

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

One-and-a-Half Syndrome Evolving Into an Eight-and-a-Half Syndrome

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Introduction:

One-and-a-half syndrome was first coined by C. Miller Fisher in 1967 to describe a combination of horizontal gaze palsy and internuclear ophthalmoplegia caused by a lesion in the median longitudinal fasciculus (MLF) or parabrachial reticular formation (PPRF).[1] The constellation of one-and-a-half syndrome plus fascicular cranial nerve VII involvement was referred to as eight-and-a-half syndrome by Eggenberger in 1998.[2] In this case, we describe a case one-and-a-half syndrome with a delayed onset of cranial nerve VII involvement.

Methods:

62 year old gentleman with a history of hypertension, hyperlipidemia, COPD, aortic insufficiency, current smoker, and history of alcohol abuse presented with new onset binocular, horizontal diplopia. On presentation, he had a right sided horizontal gaze palsy and a right sided INO. His seventh nerve was fully intact bilaterally. Lumbar puncture, CT head, as well as MRI brain and brainstem were all unremarkable. On follow-up examination 48 hours later, he was found to have developed a right sided LMN seventh nerve palsy, as well as exposure keratopathy. He subsequently underwent a temporary tarsorrhaphy. The patient was seen at follow-up 7 weeks later with resolution of his presenting signs and symptoms.

Conclusions:

One-and-a-half syndrome and eight-and-a-half syndrome differ by whether cranial nerve 7 is involved. This differentiation is paramount for many reasons, including prevention of exposure keratopathy. Here we present a unique case of delayed onset seventh nerve involvement in a patient with one-and-a-half syndrome caused by a small brainstem infarct, highlighting the importance of close follow-up of one-and-a-half syndrome.

References:

1. Fisher CM, "Some neuro-ophthalmological observations." J Neurol Neurosurg Psychiatry. 1967;30 (5):383-392
2. Eggenberger E, "Eight-and-a-half syndrome: one-and-a-half syndrome plus cranial nerve VII palsy." J Neuroophthalmol. 1998;18(2):114-116

Keywords: One-And-A-Half Syndrome, Eight-And-A-Half Syndrome, Internuclear Ophthalmoplegia, Horizontal Gaze Palsy, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 96

Brown Syndrome: An Uncommon Cause of Diplopia Following Levator Advancement

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Introduction:

Brown Syndrome, the inability to elevate an eye in abduction due to restriction of the superior oblique muscle tendon, can present as a congenital or acquired abnormality. Although uncommon, Brown Syndrome has been described following blepharoplasty.^{1, 2} In this report, we describe a patient who developed Brown Syndrome following levator advancement surgery for blepharoptosis.

Methods:

Observational case report.

Results:

Case description: A 65 year old female presented in January of 2015 for assessment of diplopia. This was first detected in March 2014, two weeks following otherwise uncomplicated levator advancement surgery. The patient stated that the primary intent of the surgery was to elevate the eyelids and was unaware of fat being excised. The operative report was not available for review. Symptoms were described as vertical binocular diplopia when looking to the right. Her evaluation was normal with the exception of well-healed eyelid crease incisions and a 7 prism diopter right hypertropia in right gaze, which increased with supraduction, and decreased with infraduction. She was orthophoric in primary and all other directions of gaze, consistent with Brown Syndrome. One and half years following surgery her evaluation remained unchanged. She was minimally symptomatic and no intervention was pursued.

Conclusions:

Brown Syndrome may result from injury to the superior oblique tendon-trochlea complex during levator advancement surgery.

References:

- 1) Kushner, Jethani. Superior oblique tendon damage resulting from eyelid surgery, *Am J Ophthalmol*, 144:943-948, 2007.
- 2) Wesley, Pollard, McCord Jr. Superior oblique paresis after blepharoplasty, *Plast Reconstr Surg*, 66:283-6, 1980.

Keywords: Brown Syndrome, Blepharoptosis, Double Vision

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 97

Long Term Follow Up of Children With Downgaze Nystagmus at Infancy

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Introduction:

Paroxysmal downgaze nystagmus of infant is an unsettling phenomenon that leads to extensive work-up, although benign outcomes have been reported in sporadic cases. However, long term outcome of these children was not published. Our aim is to report a case series of 7 healthy infants with long neurological and ophthalmological follow up. They all presented with acute onset of episodic paroxysmal tonic downgaze at the ages of 2-12 weeks of age. We describe their spontaneous resolution without neurologic or ophthalmological sequelae.

Methods:

A clinical retrospective case series from two tertiary pediatric ophthalmology centers.

Results:

Six of the seven infants included were born at term (39-41 weeks) with normal pregnancies and deliveries, and only one preterm birth (34th week). All children presented with tonic downgaze nystagmus, with increasing frequency per day, and subsequent gradual decrease until complete resolution within a maximum of 8 months. Each episode lasted a few seconds. In five children symptoms occurred while lying supine. Three infants had concurrent abnormal body movements. No other neurologic or ophthalmic pathologies were found. All infants underwent work-up to exclude metabolic, neurologic and anatomic etiologies. Diagnostic studies included EEG (5 cases), MRI (3 cases), brain US (3 cases), urinary VMA and HMA (5 cases). All tests were negative. The children were followed for up to 10 years (median 2.0 years). Six infants followed normal developmental steps whereas one infant had asymmetric development of motor skills which improved with time.

Conclusions:

Parents and clinicians are usually concerned when paroxysmal tonic downgaze occurs in normal infants born after uneventful delivery. In line with previous reports of sporadic cases, we found tonic downgaze nystagmus of infants to be a benign syndrome that occurs in healthy infants as part of the maturation of the visual system. We describe a good long term outcome. This phenomena may not require a comprehensive clinical investigation.

References: None.

Keywords: Nystagmus, Ocular Motility, Infants, Pediatric Neuro-Ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: This study was supported in part by the Zanvyl and Isabelle Krieger Fund, Baltimore, Maryland.

Poster 98**Complete Bilateral Ophthalmoplegia in the Setting of Elevated Intracranial Pressure that Improved with Transverse Venous Sinus Stenting**

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Introduction:

Elevated ICP is known to cause vision loss, abducens nerve palsy, and rarely oculomotor and trochlear nerve palsies^{1,2}. Severe dysmotility of both eyes in all gazes has not been reported. Venous sinus stenosis has been postulated as a possible pathophysiologic mechanism underlying elevated ICP in the setting of idiopathic intracranial hypertension, and stenting of the transverse sinus has been therapeutic^{3,4}. The current report describes resolution of complete ophthalmoplegia in the setting of secondary elevated ICP treated with transverse venous sinus stenting.

Methods:

Case report and literature review.

Results:

A 32-year-old woman presented after sudden onset of profound vision loss and complete ophthalmoplegia in both eyes in all directions. Neurological exam was unremarkable, but visual acuity was light perception with pallid optic disc edema bilaterally. Brain MRI showed optic nerve edema, and MRV revealed severe stenosis of the right transverse sinus. CSF opening pressure was > 50 cm H₂O. Extensive serum and CSF laboratory studies were all unremarkable. Conventional angiogram with venography and transverse sinus manometry showed venous pressure of 40 - 70 mmHg in the proximal transverse sinus and < 20 mmHg distal to the focal stenotic region. Pressures normalized to 21 - 26 mmHg following transverse sinus stenting, and repeat lumbar puncture showed an opening pressure of 14 cm H₂O. The patient reported significant improvement in her headaches and also showed improvement in her ocular motility, although her vision remained poor at hand motion bilaterally.

Conclusions:

This is a unique case of EIP presenting with complete ophthalmoplegia in addition to vision loss. The patient's findings of transverse sinus stenosis and subsequent improvement after stenting are consistent with retrospective reports in the IIH literature, and suggest that venous sinus stenting may be a viable treatment approach in other forms of elevated ICP.

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Keywords: High Intracranial Pressure/Headache, Ocular Motility, Interventional Neuroradiology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 99

Clinicopathologic Correlation in Lateral Medullary Stroke with Transient Ocular Motor Findings Mimicking Peripheral Vestibular Dysfunction

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Introduction:

Unilaterally decreased horizontal vestibulo-ocular reflex (h-VOR) gain occurs with peripheral vestibular lesions or lateral pontine strokes involving the fascicle or the medial vestibular nucleus (MVN). Vestibular reflexes are typically normal in (LMS). We describe clinicopathologic findings in an unusual LMS presenting transient unidirectional nystagmus and decreased h-VOR gain, mimicking peripheral vestibulopathy (PV). The MVN neurons, close to the stroke core (ischemic penumbra), appeared pathologically normal, suggesting that the initial vestibular signs related to transient ischemia.

Methods:

Clinicopathologic examination of a 61 year-old man admitted to ICU with an acute vestibular syndrome accompanied by aphonia and respiratory distress. He had right-beating nystagmus obeying Alexander's law, an abnormal leftward head impulse test (HIT) confirmed quantitatively by video-oculography, and no skew deviation. He had severe axial lateropulsion and Horner's syndrome. MRI showed a left LMS extending rostrally to the ponto-medullary junction and dorsally to near the MVN. The nystagmus subsided within two days and the horizontal HIT normalized clinically. Three weeks after discharge to rehabilitation, he died of sudden cardio-respiratory arrest. After autopsy, brainstem sections were stained with Luxol Fast Blue, H&E and neurofilament. To explain the ocular motor and vestibular findings, we hypothesized that the MVN was involved pathologically.

Results:

Neuropathological examination showed a left LMS whose extent matched that seen by imaging. Non-ocular motor signs correlated well with structures affected by the infarction. The nearby MVN, however, was spared. The left vertebral artery was occluded and the right was hypoplastic and 50% stenotic.

Conclusions:

We hypothesize that the ischemic penumbra of the LMS may have involved the MVN in the rostral medulla, leading to transiently abnormal h-VOR and unidirectional nystagmus. This is the first case of quantitatively proven abnormal horizontal-HIT during transient brainstem ischemia without pathologic infarction.

References: None.

Keywords: Nystagmus, Ocular Manifestations of Systemic Disorders, Stroke

Financial Disclosures: The first author serves as a non-paid consultant for GN Otometrics

Grant Support: None.

Poster 100

Chronic Progressive External Ophthalmoplegia in the Absence of Ptosis

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Introduction:

Chronic progressive external ophthalmoplegia (CPEO) is a manifestation of various disorders sharing a common pathophysiology of mitochondrial dysfunction leading to progressive extraocular myopathy. It may occur in isolation during adulthood or as part of a multi-organ mitochondrial cytopathy. Ptosis, presenting simultaneously with or preceding ophthalmoplegia, is usually the earliest clinical feature of CPEO.

Methods:

We present two cases of biopsy supported CPEO presenting with diffuse bilateral ophthalmoparesis in the absence of ptosis.

Results:

Case 1 was a 64-year-old Caucasian female who presented with intermittent binocular diplopia for five years. She had mild to moderate diffuse ophthalmoplegia bilaterally and a slightly incomitant 1-4 prism diopter intermittent esotropia. Superior eyelid margin-to-reflex distance (MRD1) measurements were 5 mm bilaterally. Quadriceps muscle biopsy showed scattered cytochrome oxidase (COX) negative fibers and moderate reductions in complex I and III enzymatic activities (25 and 27% of normal, respectively). Case 2 was a 53-year-old Caucasian female with intermittent diplopia for eleven years. Her exam showed bilateral moderate diffuse ophthalmoplegia and a comitant 2-3 prism diopter intermittent esotropia. MRD1 measurements were 3.5 mm and 3 mm. Deltoid biopsy showed numerous fibers with increased succinate dehydrogenase and reduced COX staining. Alternative causes of ophthalmoplegia were excluded in both patients with lab testing, serial exams, and neuro-imaging.

Conclusions:

Clinical heterogeneity is a hallmark feature of mitochondrial diseases; CPEO without ptosis has been reported previously and likely represents one variant along the spectrum of atypical progressive external ophthalmoplegia phenotypes.^{1,2} Timely diagnosis of CPEO with early detection of concurrent systemic disease is important, particularly given its association with cardiomyopathy and cardiac arrhythmias.³ While CPEO almost always presents with myopathic ptosis at the time of diagnosis, clinicians should be cognizant of exceptions to the rule.

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Keywords: Chronic Progressive External Ophthalmoplegia, Mitochondrial Myopathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 101

Torsional Nystagmus Associated with Palatal Tremor in Vertebral Artery Dolichoectasia

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Introduction:

A 50 year-old woman presented with three-month history of oscillopsia. This accompanied with gait disturbance. Her previous medical history was significant for right-side hemiparesis for the last year, DM type2 and essential hypertension. She denied any history of drug abuse. On examination, BCVA was 20/20 in both eyes. Anterior segment and fundus exam were unremarkable. Binocular conjugated pure counter-clockwise torsional nystagmus synchronizing with palatal tremor was observed. The amplitude and frequency of nystagmus were similar in all gazes. Null point was absent. Ocular alignment was orthotropic. Extraocular muscles function, saccadic velocity and smooth pursuit eye movement were all within normal limit. Neurological examination showed right-sided hemiparesis and hyper-reflexia. Cerebellar functions were impaired on the right-side including wide-base gaits, dysdiadokinesia and impaired Finger-to-Nose test. Thin slice axial T2 weighted MRI with fat suppression and Apparent Diffusion Coefficient(ADC) images show dolichoectatic left vertebral artery, exerting pressure effect to the left medulla. A hypersignal intensity T2 change with increased diffusion on the ADC image at the left medulla is also depicted. 3D Time of Flight (TOF) MRA of the posterior circulation reveals dolichoectatic left vertebral artery with redundancy to the right. Hypoplasia of the right vertebral artery is noted. To our knowledge, this is the first case of torsional nystagmus with palatal tremor in vertebral artery dolichoectasia.

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Keywords: Nystagmus, Ocular Manifestations of Vestibular Disorders, Ocular Motility, Vascular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 102**Impaired Rightward Saccades with Preserved Rightward Pursuit Following Right Pontine Ischemic Stroke**

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Introduction:

The pontine paramedian reticular formation (PPRF) is the brainstem saccadic generator. Pursuit axons pass through the PPRF but do not synapse there. In macaques, injection into the PPRF of neuronal toxins that spare axons selectively paralyzes saccades¹. In humans, selective impairment of horizontal and vertical saccades with preserved horizontal pursuit and vestibulo-ocular reflex has been described following cardiac surgery with or without documented systemic hypotension^{2,3}. Imaging has been negative except for one case in which focal FLAIR hyperintensity appeared in the dorsomedial pons unilaterally 10 months after the event. In one autopsied case², there was neuronal necrosis, axonal loss, and astrocytosis in the pontine paramedian reticular formation bilaterally. Ocular motor nuclei and cerebral gaze-generating centers were histologically normal. In a second case³, necropsy pathology was negative, suggesting submicroscopic damage to PPRF inputs as the explanation for saccadic paralysis. We present a patient who developed a selective right horizontal saccadic palsy in conjunction with ipsilateral dorsomedial pontine infarction in the region of the PPRF.

Methods:

Case Report

Results:

A 53 year-old woman had sudden imbalance and inability “to look to my right.” Neurologic examination disclosed left upper extremity and gait ataxia. One day later, our first examination revealed slow and incomplete rightward saccades initiated by blinking. Pursuit was normal in all directions of gaze, as were leftward and vertical saccades. (VIDEO). Diffusion-weighted brain MRI showed restricted diffusion in the right dorsomedial pons and extensive cerebral white matter T2/FLAIR hyperintensity.

Conclusions:

This is the first case to show selective impairment of unilateral horizontal saccades with restricted diffusion in the region of the ipsilateral PPRF. It supports animal evidence that selective impairment of horizontal saccades may occur from a discrete pontine lesion. It is a reminder that complete clinical assessment of eye movements must extend beyond having the patient pursue your finger!

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3. Eggers S, Moster M, Cranmer K. Selective saccadic palsy after cardiac surgery. Neurology 2008;70:318-320.

Keywords: Ocular Motility, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 103

Complete Ophthalmoplegia and Extraocular Muscle Atrophy in a Patient with Craniofacial Scleroderma with CNS Involvement

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Introduction:

Craniofacial scleroderma includes a spectrum of disease from linear scleroderma (*'en coup de sabre'*) to progressive hemifacial atrophy (Parry-Romberg syndrome). It is an uncommon cause of external ophthalmoplegia as a result of atrophic myopathy, the pathophysiology of which is incompletely understood. In addition, central nervous system changes are a not uncommon finding in this spectrum of disease.

Methods:

We report a case exhibiting extreme findings and a review of the literature.

Results:

We present a 61-year-old Caucasian woman with chronic external ophthalmoplegia of her right eye greater than her left, which was first noted at age 12, with the onset of diplopia. This gradually progressed, twice requiring strabismus surgery. Abnormalities on an unrelated brain MRI and subsequent LP revealing oligoclonal bands led to a diagnosis of multiple sclerosis. There is no history of focal neurologic deficits but a questionable seizure history. On examination her afferent visual function was normal except for a mild superior visual field defect OS on automated perimetry. Motility of the right eye was severely limited in all gazes. The left eye showed markedly limited supraduction and adduction but was otherwise relatively full. Dilated fundusoscopic examination revealed optic atrophy and enlarged cup-to-disc ratios. She had a linear indentation along her right fronto-parietal region including bone and overlying soft tissues without alopecia or significant fibrotic skin changes. MRI of brain and orbits showed multiple T2 and FLAIR white matter hyperintensities and severe atrophy of all right eye extraocular muscles and left eye medial rectus.

Conclusions:

This case highlights an unusual presentation of craniofacial scleroderma. It is atypical in both its severity of ophthalmoplegia and the contralateral involvement of both extraocular muscle atrophy and CNS changes. In addition, it underscores the need to consider craniofacial scleroderma syndromes in the differential of multiple sclerosis in atypical patients.

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Keywords: External Ophthalmoplegia, Craniofacial Scleroderma

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 104**Preservation of Reading in a Patient with Acquired Impairment of Saccadic Function**

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Introduction:

Saccadic disturbance after cardiac surgery is a well-recognized but a poorly understood phenomenon. Historical notions suggest that absence of saccadic function, at least in the horizontal plane, should significantly compromise the ability to read. We present a case of a 49-year-old man with clinically obvious loss of saccadic function after surgical repair of aortic dissection. Upon questioning, the patient reported no difficulty at work where he had to do considerable reading. This apparent discrepancy was analyzed with quantitative eye movement recordings.

Methods:

A case report with analysis of the clinical features and quantitative measures of eye movements that were obtained using Neuro Kinetics, Inc. I-Portal®-Neuro-Otologic Test Center. The test apparatus consisted of a rotatory chair, a visual stimulus, and a digital eye tracking system. We used a standard battery of tests and added one test to measure horizontal eye movements while reading text.

Results:

The clinical exam revealed essentially complete absence of volitional saccades in both the horizontal and vertical planes. Eye movement recordings showed marked slowing and hypometria of all voluntary saccades in both horizontal and vertical planes. His optokinetic quick phases of nystagmus were absent, while the optokinetic ocular pursuit reflex was normal. The horizontal and vertical sinusoidal pursuit was normal. When reading, the patient was able to generate a series of quite small, hypometric saccades without compensatory blinks and head thrusts. These hypometric saccades also replaced the large-amplitude leftward return saccade that normal subjects make at the end of each line to re-orient the eyes to the beginning of the next line.

Conclusions:

The syndrome of saccadic palsy after cardiac surgery includes a spectrum of saccadic abnormalities. This case is unique in that the patient reported normal ability to read, and quantitative recordings documented small-amplitude saccades that generally sufficed for reading.

References:

Solomon D, Ramat S, Tomsak RL, Reich SG, Shin RK, et al. Saccadic palsy after cardiac surgery: characteristics and pathogenesis. *Ann Neurol* 63:355-65 (2008).

Keywords: Saccades, Reading, Cardiac Surgery

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 105**The Clinical Overlap of Long-Standing Optic Neuropathy and Retinal Arterial Occlusion – The Value of Optic Coherence Tomography to Establish the Anatomical Diagnosis and to Guide Management**

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Introduction:

In the acute phase of blindness, the clinical distinction between an optic neuropathy and retinal arterial occlusion is straightforward. In the former, there is often edema of the optic nerve head, especially in non-arteritic anterior ischemic optic neuropathy (NAION). With occlusion of either the central or branch retinal arteries, there is usually edema of the respective area of the retina. After the acute phase, however, the clinical distinction between an old optic neuropathy and an old vascular retinopathy can be challenging given that optic nerve pallor can be present in either case. Establishing the correct anatomical diagnosis is critical because the management and systemic implications of these two conditions are quite disparate.

Methods:

We describe a case series of three patients whose initial clinical presentations were thought to be consistent with NAION. None of the patients had edema of the retina or optic nerve in the acute phase. Optic coherence tomography (OCT) was used to assess the thickness of the inner 2/3s of the retina to search for evidence of inner retinal ischemia.

Results:

All patients had reduced acuity, an afferent pupillary defect and optic nerve head pallor in the affected eye. In all three cases OCT of the retina demonstrated significant reduction of the thickness of the inner two thirds of the retina. This finding motivated a different approach to management.

Conclusions:

After the acute phase, it can be difficult to distinguish retinal from optic nerve ischemic, and one might be misled by the finding of optic nerve pallor. OCT of the retina can be used to identify evidence in support of a diagnosis of retinal ischemia. In such a case, a search for an embolic source should generally be performed. In the absence of such information, the diagnosis might be mistakenly assumed to be an optic neuropathy.

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Keywords: Retinal Artery Occlusion, Non-Arteritic Ischemic Optic Neuritis, OCT

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 106**MALT Lymphoma Masquerading as Thyroid Orbitopathy**

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Introduction:

Clinical presentation appeared c/w compressive optic neuropathy secondary to thyroid eye disease. However imaging revealed a different story.

Methods:

Case Report

Results:

67 y/o WF referred for disc edema OS, complaining of distortion OS x 1 year. No headaches. PMH: hypertension and hypothyroidism. SH: 40 pack-years of smoking. Exam revealed 20/20 and 20/25. Visual fields were FTC, and color vision was normal. Pupils: 1+ reaction OU, and no RAPD. EOM revealed mild limitations. Exam demonstrated RLL and LLL edema, bilateral brow ptosis, bilateral Queen Anne sign, and lid retraction with an MRD of 6 mm OU. Hertel was 20 and 22 with a base of 97. DFE OS revealed 2+ disc edema. TED with compressive optic neuropathy OS was suspected. CT revealed bilateral apical orbital soft tissue masses with widening of the superior orbital fissures bilaterally and extension on the left side into the left pterygopalatine fossa and along branches of the left trigeminal nerve. MRI further characterized the masses limited to the posterior third of the orbits R>L, bilateral infiltration of the adjacent tendons of the EOMs with infiltration into the muscle bellies on the right, and extension along the left petrous ridge and left free edge of the tentorium. Left upper cervical adenopathy was identified by imaging and then biopsied by ENT. Results revealed a low-grade marginal zone lymphoma (MALToma) composed of CD20+ B-cells with abnormal co-expression of BCL2. Concurrent flow cytometry identified a population of CD5-/CD10- kappa light chain restricted B-cell population. CT chest, abdomen, and pelvis was unremarkable.

Conclusions:

Low-grade extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT Lymphoma) was found occupying the posterior orbits bilaterally with widening of the superior orbital fissures, and expansion of cavernous sinus. Additionally, a cervical lymph node was luckily identified on CT. This finding obviated the need for a more difficult and risky posterior orbital biopsy or needle biopsy of the pterygopalatine fossa.

References: None.

Keywords: Lymphoma, MALT, Orbital Mass

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 107
Back to Basics

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Introduction:

A 71 year-old female with an unremarkable medical history was referred for evaluation of progressive painless vision loss in her left eye. An outside corneal specialist had diagnosed Fuch's corneal dystrophy. She had undergone cataract extraction OS, DSEK OS, and then repeat DSEK OS after the initial graft failed. However, the patient's vision had not improved following the surgery. Rather, her vision had worsened. On examination, visual acuity was 20/30 OD and HM OS. External examination showed 4 mm proptosis OS and ptosis OS. Motility was full OU. There was a 2.8 log unit RAPD OS. Anterior segment examination showed changes consistent with Fuch's corneal dystrophy, an endothelial graft OS, and a partially dislocated posterior chamber intraocular lens OS. Dilated funduscopic examination showed mild temporal optic disc pallor OD and moderate optic disc pallor OS. Goldmann visual field testing showed an inferior arcuate defect with generalized depression OD and a small nasal island of vision OS. MRI orbits with contrast showed bilateral enhancing inferior orbital soft tissue masses involving both inferior recti and infraorbital nerves, extending into both cavernous sinuses. Although there was a broad differential diagnosis, the MRI findings were felt to be most consistent with orbital inflammatory disease, possibly IgG4-related disease. A laboratory work-up was obtained, including CBC, basic metabolic panel, ESR, CRP, ANCA, and syphilis serology. Most of the studies were unrevealing, but the ESR was elevated at 38 mm/hr. A diagnostic test was then performed.

Methods:

Case Report

Results:

Evaluation of serum IgG subclasses revealed an elevated serum IgG4 at 230 mg/dL (normal range: 7-89 mg/dL). Although the clinical picture was suggestive of IgG4-related disease, a left anterior orbitotomy was performed and the inferior orbital soft tissue mass was biopsied. On histopathology, the mass consisted of collagenous tissue containing infiltrative islands of atypical epithelial cells. There were focal areas of necrosis. In some areas, the tissue was noted to be forming tubules and ductules that were lined with goblet cells; these were highlighted on periodic acid-Schiff (PAS) and mucicarmine staining. Immunohistochemistry was positive for pancytokeratin, epithelial membrane antigen, and p63 in all tumor cells. Overall, these findings were consistent with adenosquamous carcinoma, likely metastatic with features to suggest an upper respiratory tract origin. CT chest/abdomen/pelvis with contrast and mammogram were unrevealing. A PET scan showed intense activity within the superior margin of the right nasopharynx, consistent with an upper respiratory tract origin. The final diagnosis was adenosquamous carcinoma arising from the upper respiratory tract with perineural spread into the orbits and cavernous sinuses. The patient went on to receive radiation therapy with adjuvant chemotherapy, since the extent of disease precluded primary surgical resection.

MRI orbits showed changes suggesting orbital inflammation extending into the cavernous sinuses, possibly due to IgG4-related disease. Furthermore, the serum IgG4 level was significantly elevated. However, tissue biopsy revealed adenosquamous carcinoma and further imaging with PET suggested an upper respiratory tract primary.

Conclusion: Primary adenosquamous carcinoma of upper respiratory tract with perineural spread into the orbits and cavernous sinuses.

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Keywords: None.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 108

The Stuck Eyelid Syndrome: A Benign Phenomenon of Brief Intermittent Unilateral Ptosis in Children

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Introduction:

Several children have been observed at our institution with a stereotypic intermittent unilateral ptosis, with one eyelid appearing stuck and fluttering in a ptotic position, for several seconds at a time, followed by complete resolution. No etiology was identified despite detailed evaluation. We present and identify the unifying clinical features of this phenomenon.

Methods:

This is a retrospective case series using records of children seen between 1994 and 2015. The cases were identified by a search for “stuck” and “eyelid.” Patient charts were reviewed, then a phone follow-up in each case inquired about outcome.

Results:

Four (4) children, presenting between 18 months and 7 years of age, were identified with a very similar presentation of acquired, brief, intermittent episodes of unilateral ptosis during which the eyelid appeared to be stuck and faintly fluttering for several seconds. The reported ages of onset ranged from soon after birth to 7 years. The work-up for a cause of the ptosis, including acetylcholine receptor antibody testing, was negative for an underlying etiology in each case. Follow up ranged from 7 months to 5 years; one child had a complete resolution of symptoms at 12 months.

Conclusions:

The “stuck eyelid syndrome” appears to be a distinct, clinical entity of benign acquired unilateral intermittent ptosis in children. While the etiology is unclear, we speculate that it may be a type of tic involving the tarsal portion of the orbicularis oculi muscle.

References: None.

Keywords: Eyelid & Adnexal Disease, Pediatric Neuro-Ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Anesthesia Dolorosa of Trigeminal Nerve as an Early Presentation of Orbital Tumor

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Introduction:

Anesthesia dolorosa is a syndrome of numbness and pain in the same sensory distribution. This combination of symptoms is thought to be caused by an injury to the first order neurons with spontaneous firing of the second order neurons. It has been described in association of injuries related to surgery or radiation, but may present as an early sign of cancer.

Methods:

A 90 year-old woman with history of squamous cell skin cancer presented with new face pain and scalp tenderness. The initial examination showed decreased sensation in the V1 distribution the left trigeminal nerve. Giant-cell arteritis was ruled out and an MRI/MR angiogram showed evidence of a vascular loop at the left trigeminal nerve. The patient did not tolerate medical therapy for pain, and attempts at nerve blockade didn't provide relief. Six months later she underwent an uncomplicated cataract surgery in the left eye with initial improvement in vision. One month later, at a follow-up visit she noted spread of her left face pain. There was a new esotropia-deviation, with hand motion-only vision and a new APD in the left eye. At urgent neuro-ophthalmic consultation, there was immediate recognition of the ominous history, and follow-on imaging revealed the lesion.

Results:

This is a case of trigeminal neuralgia, with features of anesthesia dolorosa and an initially negative MRI/MRA. After progression of symptoms to include a larger sensory distribution, optic neuropathy and sixth nerve palsy repeat imaging showed a lesion. The tumor progressed from an undetectable lesion on initial MRI to a lesion involving the posterior orbit, cavernous sinus and Meckel's cave on the left. Given history of skin cancer concern was raised for neurocutaneous spread.

Conclusions:

Pain and numbness, "anesthesia dolorosa," is a rare but important sign suggestive of a potential infiltrative lesion, particularly in the absence of history suggesting an alternate mechanism.

Keywords: Anesthesia Dolorosa, Trigeminal Neuralgia, Orbital Tumors

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 110**Facial Venectasia 50 Years After Internal Carotid Artery Ligation for Traumatic Cavernous Sinus Fistula**

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Introduction:

CCA (Common Carotid Artery) ligation was a commonplace procedure throughout the 19th century and was first used in CCSF (Carotid-Cavernous Sinus Fistula) in 1809 after it became evident that carotid artery compression reduced pulsating exophthalmos. The first description of ICA (Internal Carotid Artery) ligation for CCSF followed in 1904. Carotid artery ligation continued to be the mainstay of treatment until the introduction of balloon occlusion of the fistula in the early 1970s. While often effective in reducing symptoms and preventing the most severe complications, ICA ligation has usually not been successful in eliminating all shunt related clinical manifestations.

Methods:

Review of clinical history, neuro-imaging and relevant literature.

Results:

In 1953, a then 17 year old man had suffered cranial trauma complicated by a high flow CCSF. Surgical ligation of the ICA was performed but could not prevent the development of chronic exophthalmos and secondary glaucoma with progressive loss of vision and blindness. Over time the patient developed mild varicosities in the ipsilateral face illustrating the extent of facial venous drainage through the cavernous sinus. The patient's CT scan of the head obtained 50 years after the procedure demonstrates bony erosion in the sellar region apparently due to dilated vascular channels and shunting of blood from the posterior circulation into the cavernous sinus.

Conclusions:

This case demonstrates very long term extracranial and intracranial sequelae of a traumatic CCSF treated with ICA ligation. It also reveals the field of facial venous drainage via the cavernous sinus.

References:

Travers, A case of Aneurism by Anastomosis in the Orbit, cured by the Ligature of the common Carotid Artery. Medico-Chirurgical Transactions, 2 #, 1–420.1 #, 1811.
Murray, The Treatment of Pulsating Exophthalmos. Annals of Surgery, 39 #, 421–432.1.#, 1904.
Ringer AJ¹, Salud L, Tomsick TA, Carotid cavernous fistulas: anatomy, classification, and treatment, Neurosurg Clin N Am, 16 #, 279–95 #, 2005.

Keywords: Orbit/Ocular Pathology, Trauma, Vascular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 111**Simbu Ptosis: Drooping Lids in the Highlands of Papua New Guinea**

Anna G. Gushchin¹, Alison V. Crum

Moran Eye Center, University of Utah Health Care, Salt Lake City, UT, USA

Introduction:

This poster focuses on identification, description and treatment of a previously undescribed myogenic ptosis found in the Eastern Highlands of Papua New Guinea.

Methods:

During the course of a 10 day surgical camp, in collaboration with local center for inclusive education 97 patients were collected from the Simbu Province and brought to a rural hospital in the Eastern Highlands of Papua New Guinea. Three oculoplastic surgeons and one neuro-ophthalmologist were involved in careful identification, diagnosis and treatment of the patients' progressive bilateral ptosis. Affected patients were aged 9 to 75 and presented with varying degrees of ophthalmoplegia, dysphagia, dysphonia and orbicularis oris weakness. These patients were systematically examined and determined to be "mild", "moderate" and "severe" in the stage of ptosis and systemic findings. The moderate patients all underwent frontalis suspension (n=31), and high risk patients were provided ptosis crutches (n=13) to assist with clearing the visual angle for activities of daily living.

Results:

In total, 97 patients presented for evaluation. Thirtyone underwent bilateral frontalis suspension, 4 received unilateral frontalis slings. 13 patients were fitted with ptosis crutch glasses.

Conclusions:

High volume surgical camps are possible in remote areas. Work is ongoing in characterizing the genetic inheritance pattern of this ptosis.

References: None.

Keywords: Myogenic Ptosis, High Volume Intervention, Frontalis Suspension, Ptosis Crutch

Financial Disclosures: The authors had no disclosures.

Grant Support: Moran Eye Center and Himalayan Cataract Project gave grants for travel to remote area as well as provided instruments for the surgical camp.

Poster 112**Vision Loss Due to Gas Gangrene of Orbit Secondary to *Clostridium bifermentans* and *Enterobacter Aerogenes***

Amanda M. Selchau¹, Margaret C. Hubbell¹, Julia Y. Chen¹, Grace Kim², Terry D. Wood¹

¹Loma Linda University Department of Ophthalmology, Loma Linda, CA, USA, ²Loma Linda University, Department of Otolaryngology, Loma Linda, CA, USA

Introduction:

We describe a case of orbital cellulitis in which the causative organisms (*Clostridium bifermentans* and *Enterobacter aerogenes*) are gas producing bacteria.

Methods:

Culture analysis along with CT imaging confirmed orbital cellulitis in a 25 year old otherwise healthy male presenting with hand motion acuity, intraocular pressure of 62 mmHg, and proptosis of the left eye. The patient was initially treated with broad-spectrum IV antibiotics. Intraocular pressure was controlled with timolol, dorzolamide, and latanoprost. The patient then underwent endoscopic sinus tissue removal and drainage as well as direct drainage of the orbital abscess through blepharoplasty incision.

Results:

CT scan revealed gas within the left orbit, globe tenting, and extensive paranasal sinus disease. Orbital biopsy culture revealed *Clostridium bifermentans* and *Enterobacter aerogenes*. Early postoperative assessment revealed no light perception acuity, despite a successful incision and drainage procedure that resulted in decompression of the orbit.

Conclusions:

Most cases of orbital cellulitis are caused by streptococcus species, staphylococcus species, or *Haemophilus influenzae*, and result in relatively good patient outcomes when appropriate antibiotic therapy is initiated. However, it appears that gas-producing organisms such as *Clostridium bifermentans* and *Enterobacter aerogenes* may require more urgent surgical and antibiotic intervention to avoid severe loss of vision. Therefore, the presence of severe proptosis, gaseous accumulations within the orbit, decreased vision, and globe tenting should prompt more aggressive and timely surgical therapy.

References: None.

Keywords: Orbit/Ocular Pathology, Orbit, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 113

Historical treatment of Carotid Cavernous Fistula

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¹*Medical College of Wisconsin/Neurology, Milwaukee, WI, USA*, ²*Zablocki VA Medical Center Milwaukee, Milwaukee, WI, USA*

Introduction:

CCA (Common Carotid Artery) ligation was a commonplace procedure throughout the 19th century and was first used in CCSF (Carotid-Cavernous Sinus Fistula) after it became evident that carotid artery compression reduced pulsating exophthalmos. The first description of ICA (Internal Carotid Artery) ligation for CCSF followed in 1904. Carotid artery ligation continued to be the mainstay of treatment until the introduction of balloon occlusion of the fistula in the early 1970s. While often effective in reducing symptoms and preventing the most severe complications, ICA ligation has usually not been successful in eliminating all shunt related clinical manifestations.

Methods:

Review of clinical history, neuro-imaging and relevant literature.

Results:

In 1953, a then 17 year old man had suffered cranial trauma complicated by a high flow CCSF. Surgical ligation of the ICA was performed but could not prevent the development of chronic exophthalmos and secondary glaucoma with progressive loss of vision and blindness. Over time the patient developed mild varicosities in the ipsilateral face illustrating the extent of facial venous drainage via the cavernous sinus. The patient's CT scan of the head obtained 50 years after the procedure demonstrates bony erosion in the sellar region apparently due to dilated vascular channels and shunting of blood from the posterior circulation into the cavernous sinus.

Conclusions:

This case demonstrates the very long term sequelae of a traumatic CCSF treated with ICA ligation. It also illustrates the extensive facial venous drainage via the cavernous sinus.

References: None.

Keywords: Orbit/Ocular Pathology, Trauma, Vascular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 114**Congenital Entropion and Hypotropia Secondary to Duplication of the Inferior Rectus Muscle!**

Tarek A. Shazly¹, S. Tonya Stefko

University of Pittsburgh Medical Center, Eye and Ear Institute, Pittsburgh, PA, USA

Introduction:

Congenital anomalies of the extraocular muscles, apart from congenital fibrosis, are rarely encountered. Duplication of extra-ocular muscles is a very rare congenital anomaly that has been seldomly reported in the literature as a cause of abnormal ocular motility. We present a case of unilateral congenital entropion and hypotropia resulting from duplication of the inferior rectus muscle.

Methods:

Case report and review of literature.

Results:

A 1-month-old caucasian male infant presented to our department for evaluation of right congenital entropion. On examination he was found to have 6 digits in each hand but otherwise normal. On ocular examination, he was found to have right hyotropia and limitation of supra-duction. On careful review of his orbital MRI, he was found to have a mass in the right inferio-temporal retrobulbar region with displacement of the optic nerve superiorly. Additionally, the inferior rectus muscle appeared to be bilobed and distorted. Heterogenous enhancement of both lobes was noted following gadolinium administration. On orbital exploration via an inferior transconjunctival approach, the mass was identified to be a skeletal muscle attached to the lateral margin of the inferior rectus and medial aspect of lateral rectus. The tissue was excised to restore normal extraocular muscle anatomy. The lower lid was allowed to heal without re-suspending it given the pre-operative lid tightness with satisfactory correction of the entropion and hypotropia. Histo-pathological examination of the excised tissues revealed skeletal muscle tissue with muscle fiber disarray, alternating hypotrophy and hypertrophy with fibrosis.

Conclusions:

We believe that the hyotropia and entropion are explainable by the attachment of the duplicate inferior rectus muscle to the globe and the lower lid retractors respectively. To the best of the authors' knowledge this is the first report of congenital entropion and hypotropia due to duplication of the inferior rectus muscle.

References: None.

Keywords: Extraocular Muscle, Entropion, Strabismus, Congenital, Anomaly

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 115**Orbital Apex Syndrome Caused By Rosai-Dorfman Disease**

Yousef Aldairy¹, Tarek A. Shazly¹, Gabrielle R. Bonhomme¹

University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Introduction:

Rosai-Dorfman Disease (RDD) is a rare idiopathic histioproliferative disease characterized by massive painless lymphadenopathy, fever and weight loss. Central nervous system (CNS) manifestations are extremely rare.

Methods:

Case report, and review of literature.

Results:

A 72 year old woman was evaluated in the emergency room for retroorbital pain and decreasing vision in the right eye to No Light Perception (NLP). She has been evaluated by her local ophthalmologists and neurologist for several months with negative workup. She reported right retroorbital pain for 3 months followed by binocular diplopia within a week. She later developed lid drooping with "resolution" of her diplopia. Her vision has been gradually worsening in the right eye until she lost it completely a month prior to presentation. She was sent to the ER to rule out giant cell arteritis (GCA).

She was found to have NLP vision in the right eye, 20/25 in the left and a 4+ right APD. The right optic nerve was diffusely pale with a pink, healthy looking left optic nerve. An MRI of the orbit was ordered that on preliminary read was normal. On careful review of the imaging, an enhancing lesion was noted along the right side of the skull base extending to the right orbital apex. An endoscopic endonasal transpterygoid biopsy and debulking of the mass was carried out using stereotactic image guidance. Biopsy revealed mixed inflammatory cell infiltrates suggestive of RDD. 3 Months later she underwent a skin biopsy for a lesion behind her left knee. The histopathology and immunohistochemistry confirmed the diagnosis of RDD. Patient has been followed for 12 months with no progression of the mass.

Conclusions:

RDD should be included in the differential diagnoses for a dural or skull base mass. Although the pathology is benign elsewhere, as with other inflammatory lesions of the orbit and skull base, this case illustrates severe vision loss resulting from RDD,

References: None.

Keywords: Rosai Dorfman, Orbit, Histiocytosis

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 116**A Case of Adult T-Cell Leukemia/ Lymphoma with Extraocular Muscle Infiltration**

Takako Sugimoto¹, Hideki Chuman, Nobuhisa Naoi

University of Miyazaki, Department of Ophthalmology, Miyazaki, Japan

Introduction:

To report a case of Adult T-cell leukemia/ lymphoma (ATLL) with confirmed infiltration into the extraocular muscles.

Methods:

Case report and review of literature

Results:

A 60-year-old man presented with complaints of diplopia and discomfort around the right eye since February 2015. He visited an eye clinic in his neighborhood, and the ophthalmologist referred him to our clinic. His past medical history was remarkable for adult T-cell leukemia with complete remission for 2 years, biopsied goiter, diabetes, and hypertension. Examination showed visual acuities of 20/20 OU. The pupils appeared round and measured 5 mm OD and 6 mm OS in darkness and 3 mm OU with exposure to light; both pupils constricted briskly to light. There was no afferent pupillary defect. After instillation of 1% apraclonidine, the pupils measured 7 mm OD and 6 mm OS in darkness. Visual field examination revealed normal OU. Proptosis was observed in the right eye, along with 80% supraduction, 100% adduction, 40% infraduction, and 60% abduction. The left eye was normal. Corneal sensation and slit-lamp and fundus examination findings were normal OU. The rest of the neurological examination results were normal. Orbital MRI showed swelling of the right lateral rectus, medial rectus, and inferior muscle. The swelling appeared as low intensity on precontrast T1 MRI, homogeneous enhancement on postcontrast T1 MRI, and high intensity on T2 MRI. The partially resected inferior rectus muscle disclosed diffuse proliferation of small- to medium-sized lymphoid cells with irregularly shaped nuclei in the soft tissue. Immunohistochemically, these lymphoid cells were positive for CD3, CD4, but negative for CD79a, CD8. These findings are consistent with ATLL.

Conclusions:

The clinician should consider extraocular muscle invasive ATLL as a potential cause of an orbitopathy. Extraocular muscle biopsy is crucial for an accurate diagnosis.

References:

1. Liu MM, Furusato E, Cao X, Shen D, Chan C-C. Ocular manifestations and pathology of adult T-cell leukemia/lymphoma associated with human T-lymphotropic virus type 1. *Rare Tumors* ;2(4):e63.2010
2. Buggage RR. Ocular manifestations of human T-cell lymphotropic virus type 1 infection. *Curr Opin Ophthalmol* ;14(6):420-5.2003
3. Merle H, Cabre P, Olindo S, Merle S, Smadja D. Ocular lesions in 200 patients infected by the human T-cell lymphotropic virus type 1 in Martinique (French West Indies). *Am J Ophthalmol* ;134(2):190-5.2002
4. Yamaguchi K, Watanabe T. Human T lymphotropic virus type-I and adult T-cell leukemia in Japan. *Int J Hematol* ;76 Suppl 2:240-5.2002

Keywords: Orbit/Ocular Pathology, Orbit, Neuro-Ophthalm & Infectious Disease, Tumors

Financial Disclosures: The authors had no disclosures.

Grant Support: None.



North American Neuro-Ophthalmology Society 42nd Annual Meeting

February 27 – March 3, 2016
JW Starr Pass Marriott • Tucson, Arizona

Program Schedule

MONDAY, FEBRUARY 29, 2016

6:00 am - 6:45 am	Yoga Class	San Ignacio
6:30 am - 5:30 pm	Registration/Help Desk	Arizona Foyer
6:30 am - 7:30 am	Breakfast	Arizona Ballroom
6:30 am - 12:15 pm	Exhibits	Arizona Ballroom
7:00 am - 7:30 am	NOVEL Editorial Board/Curriculum Committee Meeting	San Pedro
7:30 am - 9:30 am	Journal Club [2 CME]	Tucson Ballroom

Moderators: Bradley J. Katz, MD, PhD and Luis J. Mejico, MD

This symposium will cover updates on medical conditions of interest to Neuro-Ophthalmologists including recent advances of our understanding of CSF circulation, review of Susac Syndrome with an emphasis beyond the characteristic clinical triad, review of pediatric brain tumors, and the current understandings on diagnosis and treatment of brain aneurysms.

Upon completion of this course, participants should be able to: 1) List potential sites of CSF outflow and absorption and describe the evidence for lymphatics in the brain; 2) Describe ophthalmologic complications secondary to treatment for brain tumors and how ophthalmologic imaging may improve neuro-ophthalmologic monitoring of children with brain tumors; 3) Review the most recent data on intracranial aneurysms and their prognosis, recognize the neuro-ophthalmic manifestations of intracranial aneurysms, and learn to more effectively counsel patients with unruptured aneurysms; and 4) Review the most recent data that expands our knowledge of the neuro-ophthalmic manifestations of Susac syndrome.

		PAGE
7:30 am - 7:50 am	Mythbusters: What We Thought We Knew About CSF Dynamics, <i>Deborah I. Friedman, MD, MPH</i>	175
7:50 am - 8:00 am	Q&A	
8:00 am - 8:20 am	Neuro-Ophthalmologic Complications of Brain Tumors in Children, <i>Robert A. Avery, DO, MSCE</i>	181
8:20 am - 8:30 am	Q&A	
8:30 am - 8:50 am	Susac Syndrome: Expanding the Triad, <i>Robert A. Egan, MD</i>	187
8:50 am - 9:00 am	Q&A	
9:00 am - 9:20 am	Intracranial Aneurysms and Neuro-Ophthalmology, <i>Valérie Biousse, MD</i>	191
9:20 am - 9:30 am	Q&A	
9:30 am - 10:00 am	Coffee Break	Arizona Ballroom
10:00 am - 12:00 pm	Hot Topics: Today and Tomorrowland [2 CME] <i>Moderators: Patricia Johnston-McNussen, MD and Norah S. Lincoff, MD</i>	

As science and medicine move forward at astonishing speed, all physicians struggle to keep up with new information. Neuro-Ophthalmologists need to know advances in basic science, technology, diagnostic criteria, clinical evaluation and treatment of the conditions and diseases of our subspecialty. The Hot Topics session will provide updated information in areas that face Neuro-Ophthalmologists now and in the future.

Upon completion of this course, participants should be able to: 1) Describe and use OCT in evaluation of the elevated optic disc; 2) Describe the techniques and application of gene therapy in neurodegenerative disease; 3) Determine the diagnosis and management of steroid-dependent optic neuropathies; and 4) Describe the new diagnostic criteria, lab evaluation, and treatment of Neuromyelitis Optica.

10:00 am - 10:20 am	The Elevated Optic Disc: When OCT Helps and When It Does Not.	PAGE
	An Interactive Case Based Approach, Robert C. Sergott, MD	205
10:20 am - 10:30 am	Q&A	
10:30 am - 10:50 am	Genetic Manipulation for Inherited Neurodegenerative Diseases - Myth or Reality?, Patrick Yu-Wai-Man, BMedSci, MBBS, PhD, FRCOphth	211
10:50 am - 11:00 am	Q&A	
11:00 am - 11:20 am	Circle of Hell: Diagnosing and Managing Steroid-Dependent Optic Neuropathies (with Apologies to Dante Alighieri), Leonard A. Levin, MD, PhD	225
11:20 am - 11:30 am	Q&A	
11:30 am - 11:50 am	NMO: What You Need to Know, Sashank Prasad, MD	233
11:50 am - 12:00 pm	Q&A	
12:15 pm - 1:30 pm	Women in Neuro-Ophthalmology (WIN) Luncheon	Starr Circle Terrace
	Join your colleagues for a networking lunch event and participate in small group discussions on topics that are relevant to women in Neuro-Ophthalmology. An optional lunch selection will be available for purchase. All are welcome to attend even without the purchase of a lunch.	
12:15 pm - 1:00 pm	Small Group Discussions/Networking and Lunch	
1:00 pm - 1:30 pm	Break-Out for Specific Discussion Topics	
1:30 pm - 3:30 pm	Understanding OCT: Devices, Images, Artifacts, Real-time Scanning, and Interactive Cases [2 CME]	Tucson Ballroom
	<i>Moderator: Robert C. Sergott, MD</i>	
	<i>Faculty: Ari J. Green, MD, MCR & Mark J. Morrow, MD</i>	
During the past five years, optical coherence tomographic scanning [OCT] of the optic nerve and retina has transitioned from a low-resolution technology of questionable value to an imaging modality that is simultaneously improving diagnostic accuracy and unlocking mysteries of the pathogenesis of both rare and common neuro-ophthalmological diseases including Leber's Hereditary Optic Neuropathy, retinal degenerations, multiple sclerosis, Alzheimer's and Parkinson's Diseases.		
Clinical and research neuro-ophthalmologists now can visualize and measure the normal and pathological changes in the optic nerve and retina. However, to realize the full potential of spectral domain and MultiColor OCT, neuro-ophthalmologists must understand how the various devices image and measure the optic nerve and retina as well as the artifacts that must be recognized.		
Upon completion of this course, participants should be able to: 1) Identify the similarities and differences among the OCT devices for both cross-sectional and longitudinal measurements; 2) Explain a method to interpret spectral domain scans of the optic nerve, retina and Multicolor OCT images based upon following thickness measurements and reflectivity characteristics to identify and quantitate the pathological changes; 3) Understand and interpret scans after a hands-on experience where they get to perform OCT scans with state of the art equipment; and 4) Identify Interactive case presentations of clinical scenarios in which OCT scans were critical for the proper diagnosis and management of complicated neuro-ophthalmic problems.		
2:30 pm - 4:30 pm	Teaching Neuro-Ophthalmology in the Developing World [2 CME]	Arizona 8-10
	<i>Moderator: Bradley J. Katz, MD, PhD</i>	

Neuro-Ophthalmologists are occasionally invited to teach in the developing world. However, the diseases one encounters and the resources one has available in the developing world can be very different from those in

the developed world. Despite these differences, neurologists and ophthalmologists in the developing world are eager to learn from neuro-ophthalmologists. The purpose of this optional symposium is to give Neuro-Ophthalmologists who are interested in teaching outside the developed world the opportunity to become more effective instructors for this relatively new audience.

Upon completion of this course, participants should be able to: 1) Identify the diseases in the developing world that present with neuro-ophthalmic signs and symptoms; 2) Predict the resources that physicians in the developing world have to diagnose and treat these diseases; and 3) Describe the neuro-ophthalmic topics that will be of most interest to neurologists and ophthalmologists outside the developed world.

2:30 pm - 2:50 pm	Strategies for the Rational Investigation of Patients in a Low Resource Environment , <i>Mitchell Lawlor, FRANZCO, PhD</i>
2:50 pm - 3:00 pm	Q&A
3:00 pm - 3:20 pm	Neuro-Ophthalmology Education in China and Africa: The University of Oklahoma Experience , <i>Bradley K. Farris, MD</i>
3:20 pm - 3:30 pm	Q&A
3:30 pm - 3:50 pm	Teaching International Neuro-ophthalmology: Curriculum Development and E-Learning , <i>Karl C. Golnik, MD, Med</i>
3:50 pm - 4:00 pm	Q&A
4:00 pm - 4:20 pm	The Eye-Brain Interface in Cerebral Malaria , <i>Douglas Postels, MD, MS</i>
4:20 pm - 4:30 pm	Q&A

3:00 pm - 5:00 pm Forum for New and Future Neuro-Ophthalmologists Starr Circle Terrace

All are welcome to attend. This gathering, however, is especially for students, residents, fellows and Neuro-Ophthalmologists in the early years of their career. There will be small group discussions that provide an opportunity to ask questions, or listen to the questions and advice of others. Attendees can rotate between tables during the session. The first hour of discussions will be led by members of the Young Neuro-Ophthalmology (YONO) Committee who are recently out of fellowship, and is geared towards trainees, residents, and fellows. The second hour will be led by senior Neuro-Ophthalmologists, and is geared towards those in their first years of practice. Attendees can come for one or both hour-long sessions.

3:00 pm - 3:05 pm	NANOS Membership Announcement , <i>Patricia Johnston-McNussen, MD</i>
3:05 pm - 4:00 pm	Session I: What Do You Want to Know About Becoming a Neuro-Ophthalmologist?
	Table 1: Finding a Job/Negotiating Your Contract, <i>Heather E. Moss, MD, PhD</i>
	Table 2: Issues Particular to Neurology-Trainees, <i>Melissa W. Ko, MD</i>
	Table 3: Issues Particular to Ophthalmology-Trainees, <i>Seema V. Sundaram, MD, FRCS</i>
	Table 4: Starting and Building a Practice, <i>Collin McClelland, MD</i>
4:00 pm - 5:00 pm	Session II: What Do You Want to Know About Your First Few Years of Practice?
	Table 1: Balancing a Clinical and Academic Career, <i>Beau B. Bruce, MD, PhD</i>
	Table 2: Pearls to Keep a Healthy Work-Life Balance, <i>Michael S. Lee, MD</i>
	Table 3: Creating an Efficient Clinic without Compromising Care, <i>Andrew G. Lee, MD</i>
	Table 4: What Career Mistakes Have I seen Young Neuro-Ophthalmologists Make, <i>Jorge C. Kattah, MD</i>

5:00 pm - 7:00 pm SCIENTIFIC PLATFORM PRESENTATIONS: SESSION I [2 CME] Tucson Ballroom *Moderators: Rudrani Banik, MD and Marc Dinkin, MD*

8:45 pm - 10:30 pm Night at the Movies: "Three Amigos" Tucson Ballroom

MYTHBUSTERS: WHAT WE THOUGHT WE KNEW ABOUT CSF DYNAMICS

Deborah I. Friedman, MD, MPH
University of Southwestern Medical Center
Dallas, TX

LEARNING OBJECTIVES

1. List potential sites of CSF outflow and absorption
2. Describe the evidence for lymphatics in the brain
3. Name the structures involved in CSF production and secretion

CME QUESTIONS

1. The choroid plexuses secrete about 80% of the cerebrospinal fluid in the central nervous system. Where does the other 20% come from?
 - a. Arachnoid granulations
 - b. Ependymal cells
 - c. The blood-brain barrier
 - d. The pineal gland
2. The meningeal lymphatics:
 - a. Are located near blood vessels and sinuses
 - b. Contain smooth muscle cells
 - c. Contain valves
 - d. Are similar to mediastinal lymphatics
3. What is the proposed role of the glymphatic system?
 - a. Regulation of CSF secretion by the choroid plexus
 - b. Increases efficiency of venous absorption of CSF
 - c. Production of aquaporin-4 by glial cells
 - d. Clearance of solutes from the interstitial fluid

KEYWORDS

1. Cerebrospinal Fluid
2. Lymphatic System
3. Glymphatics
4. Embryology
5. Choroid Plexus

INTRODUCTION

Classical teaching posits that cerebrospinal fluid (CSF) is formed in the choroid plexus, circulates like a flowing river in the neuraxis, and is absorbed by the arachnoid granulations into the venous system. Simple. But is it really true? This review of recent publications will (1) provide an update on CSF embryology and physiology, (2) explore the evidence for lymphatic vessels in the brain and (3) describe the glymphatic system.

CSF PRODUCTION: EMBRYOLOGY AND DEVELOPMENT OF THE SUBARACHNOID SPACE, CHOROID PLEXUS AND ARACHNOID GRANULATIONS

Dziegielewska KM, Ek J, Habgood MD, Saunders NR. Development of the choroid plexus. *Microscopy Res Tech* 52:5-20, 2013.

Amniotic fluid is initially present in the cerebral recesses of the human embryo. The embryonic development of the brain begins with the formation of the notochord (a midline, mesodermic structure which induces the development of the brain and spinal cord and eventually becomes the cranium and vertebral column) at week 3, which closes the cephalic lumen of the neural tube at week 28 days of gestation to form the ventricular system. At this point, the ventricles are isolated from the amniotic cavity [Dziegielewska 2001].

The first choroid plexuses (from Latin chorion = coat, and plectere = to braid or plait) appear on the 41st day in the fourth ventricle, followed by lateral ventricles (7-9 weeks) and third ventricle. The choroid plexuses arise from blood vessels are covered by the pia mater and covered by ependyma. These vascular protrusions and their coverings of specialized ependymal cells are the choroid plexus. The choroid villi appear on the plexus at around 7 weeks. The plexus initially occupies 1/3 of the ventricular volume and secretes large amounts of mucin. The lobulations become more pronounced and many small tubules that create blind tracts filled with CSF. Completely entrapped areas form cysts. During the second trimester, the complexity of the plexus increases with the development of tubules into incipient cysts, a gradual decrease in mucin production and resolution of the cysts.

At a cellular level, there are four stages of choroid plexus development:

- Stage 1 (7th week): Pseudostratified cells with central nuclei containing no glycogen, minute in size in relation to the ventricle.
- Stage 2 (9th week): Low columnar cells with apical nuclei and abundant glycogen, extremely large in relation to the ventricle.
- Stage 3 (17th week): Cuboidal epithelial cells with central or apical nuclei and moderate glycogen, moderately large in relation to the ventricle.
- Stage 4 (29th week): Cuboidal or squamous epithelial cell with central or basal nuclei and no glycogen, small in relation to the ventricle.

Carbonic anhydrase has been identified in human lateral ventricle fetal choroid plexus as early as 9 weeks of gestation, implying that CSF may be secreted by immature (Stage 2) cells. Various plasma proteins (albumin, fetuin, α -fetoprotein, transthyretin, transferrin) are found in the epithelial cells of immature choroid plexus in the third, fourth and lateral ventricles. Only transthyretin is produced in situ and the other proteins are from the plasma.

Choroid plexus epithelial cells are linked by tight junctions early in development (i.e., blood-CSF barrier), although the blood-CSF barrier may be “leaky” in the early stages. The tight junctions are very water permeable, similar to the proximal tubule of the kidney (but in opposite directions).

The role of CSF in the developing brain may be three-fold: (1) the pressure within the ventricular system determines the shape and organization of the developing brain; this has been shown in other species, (2) transfer of proteins from the blood during certain phases of development, (3) high permeability to small molecules of immature choroid plexus, including lipid-insoluble molecules that are of nutritive or developmental significance.

PHYSIOLOGY OF CEREBROSPINAL FLUID PRODUCTION AND ABSORPTION

Damkier HH, Brown PD, Praetorius J. Cerebrospinal fluid secretion by the choroid plexus. *Physiol Rev* 93:1847-92, 2013.

CSF PRODUCTION:

Although first proposed as the sites of CSF secretion by Faivra in 1854 and Cushing in 1914, the first direct experimental evidence to support this did not occur until 1960 by Rougemont et al. The cells of the choroid plexus are among the most efficient of the body, with a transport rate paralleled only by the renal proximal tubules and pancreatic ducts. The total volume of CSF is 150 ml and 500-600 ml are produced in 24 hours (replaced 3-4 times daily). It is estimated that about 80% of CSF secretion occurs in the choroid plexuses with

the remaining 20% arising from the interstitial fluid of the brain, generated by the blood-brain barrier (BBB). In humans, the surface area of the choroid plexus is only about 0.1% of the BBB. The most convincing evidence that the choroid plexus is the major site of CSF secretion comes from studies of transgenic mice lacking specific transporter and channel proteins.

The choroid plexuses receive blood flow from the anterior and posterior circulations at a very high rate; approximately 10 times the rate of blood flow to the brain parenchyma. Blood flow is controlled by the sympathetic nervous system from fibers arising in the superior cervical ganglion. The epithelial cells of the plexus contain β_1 receptors which decrease CSF production when stimulated, possibly mediated through a decrease in carbonic anhydrase activity. There is also a parasympathetic cholinergic innervation from IX and X; parasympathetic stimulation also decreases CSF production. $\text{Na}^+\text{-K}^+\text{-ATPase}$ drives three Na^+ across the cell membrane (to the CSF) in exchange for two K^+ (into the choroid plexus epithelium) with a secondary active transport of Cl^- to drive the secretory process. Sodium transport by the choroid plexus epithelium is the most important driving force behind CSF secretion. The $\text{Na}^+\text{-K}^+\text{-ATPase}$ I is located in the luminal membrane of the choroid plexus and is blocked by ouabain. HCO_3^- is also essential for CSF secretion; this is inhibited by carbonic anhydrase inhibitors which also have vasoconstrictive effects on cerebral vessels.

The rate of CSF secretion decreases with age although the volume increases because of age-related brain atrophy. There is also increased resistance to CSF drainage, all leading to a slower turnover rate of CSF with increasing age.

CSF ABSORPTION:

Although there is not uniform agreement on this topic, CSF appears to return to the venous blood via the cerebral venous sinuses through the arachnoid granulations and arachnoid villi. The most apical portion of the arachnoid granulation is separated from the venous lumen only by a layer of arachnoid. The reabsorption rate is determined by the pressure gradient between the subarachnoid space and venous pressure. The cervical lymph nodes may also receive CSF and return it to the bloodstream. The arachnoid villi are questionably present in the fetus and start to become visible in the dura as the infant ages, after which both the villi and granulations start to increase in number. This begs the question of whether there may be another mechanism for CSF absorption. Studies by Miles Johnston and colleagues in neonatal sheep showed no direct evidence that various tracers entered the venous system in proximity to the arachnoid granulations and some sheep had no identifiable granulations. A large amount of tracer (Microfil) accumulated around the torcula under high CSF pressure conditions, with no apparent mechanism to explain the finding. They postulated that direct CSF transport into the sinuses occurs at high pressures.¹

Work in the early 2000s by Johnston et al suggested that a significant amount of CSF is absorbed by the extracranial lymphatics in the paranasal region in both human and non-human primates. Injections of yellow Microfil into the CSF compartment in 7 different species (including humans) in the immediate postmortem period revealed Microfil around the olfactory bulbs and cribriform plate, which followed the olfactory nerves and entered lymphatic networks associated with olfactory and respiratory epithelium.² Recent studies in young and aged rats also support a contribution of lymphatics in CSF egress.³ Contrast was injected into the lateral ventricles for 10 minutes with a CT scan performed every minute from the start of infusion and up to an hour afterward. CSF drained into the olfactory pathway through the cribriform plate, into the spinal canal and into the cervical lymph nodes. No contrast was seen in the sagittal sinus.

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MENINGEAL LYMPHATICS: HIDDEN IN PLAIN SIGHT?

Loveau A, Smirnov T, Keyes T, Eccles J, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015; doi: 10.1038/nature 14432

SUMMARY OF THE RESEARCH FINDINGS:

1. T cells and MHCII cells line up with endothelial cells along venous sinuses.

The authors were investigating recirculation of surveying meningeal immune cells in mice, particularly the meningeal spaces and the immune cells that occupy those spaces. Whole mount preparations of dissected mouse meninges were stained using immunohistochemistry for endothelial cells and MHCII-expressing cells. They found a high concentration of immune cells near the dural sinuses. They stained coronal sections of the dura for T cells (CD3e) and

endothelial cells (CD31) and found that the vast majority of T lymphocytes near the sinus were abluminal (i.e., forming, involving, or occurring on the outer surface of a body part or device with an internal cavity or channel: not adjacent to the lumen of a tubular organ or part). A portion of the T cells and MHCII-expressing cells was aligned linearly in CD31 expressing structures along the sinuses ("perisinusal").

2. These channels stain for a marker of lymphatic endothelial cells.

The perisinusal vessels were then tested for markers associated with lymphatic endothelial cells (LEC) using the LEC marker Lyve-1. Lyve-1 expressing vessels were found running parallel to the dural sinuses and having a distinct lumen.

3. The lymphatic character of these perisinusal vessels in the meninges was confirmed using other techniques.

Other LEC markers were expressed in the Lyve-1 vessels, including Prox1 (the main LEC transcription factor), podoplanin (found in peripheral lymphatic vessels) and vascular endothelial growth factor receptor 3 (VEGFR3). Flow cytometry showed that a CD45-CD31+ podoplanin+ population of LECs was detected in the dura, and similar to that found in the skin and dura. A potentially similar structure was found in formalin fixed samples of human dura.

4. Other characteristics

These vessels do not contain smooth muscle and do not express intergrin- α 9 which is a marker of lymphatic valves. Many aspects of the meningeal lymphatics are similar to diaphragmatic lymphatics. Electron microscopy showed a non-continuous basement membrane surrounded by anchoring filaments, similar to peripheral lymphatics. However, the meningeal lymphatics start from the eyes, travel above the olfactory bulb and align adjacent to the sinuses. They are larger and more complex in the transverse sinus than the superior sagittal sinus. They are less dense, less complex and narrow in the meninges.

5. The lymphatic vessels were shown to drain CSF.

Leukocytes (T and B cells) were found within them, as would be expected with classical lymphatic vessels. Evans blue dye injected into the ventricles in mice was transported to the meningeal lymphatics and drained into the deep cervical lymph nodes (no dye was seen in the surrounding tissue). When deep cervical lymph nodes were resected, the number of T cells in the meningeal space increased, supporting a physical connection between these structures.

Conclusion: "Meningeal lymphatics are a novel path for CSF drainage and represent a more conventional path for immune cells to egress the central nervous system. Our findings may represent the second step in the drainage of the interstitial fluid from the brain parenchyma into the periphery after it has been drained into the CSF through the recently discovered glymphatic system."

THE GLYMPHATIC SYSTEM: THE BRAIN'S GARBAGE DISPOSAL

Iliff JJ, Nedergaard M. The Microcirculation – Fantastic Voyage: Is there a Cerebral Lymphatic System? *Stroke* 44:S93-5, 2013.

The glymphatic pathways facilitate CSF and interstitial fluid (ISF) exchange and clearance of interstitial solutes from the brain. There are 3 elements to this pathway: (1) a para-arterial CSF influx route, (2) a para-venous ISF clearance route and (3) a transparenchymal pathway that is dependent on astroglial water transport via the astrocytic aquaporin-4(AQP4) water channel.

It is called the “glymphatic” system because of the glial dependence of this vascular pathway that has structural homology to the peripheral lymphatic system.

Proposed pathway in a healthy brain:

CSF → para-arterial channel influx → convective flux with interstitial fluid → solutes cleared via paravenous channel facilitated by AQP4

In diseased brain, reactive astrogliosis causes mislocation of AQP4 from perivascular endfeet to the rest of the astrocytic soma:

CSF → para-arterial channel influx → inefficient convective flux with interstitial fluid → failure of solute clearance → possible deposition of intraneuronal extracellular and intracellular protein aggregates (e.g., tau, amyloid β)

Influx seems to occur along almost all penetrating arteries but efflux is limited to a specific group of large draining veins. In AQP4 knockout mice, influx into and through the parenchyma, and interstitial solute clearance from the brain were markedly reduced (~70%). Radiolabeled amyloid β (A β) injected into the striatum of AQP4 null mice was reduced about 65% compared to the clearance in wild type mice, suggesting that the glymphatic pathway is a key mechanism of clearance of soluble A β from the brain.

AQP4 expression is typically elevated for about 14 days after ischemic or traumatic injury, possibly because of altered expression of AQP4 within a glial scar. The distribution of AQP4 expression in glial cells and reactive astrocytes is perturbed for about a month after injury with a reduction in polarity and perivascular AQP4 immunoreactivity, and higher somal AQP4 immunoreactivity. This mislocalization into the astrocytic soma (from reactive gliosis) may prevent the efficient flux of water into and out of the perivascular spaces and decrease interstitial solute clearance, resulting in the accumulation of neurotoxic metabolites.

LAGNIAPPE

1. CSF FLOW DURING CHIARI DECOMPRESSION SURGERY CHANGES WHEN THE PATIENT IS POSITIONED FOR SURGERY

Bond AE, Jane JA, Liu KC, Oldfield EH. Changes in cerebrospinal fluid flow assessed using intraoperative MRI during posterior fossa decompression for Chiari malformation. *J Neurosurg* 122:1068-75, 2015.

Background: Chiari decompression is performed to allow free flow of CSF between the posterior fossa and the upper portion of the spinal subarachnoid space. The extent of surgery needed for successful decompression varies among patients but opening the dura to expose the subarachnoid space is more likely to result in success although the risks are greater (such as CSF leak and pseudomeningocele which require additional surgery). Less invasive surgery, while associated with fewer complications, is also less likely to achieve the desired goal. The authors studied intraoperative MRI to determine at which stage of surgery a successful decompression was achieved.

Methods: 18 adult patients undergoing surgery were positioned prone with the neck gently flexed and a baseline MRI was obtained with cine imaging of the foramen magnum. 22% of patients had undergone previous Chiari decompression surgery. The average level of tonsillar descent was 12.9 mm (range 7-25 mm). All patients had obstructed dorsal flow on phase-contrast MRI studies. 15 patients had pre-incision prone MRIs performed in the operating room.

The arch of C1 was removed and repeat imaging was performed. If there was improvement in CSF flow with no significant obstruction of the dorsal CSF space at the level of the foramen magnum, the operation was completed. If there was still significant obstruction and the MRI showed no obvious change from the pre-operative scan, the dura was split and either duraplasty or stepwise coagulation of the cerebellar tonsils was performed. Repeat MRI was obtained at each stage of surgery using the same methods.

Results: Each intraoperative MRI added 1.5 hours to the surgery in the beginning of the study, and 45 minutes at the end as the team became more experienced. 93% of the patients had significantly improved dorsal CSF flow by the flexed positioning alone. Of the 14 first-time surgery patients, 8 had bone decompression alone, 4 also had dural splitting and 2 had duraplasty based on the MRI results. After a mean of 9.5 months, surgery in 6 patients (43%) clearly failed, 4 of which had bone decompression only. The authors conclude the current intraoperative assessments of CSF flow currently in use, including intraoperative ultrasound, are severely limited by surgical positioning.

2. SHUNT CATHETERS: BUY THE EXTENDED WARRANTY?

Cheatle JT, Bowder AN, Agrawal SK, Sather MD, Hellbusch LC. Flow characteristics of cerebrospinal shunt tubing: Laboratory investigation. J Neurosurg Pediatrics 9:191-7, 2012.

Background: Shunts may fail because of malpositioning, obstruction of the ventricular or distal catheter, obstruction of the shunt valve, catheter disruptions or disconnections and other causes, such as infection. Proteinaceous and cellular debris found in “sterile shunt failure” impede resistance to flow. Straight connectors may be employed in the shunt system, and their effect on shunt resistance is unknown.

The total resistance of a shunt system (R_s) is the sum of the resistances of the opening of the ventricular catheter (R_c) + the valve (R_v) + any shunt accessories (R_a) + the distal tubing (R_t). In some shunts, R_v and R_a are designed to change with position. A valve may increase the resistance of a shunt by 100-200%. A higher resistance to flow may contribute to shunt malfunction via slow flow, and a mildly increase in CSF pressure.

The authors studied new and explanted uninfected shunt catheters, including systems with connectors (2 and 3 piece catheters), to determine their hydrodynamic resistance and flow.

Methods: New distal catheter tubing was cut into lengths from 18-98 cm to match the lengths of explanted catheters ($n=23$ explanted catheters in 7 lengths). For each length, resistance was measured (5 times) using no connector, 1 connector and 2 connectors. The experiments were conducted in a water bath system using artificial CSF and assumed a constant flow.

Results: The resistance of a catheter is proportional to its length and inversely proportional to its diameter. Resistance increased significantly after the addition of connectors, with a significant difference between 2 and 3-piece catheters. Reynolds numbers were all consistent with laminar flow. Explanted tubing had a slight increase to resistance in flow compared to new tubing, of uncertain physiological significance.

CME ANSWERS

1. c
2. a
3. d

NEURO-OPHTHALMOLOGIC COMPLICATIONS OF BRAIN TUMORS IN CHILDREN

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LEARNING OBJECTIVES

1. Comprehend the short and long term treatment side effects experienced by children with brain tumors.
2. Identify specific medications that cause ophthalmologic side effects in pediatric brain tumor patients.
3. Describe the potential for how ophthalmologic imaging may improve neuro-ophthalmologic monitoring of children with brain tumors.

CME QUESTIONS

1. All of the following are typical symptoms of posterior fossa syndrome except:
 - a. Mutism
 - b. Vision loss
 - c. Emotional lability
 - d. Torsional nystagmus
2. The class of medication called "MEK inhibitors" are being used to treat brain tumors and other cancers. Which ophthalmologic side effect has been reported with this medication?
 - a. Papilledema
 - b. Nystagmus
 - c. Ptosis
 - d. Retinal edema
3. When children experience vision loss from posterior fossa syndrome, you counsel the family that:
 - a. The vision loss is permanent
 - b. 50% of children will have some residual vision loss
 - c. Treatment with Vitamin A will help their recovery
 - d. Full recovery can be expected

KEYWORDS

1. Brain Tumor
2. MEK Inhibitor
3. Posterior Fossa Syndrome
4. Moyamoya
5. Posterior Reversible Encephalopathy Syndrome (PRES)

Despite improved therapeutics, surgical techniques and overall survival rates, children with brain tumors still experience significant ophthalmologic morbidity. Neuro-Ophthalmologist should be aware of the clinical symptoms as well as medical and surgical side effects that occur in children with brain tumors. Given the improved survival rates and delayed side effects from treatment, some complications do not manifest until adulthood. This journal club will review these complications. Consider the following two cases:

Case #1

A previously healthy 5 year old male complained of persistent headache and was discovered to have mild papilledema on exam. His visual acuity was 20/20 OU with intact color vision. Visual fields to confrontation were full. His ocular motility and alignment were full. MRI of the brain revealed a posterior fossa mass that was surgically resected and determined to be a medulloblastoma. There were no surgical complications. On post-operative day 1, the patient's mother thought her child was withdrawn and was worried he couldn't see. MRI on post-operative day 2 was unremarkable without evidence of ischemia or edema. Neuro-ophthalmologic examination revealed impaired visual response manifested by absence of grimace to light, blink to threat and response to optokinetic stimuli. Pupils were briskly reactive. Motility was full, although he had an intermittent right gaze preference. Optic nerve elevation was mild and stable. How do you counsel the family about these symptoms? What is the etiology of their vision loss? Do you expect their vision to improve?

Case #2

A 20 year old female was discovered to have an incomplete right homonymous superior quadrant defect during a routine comprehensive ophthalmology examination. She was unaware of the visual field defect. An urgent head CT did not demonstrate an acute stroke, but the left

hemisphere was more atrophic than the right. Her past medical history is significant for a hypothalamic tumor treated at 12 years of age. Her treatment at that time included chemotherapy, but a recurrence at 14 years of age required radiation therapy. She had normal visual acuity and visual fields 2 years after the completion of radiation. What latent treatment side effects should you consider in an adult patient who had cancer as a child?

INTRODUCTION

Children with a current or past history of a brain tumor should always undergo a comprehensive ophthalmologic examination that includes a thorough clinical history. A review of current and past treatments for their tumor will prompt the provider to focus their examination on known short and long term side effects of these treatments. This review will cover recognizing neuro-ophthalmology symptoms, medication side effects, complications from radiation, surgical complications, associated conditions and ophthalmologic imaging.

RECOGNIZING NEURO-OPHTHALMOLOGY SYMPTOMS

It is well known that brain tumors can produce a variety of neuro-ophthalmologic signs and symptoms. The risk of these complications is related to the tumor type, growth pattern, size and location. Cranial nerve palsies, papilledema, visual acuity loss and visual field defects are common findings in which the neuro-ophthalmologist is consulted. In young children with low grade gliomas, many are not able to complete quantitative visual acuity and or visual field testing.^{1,2} To further complicate matters, children may not be aware or able to describe some of their symptoms. The lack of awareness of visual field defect can even occur in teenagers.³ A recent study by Harbert and colleagues evaluated 92 children who had not been previously diagnosed with a visual field defect and found that nearly 15% of patients had under-recognized field defects.³ Interestingly, this convenience sample determined that age, gender and tumor type were not associated with an increased risk of the visual field defect going unrecognized. The visual field deficits occurred most commonly in children with tumors involving the temporal lobe compared to other locations. On average, the missed visual field defects were identified 3.7 years after their original diagnosis.³

The high rate of unrecognized visual field deficits along with inability of young children to reliably complete formal testing should prompt the clinician to perform a comprehensive examination including kinetic or automated perimetry, even when prior examinations are reported as unremarkable.

MEDICATION SIDE EFFECTS

When surgery is not curative, an overwhelming majority of pediatric brain tumors have used cytotoxic or platinum-based chemotherapeutic agents to treat brain tumors. Since chemotherapy frequently results in systemic side effects (e.g., lowered immune system, anemia, etc), newer “mechanism focused” therapies are being used. Recently, the use of mitogen-activated protein (MAP) kinase pathway inhibitors, including inhibitors of MEK, are a relatively new biologic therapy which have shown promising activity in treating tumors demonstrating abnormalities in the BRAF gene. Early phase 1 and phase 2 clinical trials of MEK inhibitors in adults with advanced stages of cancer reported nondescript visual symptoms as well as retinal vein occlusion and optic neuropathy while taking MEK inhibitors.⁴ Recent case series have described uveitis and subfoveal neurosensory retinal detachment within days to 1 month of taking a MEK inhibitor in adults with metastatic cancer.^{5,6}

MEK inhibitors are known to alter the outer blood retina barrier.^{7,8} It is unclear whether the previously reported retinal vein occlusions in adults with advanced cancer were due to MEK inhibitor induced alteration in the outer blood retina barrier rather than the other known systemic risk factors (e.g., hypertension, atherosclerosis).⁸ Over 10 different MEK inhibitors have been developed, all of which have different chemical structures, mechanism of action and side effect profiles.⁹

Two patients in my practice have developed inner retinal layer edema while taking the MEK inhibitor selumetinib. One patient complained of positive visual phenomenon in her central visual field while the other patient was autistic and could not verbalize any symptoms. Separation of the retinal pigmented epithelium (RPE) along the interdigitation zone in both eyes was visualized with optical coherence tomography (OCT). The RPE separation resolved after stopping the medication without any appreciable visual sequela. One can only speculate how these RPE changes would evolve if they went unnoticed and whether they would ultimately result in the previously reported side effects such as retinal vein occlusion, retinal detachment, optic neuropathy or permanent RPE abnormalities.

Given the potential for RPE separation and other retinal insults, all children receiving MEK inhibitors should have a baseline ophthalmologic examination and OCT. The frequency of follow up exams is unclear, but all children with acute visual complaints should be seen urgently. The short and long term effects and natural history of RPE separation in children on MEK inhibitors needs to be elucidated.

RADIATION TREATMENT

Ophthalmologic and neurologic complications from conventional photon-based radiation treatment of brain tumors are well established and include radiation optic neuropathy, cataracts, cranial nerve palsy, chiasmal necrosis, post-treatment cerebral edema, cystic expansion, and moyamoya vasculopathy.¹⁰ Risk factors for these complications include radiation doses over 4,000 cGy, large treatment field, tumors located near the sella/skull base/orbit, and older age.¹¹⁻¹³ Post-radiation side effects involving the afferent visual system can occur anywhere between a few months and up to 3 years after treatment has started.¹³

Moyamoya syndrome—progressive stenosis of the intracranial carotid arteries and/or its branches—is a recognized vasculopathy caused by radiation treatment in children treated for brain tumors.¹⁴ Moyamoya can develop in a matter of months to upwards of seven years after treatment.^{15, 16} Since stenosis can occur in the anterior and posterior circulation, both the pre-geniculate and post-geniculate visual pathway can experience ischemia. Although not frequently studied, visual field defects, followed by visual acuity loss are the most frequent ophthalmologic side effects.¹⁷ The significantly increased risk of moyamoya in children with Neurofibromatosis type 1 is now well recognized and thus radiation therapy is avoided.¹⁵ Case #2 described above highlights a clinical scenario of moyamoya in survivors of childhood cancer who manifested post-radiation side effects in adulthood.

The evolution of radiation based therapies to reduce side effects now involves proton beam therapy (PBT) and intensity modulated radiation therapy (IMRT). These new and more focused therapies were designed to reduce the extraneous radiation and provide a more focused treatment field. Compared to conventional radiation treatments, PBT and IMRT have demonstrated a significant decrease in cataracts, cranial nerve palsies and secondary brain tumors compared to conventional radiation.¹⁸⁻²¹ Even when treating tumors in high risk locations, investigators have reported cataracts or other significant ophthalmologic complications well below 5% when using PBT or IMRT,^{18, 20-22} compared to historical photon based protocols that reported 20-40% ophthalmologic complications.¹⁹

PBT and IMRT are now more frequently used to treat pediatric brain tumors as access to these therapies has improved. The relative small number of studies from a variety of tumor types and locations suggests these therapies may have reduced short and long term neuro-ophthalmologic complications, and radiation-induced tumors compared to traditional radiation therapy. Despite these promising findings, the Children's Oncology Group still recommends yearly comprehensive ophthalmology exams for children who have received 30 Gy radiation to the brain/eye/orbit.

SURGICAL COMPLICATIONS

Biopsy and/or surgical resection of many brain tumors carries the potential to damage cranial nerve function, produce visual field defects and cause optic neuropathy. No formal studies have evaluated the frequency of these post-operative deficits—likely due to the heterogeneous tumor locations and surgical approaches.

Resection of tumors located along the midline of the posterior fossa frequently produces cerebellar mutism, also known as posterior fossa syndrome (PFS). This unique post-operative condition, although more common in children compared to adults, manifests by a combination of any of the following symptoms: ataxia, dysarthria, hypotonia, irritability, emotional lability, gaze palsy and visual impairment. The symptoms typically manifest between 1 and 5 days after the surgery and can persist upwards of 6 months.²³ While the etiology of PFS is still debated, most believe it is a consequence of damage to the dentato-thalamo cortical pathway.^{23, 24} The presence and magnitude of hydrocephalus appear to be unrelated to the incidence of PFS.²³ Often overlooked, children with PFS frequently demonstrate severe vision loss. Liu and colleagues describe four children who underwent posterior fossa surgery who demonstrated absence of a visual response (i.e., no grimace to light, blink to threat and response to optokinetic stimuli) despite having intact pupillary responses and relatively unremarkable appearance of their optic nerve.²⁵ The authors hypothesize that the diminished visual response could be due to cortical vision loss or possibly visual inattention as it is well established that cerebellar function mediates language and attention.²⁵ Case #1 of the introduction describes the typical clinical scenario of PFS and what questions a family may ask the neuro-ophthalmologist. The provider would provide reassurance to the family that the child's vision will typically recover at the same pace as their other clinical symptoms (i.e., dysarthria and ataxia).

ASSOCIATED SYMPTOMS

Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS), most commonly presents with seizures and encephalopathy, along with visual disturbance (i.e., vision loss, visual field cut, or hallucinations). Beyond the typical medications known to cause PRES, many of the medications used to treat pediatric brain tumors have also been associated with PRES and include: vincristine, methotrexate, sorafenib and anti-VEGF agents (cediranib, bevacizumab).²⁶

Visual disturbances can occur in up to one-third of children and adults with PRES.²⁷⁻²⁹ One retrospective study reported the frequency of visual disturbance to be much lower in children (10%) compared to adults (35%), which they attributed to a greater predominance of frontal rather than occipital neuroimaging changes.³⁰ These visual symptoms

can resolve quickly if the etiology (e.g., hypertension) is immediately treated, or in some cases can persist for nearly two weeks.²⁸ The most commonly reported long term side effect from PRES is epilepsy. In some cases, the vasogenic edema of PRES results in parietal and occipital lobe atrophy.^{27, 28} Furthermore, upwards of 10-20% of patients experience life threatening complications that include hemorrhage in the occipital cortex.³¹ It is unclear if these injuries result in permanent visual deficits as to the best of my knowledge, none have been reported in children with PRES.

OPHTHALMIC IMAGING TOOLS TO MANAGE COMPLICATIONS

Brain tumors frequently cause ventriculomegaly and elevated intracranial pressure (ICP), even after the tumor

has been partially or fully resected. The persistence of enlarged ventricles, with or without placement of a ventriculoperitoneal shunt, typically requires close monitoring for increased ICP. In children with enlarging ventricles or symptoms of elevated ICP, optical coherence tomography (OCT) imaging may be an informative ancillary test to detect early signs of papilledema.³²⁻³⁴ For example, a sixteen year old male with pilocytic astrocytoma of the optic chiasm demonstrated a progressive increase in ventricle size without other signs or symptoms of elevated ICP. OCT imaging revealed a progressive increase in optic nerve head volume and retinal nerve fiber layer thickness over consecutive visits (Figure 1). Although not formally studied in pediatric brain tumor patients, previously established OCT imaging protocols³²⁻³⁴ may eventually prove helpful in monitoring children for evolving papilledema.

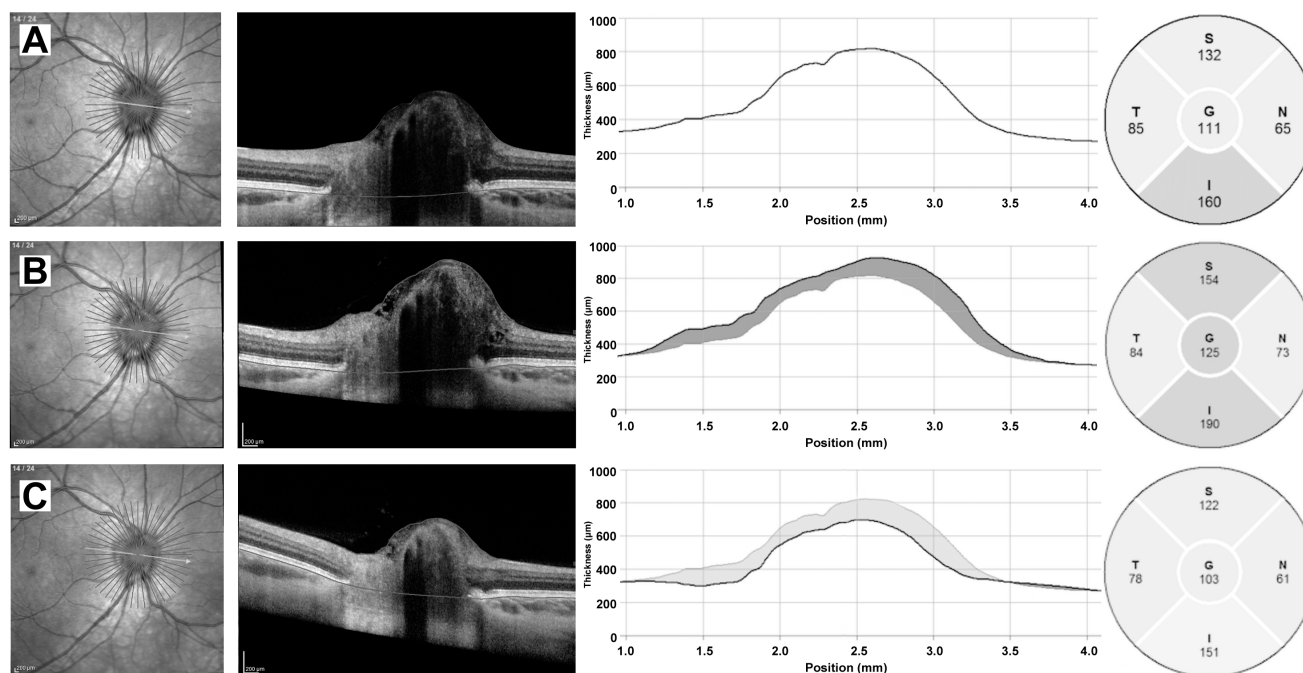


Figure 1. Sixteen year old male with previously normal retinal nerve fiber layer thickness and optic nerve volume (Row A), developed increasing ventriculomegaly and subtle signs of papilledema (Row B). After placement of a ventriculoperitoneal shunt, his retinal nerve fiber layer thickness and optic nerve volume significantly decreased (Row C).

SUMMARY

Despite the lack of rigorous prospective research, multiple treatment and disease-based complications of brain tumors in children have been identified. Neuro-ophthalmologist should be able to recognize these complications, some of which do not manifest until adulthood.

CME ANSWERS

1. d
2. d
3. d

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SUSAC SYNDROME: EXPANDING THE TRIAD

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LEARNING OBJECTIVES

1. Recognize that patients with active disease often present with Gass plaques and fluorescein leakage distant from occluded retinal arterioles.
2. Recognize that bowel and bladder dysfunction may occur in this disorder secondary to cord or cauda equina involvement. Livedo and psychosis are common co-participants in this disorder.
3. Recognize that despite usage of B cell mediated drugs like steroids, mycophenolate, and rituximab, intravenous immunoglobulin is a mainstay in the treatment of active disease.

CME QUESTIONS

1. A Gass plaque is:
 - a. An occlusive embolus that obstructs blood flow
 - b. Orange and refractile in color that lodges at retinal bifurcations
 - c. Yellow and may be refractile and caused by local arteriole wall damage
 - d. A name given to the plaque by Dr. Gass himself
2. The correct next test in an encephalopathic patient with Gass plaques and callosal lesions on MRI who suddenly cannot walk is:
 - a. An electromyogram
 - b. A lumbar puncture
 - c. A brain biopsy
 - d. An MRI of the cervical spine with and without gadolinium
3. The highest risk of Susac Syndrome is with the following:
 - a. A young woman with a branch retinal artery occlusion with fluorescein leakage at the site of the occlusion.
 - b. A young woman on the locked psychiatry unit who suddenly goes blind
 - c. A young man with sudden hearing loss in one ear.
 - d. A young woman with 10 white matter lesions on MRI with one in the corpus callosum.

KEYWORDS

1. Retinal Artery Occlusion
2. Psychosis
3. Livedo
4. Cauda Equina
5. Myelopathy

INTRODUCTION

Susac Syndrome presents with the clinical triad of retinal artery occlusion, sensorineural hearing loss, and encephalopathy and the neuroimaging triad of white matter lesions with callosal involvement, deep grey lesions, and leptomeningeal disease. Since the initial descriptions of both triads, increasing awareness has been made of further clinical manifestations in the retina of Gass plaques caused by local arterial wall damage and fluorescein leakage that occurs in normal appearing retinal arterioles far distant from involved vessels. Many patients appear psychotic when encephalopathic and have skin changes resembling livedo. When bowel and bladder involvement is present in fulminant presentations, cervical cord or cauda equina involvement should be searched for.

Susac syndrome (SS) is an autoimmune disorder that presents with the clinical triad of encephalopathy, deafness, and vision loss.^{1,2} This is due to microinfarction in the brain and corpus callosum, cochlea, and retina. The pathology affects very small arterioles in each of these structures which has led some investigators initially by John Susac to believe that end arteries were involved or pre-capillary arterioles. In patients that had significant clinical involvement, these patients were found to have an imaging triad of white matter disease including the corpus callosum, deep grey matter involvement, and leptomeningeal disease.³

In 2000, I saw a 27 year old man who awoke with an inferior visual field cut 9 months prior to my evaluation. Four months later he lost vision inferiorly on the right eye associated with bitemporal headaches. Evaluation revealed that he had suffered a branch retinal artery occlusion OD and there were these particles in his retinal arterioles that were yellow and located at mid-arteriolar segments in both fundi. Five months later he suffered another branch retinal artery occlusion OS. An audiogram confirmed low frequency sensorineural hearing loss. An MRI scan showed

several white matter lesions including a callosal lesions and a diffusion weighted lesion in the left basal ganglia. The patient had the clinical triad of SS but was worried about the other retinal findings which had never been reported before that might suggest a different diagnosis.

I did not know what to make of these “emboli” and spoke with a neuroimmunologist at my university who bluntly stated that patients with SS do not get retinal emboli. Frustrated, I looked up John Susac’s name in the American Academy of Neurology’s registry and called him up and he was more than willing to speak with me. He asked me if I had seen any other cases of patients with his syndrome and I relayed that I had seen one as a fellow but that this patient did not have “emboli.” I saw her in follow up with Joe Rizzo after she had been treated and she was now in remission.

This patient was a 32 year old woman who experience sudden painless loss of vision in the lower part of her visual field OD associated with forgetfulness, fatigue, vertigo, and tinnitus. She had been suffering from depression. She had normal acuity and pupillary responses but she had a superonasal visual field defect OD. I had the fundusoscopic pictures on my shelf and pulled them down onto my lightbox and placed my magnifier over them and was stunned when I stared right at an “embolus” that I did not realize was present in the superior temporal arcade; there was an area of ischemic retinal whitening in the inferior retina consistent with a branch retinal artery occlusion. Audiometry showed bilateral low to medium frequency hearing loss and her MRI revealed white matter lesions bilaterally.

John had 2 other cases of “emboli” with photographic evidence in one and we wrote these up with Dr. Rizzo and Don Gass.⁴ Dr. Gass and coworkers had described multiple yellow retinal arterial wall plaques (RAWPs) simulating emboli in six of nine patients with idiopathic branch retinal artery occlusions.⁵⁻⁸ It was concluded that the multiple artery occlusions are caused by a localized reaction, perhaps immune mediated, in the retinal artery wall and that the reaction may occasionally affect arteries in the inner ear and brain. These were also described with other disorders that cause acute focal damage to the retinal arterial wall and he attributed the RAWPs to atheromatous deposits to slow extravasation of blood lipids into the arterial wall at the sites of arterial wall damage.

RAWPs are therefore not true emboli and the acronym sounds somewhat harsh. The term pseudoemboli has been bantered about and at the request of Dr. Susac, I wrote Dr. Gass asking if he minded if we called them Gass plaques to which he responded rather negatively. Unfortunately and rather sadly, Dr. Gass passed away from pancreatic cancer prompting Dr. Susac to insist that we call the pseudoemboli by the eponym Gass plaques in his honor. Since the initial description of Gass plaques in SS, these plaques are seen in virtually all cases of active

SS and help make the diagnosis in questionable cases or cases without the full clinical triad. Their appearance can wax and wane depending on the degree of inflammation present in the patients.

Fluorescein angiography (FA) is a useful tool in the evaluation of the patient with SS. It is important in differentiating embolic from focal arterial wall damage unrelated to emboli in patients present with multiple acute branch retinal artery occlusions in one or both eyes. This arteriolar wall hyperfluorescence (AWH) can be seen at the site of infarction but also at the site of vessel wall damage where infarction has not occurred yet. This was demonstrated in a patient with SS who five days later developed the characteristic branch retinal artery occlusion in the abnormally staining vessel.⁹ Another patient with confirmed SS with AWH seen on FA was treated with tacrolimus and the AWH resolved without retinal infarction.¹⁰ There are a couple of case reports in the literature demonstrating the findings of AWH in SS¹¹⁻¹² and we published our own series of 4 patients following this.¹³ Like Gass plaques, AWH on FA in a patient without the full clinical triad of SS should alert the practitioner to the potential diagnosis of SS since I am currently unaware of another diagnosis that either of these processes are seen in. Gass plaques are not seen on FA, only on funduscopy. Remember, the key feature is seeing the AWH located distant to the site of retinal damage or infarction not near it or at it.

Advances in neuroimaging with magnetic resonance imaging have helped in the diagnosis of this disorder. Since the publication of the imaging triad³ a number of papers have been published with emphasis on the neuroimaging findings. The imaging triad consists of white matter lesions including the corpus callosum, deep grey matter lesions, and leptomeningeal involvement usually seen as enhancement after gadolinium. The most important point of the imaging paper is that the corpus callosum is involved in all cases of SS and was so in the seminal paper published in 2003.³ These callosal lesions are caused by infarction of very tiny arterioles in the central part of the callosum which cause the appearance of a “snowball” or a “spoke” and over time will cause cavitation that typically does not appear in other parts of the brain. This is similar to the T1 hole that develops in multiple sclerosis patients but obviously in a different area of the brain. The location of these central callosal lesions is also different than the callosal lesions seen in multiple sclerosis since those lesions tend to be more basal and likely are related to the different pathologies between these two diseases. What is more important is that SS loves the corpus callosum and if a multiple sclerosis patient has white matter lesions perhaps one will be in the callosum; if a SS patient has white matter lesions perhaps eight will be in the callosum!

Interestingly what was not emphasized in the imaging paper is that when the imaging triad was present, the last finding seen was typically the leptomeningeal

enhancement. The leptomeningeal enhancement was never seen as an isolated finding in a patient with SS. This suggests that it is a finding in patients with more active or severe disease. This latest imaging finding is important in 2 recent cases of SS which presented with new clinical findings that may expand the clinical triad seen in this disorder. Both patients presented with severe fulminant disease.

The first patient was a 43 year old man who developed headache and progressive confusion. He was inattentive and perseverated. Initially his examination was completely normal including his funduscopy examination. His MRI showed white matter lesions including numerous lesions in the corpus callosum. He had no leptomeningeal enhancement at that time or grey matter lesions. His work up revealed non-specific inflammatory abnormalities in his cerebrospinal fluid and he was treated with prednisone which was eventually tapered. His headache and confusion remitted and then relapsed as his steroid was tapered. A repeat work up revealed new callosal lesions and some of the old callosal lesions now appeared as holes. He was given intravenous steroids and when switched to oral prednisone he developed urinary and bowel retention and saddle anesthesia with ankle clonus. He also developed livedo diffusely. Repeat MRI of the brain now showed the full imaging triad including leptomeningeal enhancement. Spinal lumbar MRI showed thickening and enhancement of the nerve roots of the cauda equina. Several days later a repeat funduscopy examination showed fresh branch retinal artery occlusions in both eyes and FA showed bilateral AWH. Audiometry revealed moderate sensorineural hearing loss AU. This patient shows a distinct clinical and neuroimaging triad of SS plus this new cauda equina syndrome. We suspect that this may occur in more fulminant cases of SS when leptomeningeal enhancement occurs.

The second patient was a pregnant 25 year old, 14 week gestation woman with encephalopathy and excessive sleepiness. She complained of vertigo and blurry vision and was having difficulty with gait and toileting. Her initial MRI scan of the brain showed a number of white matter lesions including callosal lesions; gadolinium was not given due to her pregnancy. An MRI of the cervical spine was allegedly normal. She improved with steroids and was discharged with a walker but returned to the ER with no memory of being married or pregnant. She was treated again and did well until she delivered her baby when she relapsed again. She had a repeat MRI of the brain and cervical spine at that time and was found to have more white matter and callosal lesions with enhancement although no leptomeningeal enhancement at that time. A high C2 and C3 lesion was seen and review of the old non-enhanced MRI from the year prior revealed this lesion. It is unknown if this lesion ever enhanced since no gadolinium was given initially. At the time of the presentation of this patient's last relapse she was found to have hearing loss and branch retinal artery occlusions confirming the clinical triad. This finding

of a cervical myelopathy expands the clinical triad of SS.¹⁵ Therefore when patients present with acute gait disorders, imaging of the whole neuraxis may be required to look for myelopathic findings as well as cauda equina involvement. What is also clear about these 2 case presentations is that both of them had findings on MRI that were highly suggestive of SS but the diagnosis was delayed due to lack of recognition of the findings. Both cases clearly showed central callosal lesions on the initial MRI scans.

Livedo reticularis seems to have been forgotten in SS. It was seen in the fulminant case of SS with the cauda equina syndrome¹⁴ but JOS described it in his initial report way back in 1979 with his first 2 patients!¹ This is a finding that should not be overlooked. The psychiatric manifestations of this illness should not be overlooked either. Many patients are paranoid at onset or have other psychiatric comorbidities. JOS also described this early on¹ and the first patient described with Gass plaques⁴ had numerous psychiatric admissions until his disease was stabilized. An experiment conducted through the social media site Facebook in 2014 on the Susac Syndrome Patient Group asked 479 subjects about different symptoms. There were 37 respondents and 17 (46%) reported paranoia and 8 (22%) livedo.¹⁶ Biopsy specimens of skin affected by livedo show platelet thrombi and a perivascular and intramural lymphocytic infiltrate.¹⁴

Further directions in this disorder include most importantly how to best treat the illness. The current thinking is that all patients need to be initially treated with an oral steroid like prednisone as well as intravenous immunoglobulin. There have been many individual experiences of practitioners who have seen relapses of retinal infarctions once IVIg has been stopped. What needs to be determined is what the next best agent should be whether it be mycophenolate, rituximab, cyclophosphamide, or some other agent.

The site of injury in this illness appears to be the endothelial cell and antibodies have been identified against this target. Currently it is unknown whether the antibodies are pathologic or if they are an epiphenomenon that results from the real cause of the disease. Support for this may be from the fact that several patients have been successfully treated with the T cell drug natalizumab which is unexpected. Hopefully more work on this is upcoming.

CONCLUSIONS

SS is a rare disorder that may be more common than once thought. Diagnosis is often delayed due to lack of recognition of clinical and radiologic findings. Attention to newer clinical ophthalmic findings such as Gass plaques and AWH remote from arteriolar disease, radiologic findings such as callosal lesions and leptomeningeal enhancement, cervical myelopathy or cauda equina syndrome in a delirious patient, complaints of paranoia in a blind patient, or livedo in a confused patient should raise the specter of SS.

I would like to introduce the concept of the Diagnostic Triad which includes any one of the following:

1. Gass plaques
2. Arteriolar wall hyperfluorescence remote from branch retinal artery occlusions
3. Central callosal lesions

In a patient who presents with the incomplete clinical or neuroimaging triad who is found to have a single finding of the Diagnostic Triad, the diagnosis of Susac Syndrome should be as good as confirmed.

CME ANSWERS

1. c. Gass plaques are not true emboli and they do not occlude vessels. They are typically yellow in color and Dr. Gass' first description were that they were non-refractile but I have seen many that are indeed refractile. Hollenhorst plaques are orange and refractile and lodge at arteriolar bifurcations. Gass plaques are caused by local arteriole wall damage. And Dr. Gass hated the fact that Dr. Susac and I wanted to call them Gass plaques!
2. d. Although a patient who suddenly cannot walk could have a large new hemispheric lesion one must rule out a cord lesion or cauda equina lesion. Cauda equina was purposely left out of the list of answers here. Spinal fluid is often abnormal in SS with high protein and moderately elevated white cells. An EMG would be useless in this condition as far as we know although there has been muscle pathology described in this disorder when there are small microinfarcts present due to the endothelial disease there. A brain biopsy would likely be overkill and not necessary.
3. b. Just about all branch retinal artery occlusions cause fluorescein leakage at the site of occlusions. What makes FA leakage special in SS is when you see it located in an area of completely normal appearing retinal arterioles. Sudden hearing loss in one ear is fairly common although could be a harbinger of SS. Ten white matter lesions in the brain without only one in the callosum is fairly generic for multiple sclerosis; a more common finding in SS would be to find six in the callosum and four in the rest of the white matter since SS loves the callosum! Therefore the most appropriate answer is B with the young patient who suddenly goes blind on the psychiatry ward which is also one of the two patients that John Susac first described in his original paper on t his syndrome.

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INTRACRANIAL ANEURYSMS AND NEURO-OPHTHALMOLOGY

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LEARNING OBJECTIVES

1. Review the most recent data regarding intracranial aneurysms and their prognosis
2. Evaluate and counsel patients with un-ruptured intracranial aneurysms
3. Recognize neuro-ophthalmic manifestations of intracranial aneurysms

CME QUESTIONS

1. When do patients with un-ruptured intracranial aneurysms revealed by a third nerve palsy need to be treated?
 - a. Immediately
 - b. At the neurosurgeon's convenience
 - c. It is not an emergency because the aneurysm is un-ruptured
2. What is the correct answer regarding intracranial aneurysms?
 - a. They are acquired lesions.
 - b. They can develop at any time during adult life and patients with known aneurysms should be followed to screen for new aneurysms.
 - c. Enlargement of un-ruptured untreated aneurysm is associated with a higher risk of subarachnoid hemorrhage.
 - d. All of the above are correct.
3. What is the correct answer regarding the treatment of intracranial aneurysms?
 - a. Endovascular treatment should always be preferred because it is easier and safer in all patients.
 - b. Surgical clipping is definitely associated with a better outcome of compressive cranial nerve palsies than endovascular treatment.
 - c. Endovascular treatment does not resolve the mass effect on a cranial nerve, and therefore cannot result in improvement of the cranial neuropathy.
 - d. None of the above is correct.

KEYWORDS

1. Intracranial Aneurysm
2. Third Nerve Palsy
3. Terson Syndrome
4. Subarachnoid Hemorrhage

INTRODUCTION

Intracranial aneurysms are acquired lesions that are most commonly located at the branching points of the major arteries coursing through the subarachnoid space at the base of the brain¹. Cerebral aneurysms in any location can cause numerous neuro-ophthalmic findings. Advancement in non-invasive imaging and emerging endovascular treatments have contributed to an explosion of large studies on all aspects of cerebral aneurysms over the past 10 years. Detailed guidelines for the management of patients with un-ruptured intracranial aneurysms were recently published by the American Heart Association/American Stroke Association². This review will highlight specific points relevant to neuro-ophthalmology.

I. IMPORTANT NUMBERS AND STATISTICS ON INTRACRANIAL ANEURYSMS

Intracranial saccular aneurysms are common acquired lesions that occur in about 3% of the adult (mean age 50 years) population worldwide; their importance is highlighted by the severe morbidity and mortality associated with subarachnoid hemorrhage (SAH) that results from rupture of cerebral aneurysms.¹⁻⁶

Intracranial aneurysms are more common in men in the fourth decade of life and in women in the 5th decade. The women-men ratio is approximately 3 to 1.¹⁻³

The majority of intracranial aneurysms are located in the anterior circulation (85%), most commonly at the junction of the internal carotid artery and the posterior communicating artery, the anterior communicating artery complex, or the trifurcation of the middle cerebral artery. Aneurysms of the posterior circulation are most frequently located at the tip of the basilar artery or the junction of the vertebral artery and the ipsilateral posterior inferior cerebellar artery¹.

Multiple intracranial aneurysms are found in 15-30% of patients¹⁻³.

Unruptured intracranial aneurysms are more common in elderly people and are uncommon in children. Aneurysms in children most often occur in the setting of other conditions (such as type IV Ehlers-Danlos or Marfan syndrome) and occur more commonly in the posterior circulation (40-45%) with a boy to girl ratio of about 2.1.¹⁻³

Estimates of the frequently of familial occurrence of intracranial aneurysms range from 7 to 20%.¹⁻³

SAH due to the rupture of an intracranial aneurysm is a devastating event associated with high rates of morbidity and mortality (>50%):

- Approximately 12-15% of patients die before receiving medical attention.
- 40% of hospitalized patients die within one month after the event.
- More than 1/3rd of those who survive have major neurological deficits.
- Most patients considered to have a good outcome have persistent cognitive deficits.

SAH is a major clinical problem in the United States, with an annual incidence of approximately 1 per 10,000 people.

Intracranial aneurysms are acquired lesions and are the cause of most cases (80-85%) of nontraumatic SAH; however, the proportion of intracranial aneurysms that rupture is unknown.

Each year, approximately 27,000 Americans have ruptured intracranial aneurysms, which are fatal in 14,000.

The incidence of aneurysmal SAH is higher than many other major neurologic disorders, including primary brain tumors and multiple sclerosis.

Although the incidence of other types of stroke has decreased significantly over the past 60 years, the incidence of aneurysmal SAH has not changed.

Patients who had an aneurysmal SAH are at increased risk of developing a new aneurysm. Each year, new aneurysms develop in at least 2% of patients with previously ruptured aneurysm. The incidence of aneurysm rupture in this subgroup of patients is 6 per 10,000 (higher than in the general population).^{1,4,5}

II. NEURO-OPHTHALMOLOGY AND INTRACRANIAL ANEURYSMS (SEE TABLE 1)

Although the overwhelming majority of patients with intracranial aneurysms present acutely with a SAH, new, otherwise unexplained, cranial nerve or visual field deficits may reveal an unruptured intracranial aneurysm (see table 1). Indeed, although aneurysms represent only a small

fraction of disorders causing isolated cranial nerve palsies or compressive optic neuropathies or chiasmopathies, it is not unusual for an unruptured intracranial aneurysm to be discovered in neuro-ophthalmology. These unruptured intracranial aneurysms, when presumed to be responsible for neuro-ophthalmic symptoms and signs, always need to be evaluated and treated emergently. Indeed, it is well established that a change in morphology of an unruptured intracranial aneurysm sufficiently large to cause compressive symptoms signals an increased risk of impending rupture; in these patients, prompt diagnosis may lead to urgent treatment to prevent a devastating SAH⁷⁻⁹. Patients who suffer a SAH may subsequently develop neuro-ophthalmic signs in addition to those caused by the compressive effect of unruptured intracranial aneurysm.^{1,5,8,9}

INTRACRANIAL ANEURYSMS

1. May be asymptomatic, found on imaging performed for another reason:
 - They are often incidentally found on brain MRI and MRA or CTA obtained for another reason.
2. Compression of adjacent structures (mass effect of the aneurysm):
 - Compression of adjacent cranial nerves (such as the optic nerve and the ocular motor nerves) is particularly common, explaining why aneurysms are often diagnosed by neuro-ophthalmologists.
3. Distal emboli from the sac of the aneurysm:
 - Such emboli may involve the retina in aneurysms involving the anterior circulation below or at the level of the origin of the ophthalmic artery, or may involve the posterior fossa and occipital lobes with aneurysms involving the posterior circulation.
4. Rupture with devastating SAH and resulting Terson syndrome, obstructive hydrocephalus (and papilledema) and vasospasm with subsequent cerebral ischemia.

A FEW REMINDERS ON TERSON SYNDROME¹⁰⁻¹²

- SAH produces a very acute increase in intracranial pressure, sometimes associated with "Terson syndrome" (defined as any intraocular hemorrhage, including subretinal, intraretinal, subhyaloid, or vitreous).
- Terson syndrome is often associated with papilledema.
- Prevalence estimates for Terson in SAH vary widely in the literature (12-45%), perhaps because of a lack of consensus on what types of intraocular hemorrhage constitute Terson syndrome.

- The mechanism of Terson syndrome remains controversial. Intraocular and optic nerve sheath hemorrhage frequently co-occur, but the multifocality of nerve sheath hemorrhage makes direct extension of subarachnoid blood unlikely. A leading hypothesis states that orbital venous hypertension caused by a sudden rise in intracranial pressure leads to distention and rupture of the papillary, peripapillary, and retinal capillaries. However, because of the intraorbital anastomoses, intracranial hypertension may not produce a great enough rise in ophthalmic venous pressure to cause hemorrhage. Instead, effusion of cerebrospinal fluid through the intravaginal spaces of the optic nerve may compress and occlude the central retinal vein in the retrobulbar space.

A few studies have suggested that Terson syndrome may be related to worse outcomes in SAH patients and that Terson syndrome may serve as a useful clinical marker in this patient population.

In many cases, the ocular hemorrhages resolve spontaneously over a few weeks or months. Macular hemorrhages may result in permanent visual loss. Persistent vitreous hemorrhage may require a vitrectomy for removal of the blood. Traction retinal detachment may develop.¹¹

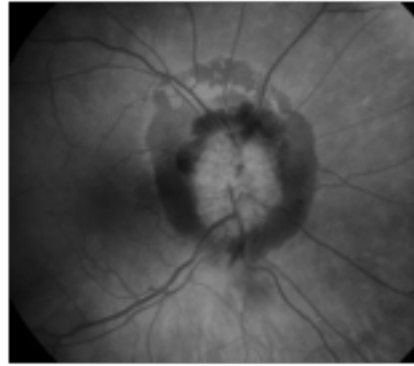


Fig 3: Optic nerve edema and peripapillary hemorrhages in a patient with aneurysmal rupture and subarachnoid hemorrhage. (from Biousse V, Newman NJ. Neuro-Ophthalmology Illustrated 2nd ed; 2016. With permission)

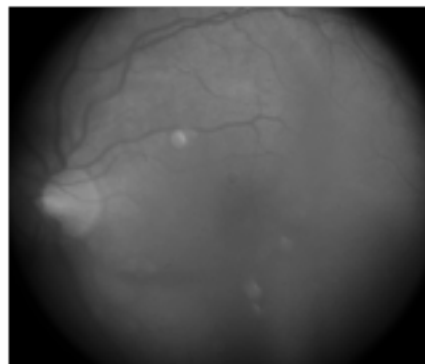


Fig 4: Vitreous hemorrhage in the left eye in a patient with aneurysmal rupture and SAH. (from Biousse V, Newman NJ. Neuro-Ophthalmology Illustrated 2nd ed; 2016. With permission)

Table 1: Clinical manifestations of intracranial aneurysms according to their anatomic location on the circle of Willis

Aneurysm's location	Frequency	Neuro-ophthalmic manifestations
Carotid-ophthalmic aneurysms <ul style="list-style-type: none"> • Ophthalmic artery • Superior hypophyseal artery 	5%	<ul style="list-style-type: none"> • Compression, ischemia, hemorrhage of anterior visual pathways: <ul style="list-style-type: none"> - Retinal ischemia - Optic nerve (monocular visual loss, junctional scotoma) - Chiasm (bitemporal hemianopia) - Optic tract (homonymous hemianopia) • Orbital pain
Anterior communicating artery aneurysm	30%	<ul style="list-style-type: none"> • Compression, ischemia, hemorrhage of anterior visual pathways: <ul style="list-style-type: none"> - Optic nerve (monocular visual loss, junctional scotoma) - Chiasm (bitemporal hemianopia) • Orbital pain, headache
Internal carotid artery bifurcation aneurysm	4%	<ul style="list-style-type: none"> • Compression, ischemia, hemorrhage of visual pathways: <ul style="list-style-type: none"> - Optic nerve (monocular visual loss, junctional scotoma) - Chiasm (bitemporal hemianopsia) - Optic tract (contralateral homonymous hemianopia) • Orbital pain, headache

Continued →

(Table 1 continued)

Aneurysm's location	Frequency	Neuro-ophthalmic manifestations
Cavernous sinus aneurysm	2%	<ul style="list-style-type: none"> • Sixth nerve palsy • Horner's syndrome • Third, fourth, and fifth (V1 and V2) nerve palsies • Compression of anterior visual pathways: <ul style="list-style-type: none"> - Optic nerve (monocular visual loss) - Chiasm (bitemporal hemianopia) • Orbital pain
Middle cerebral artery aneurysm	20%	<ul style="list-style-type: none"> • Compression, ischemia, hemorrhage of retrochiasmal visual pathways: <ul style="list-style-type: none"> - Optic radiations (contralateral homonymous hemianopia) - Headache
Posterior communicating artery aneurysm	35%	<ul style="list-style-type: none"> • Third nerve palsy: ipsilateral • Orbital pain, headache
Basilar artery aneurysm	3-5%	<ul style="list-style-type: none"> • Third nerve palsy: uni or bilateral • Compression of the adjacent midbrain or pons: <ul style="list-style-type: none"> - Horizontal gaze palsy, skew deviation, internuclear ophthalmoplegia - Lid retraction - Nystagmus - Sixth nerve palsy • Occipital headache
Posterior cerebral artery aneurysm	<3%	<ul style="list-style-type: none"> • Third nerve palsy • Compression of the retrochiasmal visual pathways: <ul style="list-style-type: none"> - Optic radiations (contralateral homonymous hemianopia) • Occipital headache
Superior cerebellar artery aneurysm	<3%	<ul style="list-style-type: none"> • Third nerve palsy • Occipital headache
Anterior inferior cerebellar artery (AICA) aneurysm	<3%	<ul style="list-style-type: none"> • Sixth nerve palsy • Occipital headache
Posterior inferior cerebellar artery (PICA) aneurysm	<3%	<ul style="list-style-type: none"> • Sixth nerve palsy • Occipital headache
Vertebral artery aneurysm	<3%	<ul style="list-style-type: none"> • Sixth nerve palsy • Occipital headache
Rupture of the aneurysm (subarachnoid hemorrhage)		<ul style="list-style-type: none"> • Papilledema (raised intracranial pressure) • Sudden headache • Terson syndrome • Cerebral infarction and homonymous hemianopia (vasospasm)

III. PREDICTING THE RISK OF RUPTURE OF AN UNRUPTURED INTRACRANIAL ANEURYSM AND DECISION TO TREAT OR NOT

Because neuro-ophthalmologists often consider intracranial aneurysms in the differential diagnosis of numerous neuro-ophthalmologic symptoms and signs, and because neuro-ophthalmologists often order brain imaging, the discovery of an unruptured intracranial aneurysm is relatively common and raises many questions regarding outcome and treatment.

THERE ARE THREE VERY DIFFERENT SITUATIONS WHEN CONSIDERING WHETHER AN UNRUPTURED INTRACRANIAL ANEURYSM SHOULD BE TREATED OR NOT

1) The aneurysm is *symptomatic* and was discovered because of mass effect on adjacent structures (most often cranial nerves such as a third nerve palsy from a posterior communicating aneurysm) (Table 1). These symptomatic aneurysms are considered emergencies and must be treated as quickly as possible; indeed, it is felt that the development of new symptoms and signs relating to mass effect of an unruptured aneurysm relate to change in morphology and enlargement of the aneurysm which classically precedes impending rupture. **This is why guidelines suggest that symptomatic unruptured aneurysms should be treated in principle. The most recent guidelines² state that "sudden onset of third nerve palsy related to an unruptured intracranial aneurysm is generally considered an expansion and concern for imminent rupture, necessitating rapid workup and intervention".**

2) The aneurysm is discovered during the evaluation of thunderclap headache which should prompt a lumbar puncture looking for SAH and xanthochromia in the CSF. The presence of xanthochromia in the CSF confirms rupture of the aneurysm and should prompt immediate treatment.

3) The aneurysm is *asymptomatic* and was discovered incidentally or as part of screening in patients with specific disorders (such as polycystic kidney disease) or in patients with a family history of aneurysms. Despite a number of recent large studies, the natural history of such unruptured asymptomatic intracranial aneurysms remains unknown. A problem with many of the natural history studies is that the definition of unruptured aneurysm is the absence of SAH; some of these studies likely included unruptured aneurysms with mass effect on adjacent structures and not just asymptomatic unruptured aneurysms, although this is not clear in many studies. Aneurysm size and a previous history of SAH (from another intracranial aneurysm) are important predictors of rupture risk and should be considered preferentially in determining whether to treat.

SUMMARY OF RECENT STUDIES EVALUATING THE RUPTURE RISK OF UNRUPTURED INTRACRANIAL ANEURYSMS

ISUIA (International Study of Unruptured Intracranial Aneurysms) published in 2003:^{13,14} large multicenter, prospective cohort study done in 60 centers in the USA, Canada, and Europe. The cohort included 1692 patients (with 2686 unruptured saccular aneurysms ≥ 2 mm) among whom 51 had a SAH (3 % overall rupture risk). Followup was 4.1 months (6544 patients-year of followup).

Aneurysm size	7-12 mm	13-24 mm	25 mm
Yearly rupture rate	1.2%	3.1%	8.6%

The highest risks of rupture involved aneurysms located in the posterior circulation or posterior communicating artery and large aneurysms.

5-year cumulative aneurysm rupture rates according to size and location of ruptured aneurysms in ISUIA:

Location (number of aneurysms)	< 7 mm		7-12 mm	13-24 mm	≥ 25 mm
	No history of SAH	History of SAH from another aneurysm			
Cavernous carotid artery (n=210)	0%	0%	0%	3.0%	6.4%
ACA, Acom, MCA, ICA (outside the cavernous sinus) (n=1037)	0%	1-5%	2-6%	14.5%	40%
Posterior circulation or Pcom (n=455)	2-5%	3-4%	14.5%	18.4%	50%

***Juvela study (Finland) published in 2014:**^{15,16}

Retrospective and prospective study of 118 patients with unruptured intracranial aneurysms followed for 28.5 years (until death or SAH).

Yearly rupture rate	1.6%
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Female gender (RR, 2.50; 95%CI, 0.87-7.17), current smoking (RR, 3.44; 95%CI, 1.11-10.68), and aneurysm size

of ≥ 7 mm in diameter (RR, 4.02; 95%CI, 1.14-14.19) were risk factors for a lifetime SAH. Based on the risk factors, the annual rupture rate varied from 0% to 6.5%. Of the 96 patients with small (< 7 mm) unruptured intracranial aneurysms, 24 (25%) had an aneurysmal SAH during the followup.

Güresir Study (Germany) Published in 2013:¹⁷

Prospective study of 384 unruptured intracranial aneurysms < 7 mm of the anterior circulation followed for 48.5 months. 3 aneurysms enlarged during the followup period and were treated; 3 patients had a SAH, with an overall rupture rate of 3/384 (0.78%)

Aneurysm size	
Yearly rupture rates	0.2%

Lee Study (Korea) Published in 2012:¹⁸ Prospective longitudinal study of 5963 unruptured untreated intracranial aneurysms followed for 3.3 years. Rupture occurred in 163 patients with an overall rupture rate of 2.73%.

SUAV (Small Unruptured Aneurysm Verification)

Published in 2010:⁹ Multicenter, prospective study done in 12 centers in Japan. The baseline evaluation included 374 patients with 448 unruptured saccular aneurysms less than 5 mm in diameter. 7 had a SAH during followup (1.87% overall rupture risk). Followup was 41 months.

Aneurysm size	< 5 mm
Overall yearly rupture rate	0.54%
Yearly rupture rate for single aneurysms	0.34%
Yearly rupture rate for multiple aneurysms	0.95%

Factors increasing the rupture rate of small aneurysms:

- patient < 50 years of age: hazard ratio 5.23 [95% CI, 1.03-26.52]
- aneurysm diameter ≥ 4 mm: hazard ratio 5.86 [95% CI, 1.27-26.95]
- hypertension: hazard ratio 7.93 [95% CI, 1.33-47.42]
- aneurysm multiplicity: hazard ratio 4.87 [95% CI, 1.62-14.65]

UCAS (Unruptured Cerebral Aneurysm Study of Japan) Published in 2012²⁰

Large multicenter, prospective cohort study. Including 1930 unruptured untreated saccular aneurysms ≥ 3 mm in diameter. 111 patients had a SAH during followup with a 5.75% overall rupture risk). Followup was 1.7 years (11,660 aneurysm-years).

Aneurysm size	Overall	3-4 mm	5-6 mm	7-9 mm	10-24 mm	≥ 25 mm
Yearly rupture rate	0.95%	0.36%	0.50%	1.69%	4.37%	33.4%

Ishibashi Study (Japan) Published in 2009:²¹

419 patients with 529 unruptured saccular intracranial aneurysms were observed for a mean of 2.5 years. 19 aneurysms ruptured during followup (3.5%).

Overall yearly rupture rate	1.4%
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The rupture rate was higher in those with larger aneurysms, posterior circulation location, and a history of SAH.

Meta-analysis of 19 studies published between 1966 and 2005:²² 4705 patients (6556 unruptured aneurysms) (followup 26 122 patient-years)

Overall rupture rate	1.2% for those with mean followup < 5 years 0.6% for those with mean followup of 5 to 10 years 1.3% for those with mean followup > 10 years
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Age > 60 years (RR, 2.0; 95% CI, 1.1-3.7), female sex (RR, 1.6; 95% CI, 1.1-2.4), Japanese or Finish descent (RR, 3.4; 95% CI, 2.6-4.4), **symptomatic aneurysm (RR, 4.4; 95% CI, 2.8-6.8)**, diameter > 5 mm (RR, 2.3; 95% CI, 1.0-5.2), and posterior circulation aneurysm (RR, 2.5; 95% CI, 1.6-4.1) were found to be risk factors for rupture.

ANEURYSMAL RUPTURE IN FAMILIAL FORMS

The large FIA (Familial Intracranial Aneurysm) study²² followed 113 patients with 148 unruptured aneurysms, nearly all < 7 mm and none with a history of SAH, for a mean of 1.5 years. Among these patients, there were 2 SAHs in patients with 3 and 5 mm anterior communicating artery aneurysms, respectively, for a rupture rate of 1.2% per year, 17-fold higher than that seen in patients with comparable sized and positioned aneurysms in ISUIA.

ANEURYSMAL RUPTURE RATE BASED ON GROWTH OF KNOWN UNRUPTURED UNTREATED INTRACRANIAL ANEURYSMS:

A recent prospective observational study by Inoue²⁴ of 1002 patients with 1325 aneurysms reported a dramatically increased risk of spontaneous hemorrhage from aneurysms with documented growth on serial MRAs.

Aneurysms with growth on serial MRAs	18/1325
Yearly rupture rate for these 18 aneurysms	18.5%

In another smaller prospective longitudinal study by Villablanca²⁵, 165 patients with 258 unruptured untreated intracranial aneurysms were followed for a mean of 2.24 years.

Followup of 258 unruptured, untreated aneurysms	46/258 (18%) with growth	82% did not rupture
Yearly rupture rate	2.4%	0.2%

In both studies, some aneurysms were treated before they ruptured, suggesting that the rupture rate of growing aneurysms should be higher.

Therefore, routine screening by noninvasive vascular imaging techniques to detect aneurysmal growth is indicated, and treatment of aneurysms with documented growth is reasonable².

Guidelines have been developed around the world to guide clinicians with the management of unruptured intracranial aneurysms (Table 2)²⁻⁴.

PHASES score

In 2013, Greving introduced the PHASES score for prediction of risk of rupture of intracranial aneurysms (Table 3). The final results of the study were published in 2014.²⁶ The scoring system was developed from a pooled analysis of individual patient data from 8382 participants in six prospective cohort studies. Rupture occurred in 230 patients during 29166 person-years of followup. The mean observed 1-year risk of aneurysm rupture was 1.4% (95% CI, 1.1-1.6) and the 5-year risk was 3.4% (95% CI, 2.9-4.0). In study populations from North America and European countries other than Finland, the estimated 5-year absolute risk of aneurysm rupture ranged from 0.25% in individuals younger than 70 years without vascular risk factors with a small-sized (<7 mm) internal carotid artery aneurysm, to more than 15% in patients aged 70 years or older with hypertension, a history of subarachnoid haemorrhage, and a giant-sized (>20 mm) posterior circulation aneurysm. By comparison with populations from North America and European countries other than

Table 2: Recommendations for the treatment of unruptured intracranial aneurysms²⁻⁴

1. For patients with an unruptured intracranial aneurysm that are managed conservatively without treatment, treatment of high blood pressure, cessation of smoking, and regular vascular imaging follow-up, even without symptoms, are recommended (unruptured asymptomatic intracranial aneurysms are generally monitored annually with MRA or CTA for 2-3 years and then every 2 to 5 years thereafter if the aneurysms remain asymptomatic and radiologically stable).
2. Treatment is not generally recommended for an asymptomatic extradural intracranial aneurysm.
3. Symptomatic unruptured intracranial aneurysms should be treated in principle
4. Considering the natural course of asymptomatic unruptured intracranial aneurysms, treatment might be considered for patients who have a life expectancy of more than 10-15 years and have one or more of following conditions. <ul style="list-style-type: none"> • Size of 5 mm or more • Size under 5 mm at high risk of rupture • Symptomatic intracranial aneurysm • Aneurysm located in the posterior circulation, anterior communicating artery, or posterior communicating artery • History of previous SAH • Aneurysm undergoing increase in size or change in morphology during follow-up • Patients with age less than 50 years, hypertension, and multiple aneurysms • Aneurysm with high aspect ratio (the ratio of aneurysm height to neck width) or high size ratio (the ratio of aneurysm size to the parent artery size), or aneurysm with multilobule or bleb • Patients who have anxiety or depression because of the diagnosis of an aneurysm
5. It is recommended that the treatment decision for unruptured intracranial aneurysms should be determined after taking into account the patient-specific factors of age, comorbidity, and health condition and aneurysm-specific factors of size, location, and morphology. The facility and performance of centers also should be considered for the selection of the treatment method. In the decision making process, informed consent should be obtained after providing sufficient explanation to the patient or the patient's family.
6. In the decision-making process, the PHASES score (see below) may be considered for predicting a patient's risk of aneurysm rupture.

Finland, Finnish people had a 3.6-times increased risk of aneurysm rupture and Japanese people a 2.8-times increased risk.

Predictors included age, hypertension, history of SAH, aneurysm size, aneurysm location, and geographical region, and were independently associated with the

rupture risk of an intracranial aneurysm. According to the PHASES score, a high PHASES score corresponds to a great 5-year risk of aneurysm rupture (table below). Higher PHASES scores were also associated with an increased risk of aneurysm growth²⁷.

Table 3: PHASES Aneurysm Risk Score (adapted from²⁶)

	Points
P: Population	
North American, European (other than Finish)	0
Japanese	3
Finnish	5
H: Hypertension	
No	0
Yes	1
A: Age	
< 70 years	0
≥ 70 years	1
S: Size of aneurysm	
< 7 mm	0
7.0-9.9 mm	3
10.0-19.9 mm	6
≥ 20 mm	10
E: Earlier SAH from another aneurysm	
No	0
Yes	1
S: Site of aneurysm	
Internal carotid artery	0
Middle cerebral artery	2
Anterior cerebral artery/Posterior communicating artery/Posterior cerebral circulation (including the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery).	4

To calculate the PHASES risk score for an individual, the number of points associated with each indicator is added up to obtain the total risk score.

In addition to the risk factors included in the PHASES score, several other risk factors for aneurysm growth have been described, such as female sex, cigarette smoking, a family history of SAH, irregular aneurysm shape, and the presence of multiple aneurysms. Implementation of additional (aneurysm-related) risk factors for aneurysm rupture, such as aspect ratio (aneurysm neck-to-dome length/neck-width), size ratio (maximum aneurysm diameter/average vessel diameter), and irregular aneurysm shape, might improve current rupture risk assessment.

IV. TREATMENT STRATEGIES

The goal of the treatment of an aneurysm is to completely obliterate the aneurysm to keep it from expanding and rupturing. The most appropriate treatment option of any intracranial aneurysm is that which provides an optimal balance of procedural safety and long-term efficacy based on patient and aneurysm characteristic. To date, there has been no completed randomized comparison of either clipping or coiling treatment with regard to natural history to evaluate its risk/benefit ratio. Endovascular treatment of intracranial aneurysms has evolved over the past 20 years. Endovascular coiling, stent-assisted coiling and flow diverters are now routinely used for treatment of an expanding population of intracranial aneurysms. In general, the decision on whether to surgically clip or to treat

endovascularly depends on several factors related to two major components:

- Patient: age, comorbidities, presence of intracerebral hemorrhage, SAH grade, aneurysm size, aneurysm location and configuration, status of collaterals.
- Procedure: competence, technical skills and availability.

The morbidity/mortality of surgical clipping is higher than that of endovascular intervention.²⁻⁴ In a 2007 retrospective study from 429 hospitals in 18 states in the US, neurosurgical cases had 70% greater odds of an adverse outcome, 30% increased hospital charges, and 80% longer length of stay compared with endovascular cases.²⁸ However, the risk of aneurysm recurrence is higher with endovascular treatment than with surgical clipping,² and the data are likely skewed because more difficult-to-approach aneurysms or more complex aneurysms are often preferentially treated with surgical clipping.

The treatment of ruptured intracranial aneurysms is essentially aimed at saving the patient's life by treating the SAH. Early treatment of the ruptured aneurysm is necessary to reduce the rate of rebleeding which is maximum within the first 2 to 12 hours after SAH.

The treatment of unruptured aneurysm remains decided on a case-by-case basis.

Surgical aneurysm clipping and endovascular treatment yield comparable results. The selection of treatment is determined based on the type of aneurysm (location, size, anatomy) and the risk of treatment and recurrence rate.

Long-term followup is recommended after treating an unruptured cerebral aneurysm. In particular, for patients managed with endovascular treatment, angiographic followup is recommended to detect incomplete occlusion or recurrence.

Findings from several studies have suggested that rupture risk is reduced in patients taking aspirin. In a study of 747 consecutive patients with intracranial aneurysms,²⁹ the rate of hemorrhagic presentation was higher among those not taking aspirin (40%) than among those taking aspirin (28%); the overall outcome of those experiencing SAH was not affected by aspirin use. In an analysis of data from the ISUIA untreated cohort,³⁰ patients who used aspirin most frequently had the lowest risk of aneurysm rupture during

followup. In a case-control study on the protective effect of aspirin for patients with untreated intracranial aneurysms, patients who used aspirin 3 times weekly to daily had a significantly lower odds of hemorrhage (adjusted OR, 0.27; 95% CI, 0.11-0.67) compared with those who never used aspirin.

Outcome of neuro-ophthalmic signs after treatment of an intracranial aneurysm:

Whether ocular motor nerve palsies and optic neuropathies secondary to compression by an unruptured intracranial aneurysm recover better after surgical clipping or endovascular therapy remains debated. Almost all studies are retrospective and a number of the cases reported had followup duration less than 1 year, making it difficult to evaluate late recovery of ocular motor deficits. Additionally, these retrospective studies included heterogeneous patients making it impossible to draw definite conclusions; indeed aneurysms of various size, ruptured and unruptured aneurysms, patients with complete and partial cranial nerve palsies were included (Table 4).

Both microsurgical clip ligation of posterior communicating artery aneurysms, and endovascular intervention have been shown to effectively treat the resultant third nerve palsy with a high proportion of complete resolution.³¹⁻⁴² Overall, the data are conflicting because some authors report greater rates of complete resolution with microsurgical clipping, whereas others report that endovascular treatment of posterior communicating aneurysms in the setting of third nerve palsy is equally as effective as surgery (see table 4).

The theoretical advantage of surgery over endovascular therapy in this regard is that, after complete exclusion from the circulation, the aneurysm may be punctured to immediately reduce mass effect.⁷ Many neurointerventionalists report that post-treatment aneurysm involution achieves the same effect, albeit more slowly. Mass effect from the aneurysm is not the only mechanism responsible for cranial nerve palsies; aneurysm pulsatility on the cranial nerve and the blast effect of aneurysm rupture also contributes to cranial nerve palsies. It is often said that the blast effect of SAH is associated with poorer recovery regardless the treatment modality. It is also suggested that elimination of the aneurysm pulsatility either by surgical clipping or endovascular treatment may be enough to improve the cranial nerve palsy.

Table 4: Outcome of cranial nerve palsies after treatment of intracranial aneurysms – review of recent studies comparing surgical clipping with endovascular treatment

Study (year) Design	Outcome	Study population	Treatment	
			Surgical clipping	Endovascular
Patel et al (2014) ³¹ Retrospective	No difference	18 patients with CNIII -15 ruptured aneurysms -3 unruptured	9 patients 6/9 (66.6%) recovery of III at 6 months	9 patients 5/9 (55.5%) recovery of III at 6 months
Brigui et al (2014) ³² Retrospective	No difference	22 patients with CNIII	7 7/7 (100%) recovery	14 13/14 (92.8%) recovered but 3 recurred
Schuss et al (2011) ³³ Retrospective	Surgical clipping better	20 patients with CNIII -All unruptured	12 patients 9/12 (75%) recovery	8 patients 3/8 (38%)
Guresir et al (2011) ³⁴ Retrospective review of 26 studies	Surgical clipping better	15 patients with CNIII combined with systematic review of the literature =Total of 186 treated CNIII Pcom aneurysms	132 patients 72/132 (55%) recovery	54 PATIENTS 17/54 (32%)
Chen et al (2006) ³⁵ Retrospective	Surgical clipping better	13 patients with CNIII -9 ruptured -4 unruptured	7 patients 6/7 (85.7%) recovery	6 patients 2/6 (33.3%) recovery
Ahn et al (2006) ³⁶ Retrospective	No difference	17 patients with CNIII -All unruptured	7 patients 3/7 (42.9%) recovery	10 patients 6/10 (60%) recovery

CONCLUSION

The decisions regarding the management of unruptured intracranial aneurysms are complex and are based on natural history data compared with interventional morbidity and mortality specific to the aneurysm size and location.

Table 5: Pearls of wisdom: Intracranial aneurysms for Neuro-ophthalmologists (we are not talking about carotid cavernous aneurysms)

<p>You will find incidental aneurysms on about 3% of brain imaging you order.</p> <ul style="list-style-type: none"> • These patients need to be referred to an expert (neurosurgeon, interventional radiologist, stroke neurology) for evaluation of the rupture risk and patient education and counselling. • These patients will need long-term followup with noninvasive imaging; because they have no neuro-ophthalmic problems related to the aneurysm, you should not be the one obtaining these tests.
<p>It is not because you find an intracranial aneurysm on brain imaging, that the aneurysm is responsible for the patient's symptoms.</p> <ul style="list-style-type: none"> • It is essential to determine whether an intracranial aneurysm is symptomatic or not: <ul style="list-style-type: none"> • all symptomatic aneurysms are treated. • many asymptomatic aneurysms are not treated. • This is a common and important source of referral from neurosurgeons and interventional radiologists and we must have the expertise necessary to determine this.
<p>Know when to look for intracranial aneurysms and make sure your center is equipped with the appropriate equipment and personnel to diagnose and treat intracranial aneurysms.⁴³</p>

All symptomatic aneurysms need to be treated.

- SAH is always an emergent situation that can only be addressed in a highly specialized center
- Compression of a cranial nerve is also an emergency and treatment is usually immediate or delayed by only a few days.

Think about systematically looking for Terson syndrome in all SAH patients if you can:

- It may correlate with worse neurologic outcomes.
- It helps the ICU care providers, the rehabilitation team, patients and families to know that vision may be impaired.

In most cases, neuro-ophthalmologists should refrain from obtaining a diagnostic catheter angiogram

- Noninvasive vascular imaging with MRA and CTA is highly sensitive to detect even small aneurysms as long as you communicate well with the neuroradiologist and your radiologist is really good.
- When a catheter angiogram is needed, it is best to refer the patient to an interventional radiologist who may decide to plan endovascular treatment at the same time (or at least will discuss it with the patient in advance).

Do not talk too much to your patients about the type of treatment they will receive because you will usually be wrong (and the patient will be disappointed): it may be endovascular or it may be surgical clipping. You cannot predict what will be decided because the choice of treatment depends on numerous factors that will be considered by the treating physician – it is therefore easier to refer such patients to centers that routinely perform both open surgery and endovascular procedures.

Do not worry about the neuro-ophthalmic findings associated with the aneurysm: you will deal with what remains after the appropriate treatment is performed.

- There is no convincing data showing that neuro-ophthalmic outcome is better with surgery than with endovascular treatment or vice-versa; let the expert decide what is best for the patient's long-term outcome overall.

CME ANSWERS

1. a. The most recent guidelines² state that “sudden onset of third nerve palsy related to an unruptured intracranial aneurysm is generally considered an expansion and concern for imminent rupture, necessitating rapid workup and intervention”.
2. d. Intracranial aneurysms are acquired and their prevalence increases with age; patients with known aneurysms have a higher risk of developing new aneurysms. Enlargement of an unruptured aneurysm is associated with a high risk of subarachnoid hemorrhage.
3. d. The treatment of intracranial aneurysms is individualized based on the patient's and aneurysm's characteristics. Although surgical clipping is associated with higher morbidity/mortality, the risk of recurrence is higher with endovascular treatment. Both surgical clipping and endovascular treatment often result in improvement of the cranial nerve palsy.

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THE ELEVATED OPTIC DISC: WHEN OCT HELPS AND WHEN IT DOES NOT. AN INTERACTIVE CASE BASED APPROACH

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LEARNING OBJECTIVES

1. Develop a systematic approach to the clinical challenge of the elevated optic disc using a multi-modal imaging approach incorporating recent advances with spectral domain optical coherence tomography (SD-OCT)
2. Identify the specific issue of papilledema versus optic disc drusen adding fundus autofluorescence (FAF) and MultiColor OCT (MC-OCT) to the diagnostic evaluation
3. Describe the clinical syndrome of vitreo-peripapillary traction (VPT) with epiretinal membranes in the differential diagnosis of chronic optic disc edema
4. Recognize the correlation between SD-OCT and MC-OCT findings with visual acuity and visual fields to alert clinicians to vision-threatening papilledema

CME QUESTIONS

1. SD OCT can help with all of the following except:
 - a. Verification of papilledema
 - b. Quantification of the degree of edema for retinal nerve fiber thickening
 - c. Evaluation of macular involvement for subretinal fluid
 - d. Identification of peripapillary choroidal neovascular membranes
 - e. Differentiation of cone pigment types
2. Buried optic disc drusen are easily seen in OCT.
 - a. True
 - b. False
3. Macular pigmentary changes sometimes noted after severe papilledema
 - a. Is due to deposited lipids
 - b. Is due to disruption of the myoid and ellipsoid zones
 - c. Is secondary to inflammation

KEYWORDS

1. Spectral Domain Optical Coherence Tomography
2. Multi-Color Optical Coherence Tomography
3. Papilledema
4. Optic Disc Drusen
5. Epiretinal Membranes

INTRODUCTION

The differentiation of acquired optic disc edema representing a pathological process such as papilledema caused by increased intracranial pressure versus a usually benign, pre-existing condition such as optic disc drusen is one of the most classic, and most important, clinical challenges in neuro-ophthalmology, dating back to the days of Harvey Cushing and Llewelyn Paton.

For years, the direct and indirect ophthalmoscopes and the Hruby lens and hand held 60 and 90 diopter lenses supported by fundus photography were the primary clinical evaluations to determine if the optic disc or discs were pseudo-papilledema or as the late Joel Glaser like to say, "papilledema vera". This clinical evaluation and analysis of the 2-dimensional monochromatic photographs and stereoscopic "pair" photographs lead to a list of characteristics associated with papilledema.

Some clinicians have advocated intravenous fluorescein angiography as a potential means to differentiate papilledema from pseudo-papilledema but the results have been disappointing. B-scan ultrasonography with the 30 degree test also has had its supporters but often is dependent upon the skill of the technician performing the test.

Since its commercialization in 1993, optical coherence tomography has revolutionized the evaluation of the retina and optic disc. Although developed primarily for retinal diseases and glaucoma, OCT, especially in its most recent spectral domain version, has enhanced not only the qualitative assessment of the posterior pole but also functions a quantitative ophthalmoscope with reproducible, low variability measurements meeting regulatory standards

for structural metrics in clinical trials. The utility of SD-OCT has been enhanced by comparing the patient's peripapillary retinal nerve fiber layer and macular thickness and volume measurements to an age and gender matched database. (Figure 1, top right)

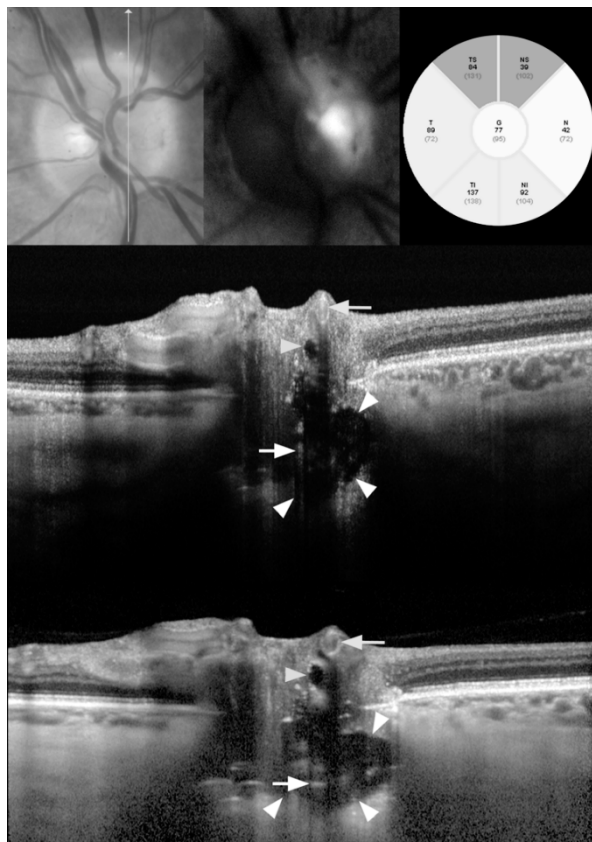


Figure 1: (Top left) A magnified view of the optic disc shows buried optic disc drusen and an irregular contour from nasal to superonasal sector. The green line is the scanned lines of the swept source optical coherence tomography (OCT) images in shown (Second row) and the enhanced depth imaging (EDI) OCT images in shown (Bottom). (Top middle) Fundus autofluorescence image shows hyperautofluorescence. (Top right) Retinal nerve fiber layer thickness chart shows outside normal limits results at the supertemporal and supernasal sectors. (Second row, Bottom) Swept source OCT (Second row) and EDI-OCT (Bottom) show large ovoid regions of lower reflectivity (arrowheads) with several hyperreflective foci (white arrows). A retinal artery (blue arrow) demonstrates an oval region of medium reflectivity and subjacent shadowing. A small optic disc druse was visualized as a hyporeflective oval region without shadowing (green arrowhead).¹

SD-OCT AND FAF FINDINGS IN OPTIC DISC DRUSEN

Sato, Mrejen, and Spaide evaluated optic disc drusen in a retrospective series with enhanced depth imaging [EDI]-OCT, swept source OCT, and fundus autofluorescence [FAF]¹. The disc drusen occupied primarily a location anterior to the lamina cribrosa with an oval shape. The reflectivity pattern was usually hypo-reflective centrally with a hyper-reflective border [Figures 1 and 2]

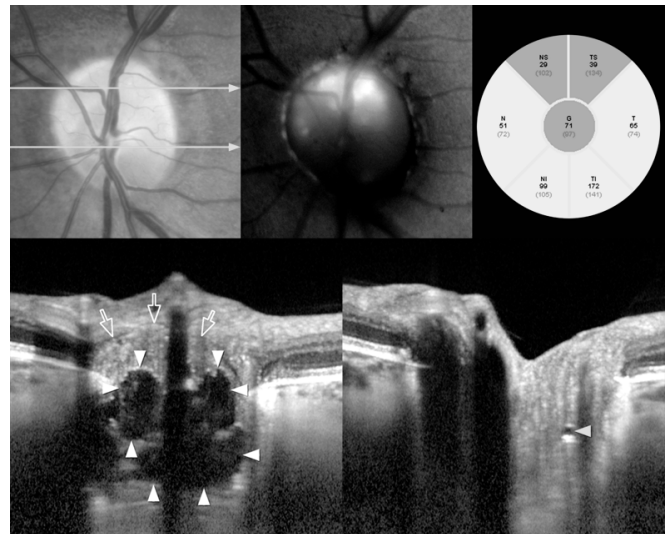


Figure 2: (Top left) Magnified view of the optic disc shows buried optic disc drusen and an irregular contour from nasal to superotemporal sector. The green lines are the scanned lines of the enhanced depth imaging optical coherence tomography (EDI-OCT) images shown in (Bottom left: upper line) and (Bottom right: lower line). (Top middle) Fundus autofluorescence image shows hyperautofluorescence at nasal, superonasal, superotemporal, and temporal sectors. (Top right) Retinal nerve fiber layer thickness chart shows that results were outside normal limits at the supertemporal and supernasal sectors. (Bottom left) EDI-OCT shows three oval regions with relatively high reflective border (arrowheads). Two components were seen anterior to optic disc drusen. Open arrows indicate the border of two components. The inner region close to the optic nerve drusen shows more granular reflectance materials (Bottom right) EDI-OCT shows small round optic disc drusen in the middle of optic nerve head (green arrowhead). This optic disc drusen was only detected by EDI-OCT.

Lee, Woo, and Hwang also studied optic disc drusen with SD-OCT. They also showed that drusen exhibited hyper-reflective borders and homogeneous internal reflectivity. They also found peripapillary intraretinal cysts in optic discs with large drusen and small disc diameters. [Figure 3].

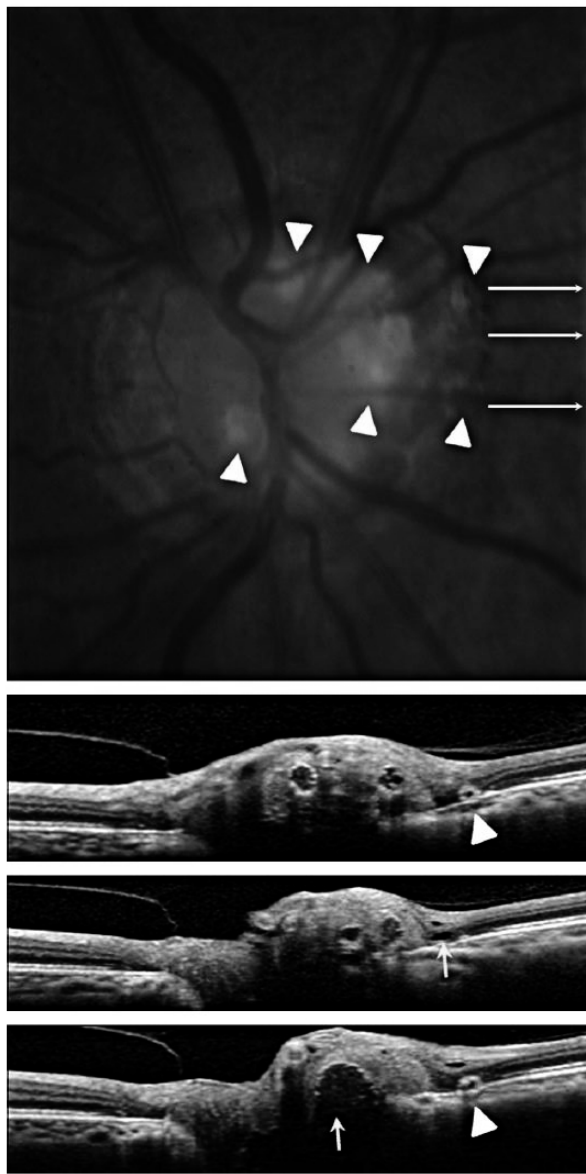


FIGURE 2. Configuration of visible optic nerve head drusen on spectral-domain optical coherence tomography (SD OCT; right eye). (Top) Fundus photograph. (Second row, Third row, Bottom) Horizontal sections of SD OCT (Second row, top line; Third row, middle line; Bottom, bottom line). Optic nerve head drusen are visible from (Top) the fundus photograph (arrowheads) and (Second row, Third row, Bottom) SD OCT. The SD OCT images reveal a hyperreflective subretinal mass with multiple hyporeflective spaces or cysts with calcified hyperreflective walls. Some small cysts or daughter optic nerve head drusen are observed surrounding the optic nerve head drusen (Top, Second row, Bottom, arrowheads). Multiple intraretinal cysts can be seen in (Third row) the nasal retina (arrow). (Bottom) Deeply located optic nerve head drusen containing fluid can be visualized on SD OCT (arrow), but not on fundus photography.

Figure 3²:

Therefore, SD-OCT can be very useful in the evaluation of suspected optic disc drusen and ultimately may help to quantify the size of the drusen in the event of treatment

trials as well as measurements of the peripapillary retinal nerve fiber layer. FAF adds confirmatory evidence.

PAPILLEDEMA

Neuro-ophthalmologists, neurologists, neurosurgeons, and ophthalmologists should define papilledema only as optic disc edema associated with increased intracranial pressure. The term should never be used for inflammatory, ischemic, infectious, or infiltrative optic neuropathies.

SD-OCT has demonstrated significant value for papilledema in five ways: 1) verification of the diagnosis of papilledema; 2) quantification of the degree of edema for retinal nerve fiber thickening to provide an additional parameter to visual fields and disc appearance for longitudinal analysis and correlation with treatment; 3) evaluation of macular involvement both for subretinal fluid and its impact upon the myoid and ellipsoid zones of the photoreceptors; and⁴ identification of peripapillary choroidal neovascular membranes that can form in association with papilledema.

In any clinical disease, clinicians need to communicate in consistent, reproducible expressions that can be applied by different practitioners at different times. The Frisén grading system has been proposed as a means of this necessary communication. However, work by Scott et al demonstrated a disturbing lack of concordance when four neuro-ophthalmology experts independently graded papilledema.³ One grade scale discrepancy was occurred in 43% of cases and 3.6% of cases showed 2 grading scales of variance at the more advanced stages of papilledema.

Therefore, SD- and MultiColor OCT offers an opportunity to enhance a subjective appraisal—ophthalmoscopy and monochromatic fundus photos—with objective assessments such as retinal nerve layer [RNFL] thickness, macular thickness, and measurements of the pre-laminar optic nerve.

For over 20 years, clinicians have realized that macular pigmentary changes may occur following papilledema. However, the mechanism and significance of these findings has not been elucidated. Now, SD-OCT and MC-OCT may decipher the pathophysiology of these changes. Investigators from Duke University, reviewed the macular OCTs of 94 patients with papilledema less than or equal to Frisén grade 1. SD-OCT revealed thinning of the fovea and outer macular ring of the outer plexiform layer.⁴

Evaluation of patients with severe papilledema with Frisén grade > 3 has disclosed some insight into the macular pathology in this clinical syndrome. As can be seen in Figure 4 in this example of Grade 4 papilledema, hyporeflectivity consistent with cerebrospinal fluid extends into the subretinal space in the papillo-macular bundle and disrupts the normal structure of the ellipsoid and myoid zones. The MC-OCT confirms these changes with the source images from the infrared and green sources.

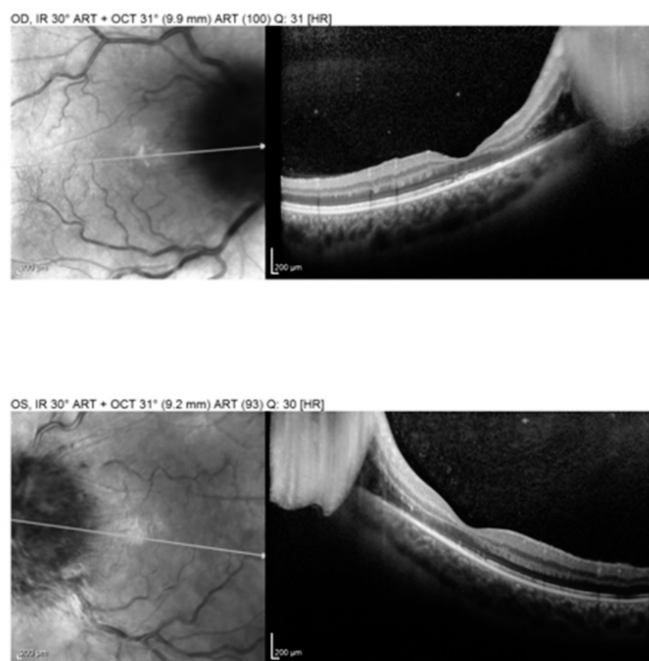
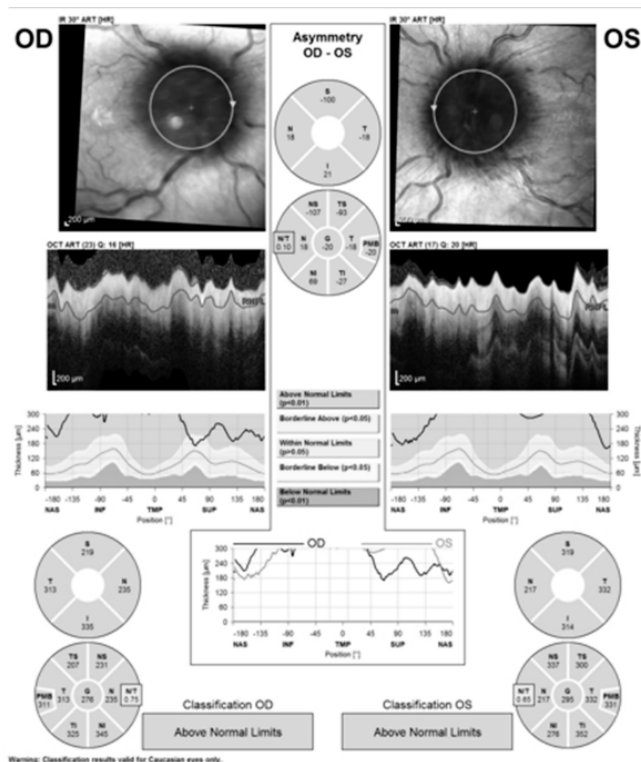


Figure 4a, b [left] markedly increased retinal nerve fiber layer thickness in grade 4 papilledema with bilateral central visual loss and severely constricted visual fields. Line scans [right] through the papillo-macular bundle demonstrate edema tracking from the optic nerve towards the fovea associated with loss of the normal myoid/ellipsoid zone.

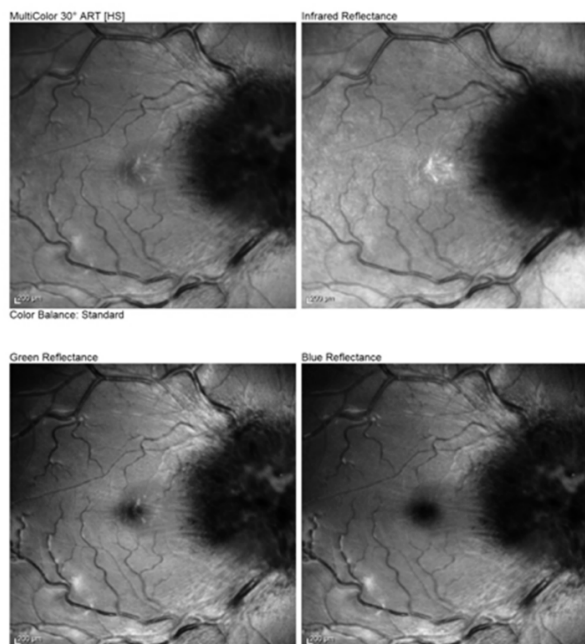


Figure 4c MC-OCT of the same patient shown in Figure 4 a, b. Note the massive papilledema and hyper-reflective changes in the fovea in the infrared images representing photoreceptor damage as seen in the line scan, Figure 4b. The foveal changes extend into the mid-retina and are associated with folds in both the peripapillary area and papillo-macular bundle.

Table 1 – Ophthalmoscopic Characteristics of Papilledema in Order of Importance

1. Peripapillary optic disc hemorrhages
2. Peripapillary retinal nerve fiber layer edema
3. Lack of spontaneous venous pulsations
4. Optic disc hyperemia
5. Absence of an optic cup, when
6. Distention of the retinal venous system
7. Optic disc elevation

INFLAMMATORY/ INFECTIOUS OPTIC NEUROPATHIES

The differentiation between non-arteritic ischemic optic neuropathy and inflammatory/infectious optic neuropathies is often very elementary. However some atypical cases can be challenging even for the most experienced neuro-ophthalmologists. In our experience, this differentiation is most difficult and most critical for the papillitis associated with lyme disease and diabetic papillopathy.

In both lyme disease and diabetes mellitus, SD-OCT can provide invaluable data not because of the optic nerve findings but because of associated macular edema in the majority of these cases.

Figure 5 illustrates a case of lyme papillitis in which the detection of macular edema made the initial diagnosis of NAION unlikely and raised the index of suspicion for an infectious etiology.

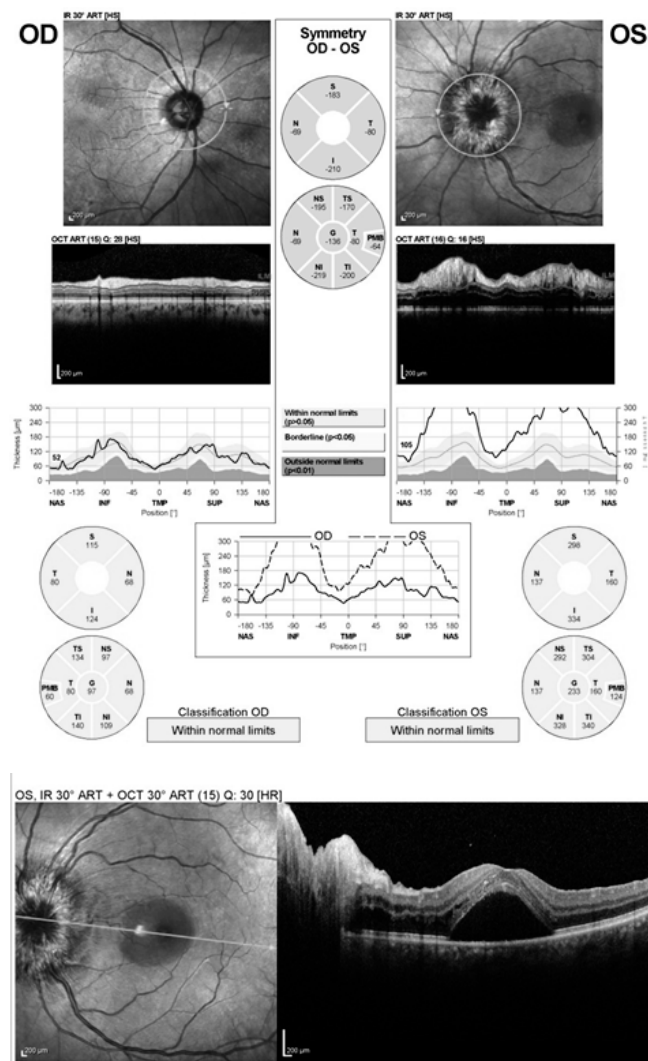
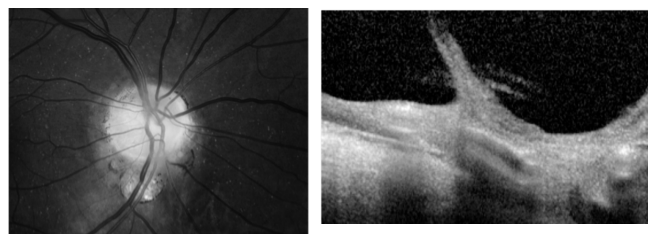


Figure 5: Increased RNFL thickness of the left eye. The right is normal. The line scan through the papillo-macular bundle is showing a dome-shaped elevation of hypo-reflectivity elevating the foveal-macular contour. Notice that the hypo-reflectivity seems to be extending from the temporal margin of the optic disc.

EPI-RETINAL MEMBRANES – VITREOUS PERIPAPILLARY TRACTION

The transition from time domain OCT to SD-OCT has increased not only the resolution and definition of all layers of the retina but also the delineation and demarcation of the vitreo-retinal interface. Epi-retinal membranes [ERMs] now are readily and easily defined in vitreo-macular traction syndromes, macular holes, diabetic retinopathy, and age-related macular degeneration.

This improvement in imaging is now enabling exploration of the vitreous-disc interface and vitreous-peripapillary traction. The vitreous is proving to be much more than a passive bystander in diseases of the inner retina and the same active role may be operative in some optic neuropathies. We have found vitreous traction to be operative in two clinical syndromes: 1) cases of chronic disc edema that have followed an acute inflammatory syndrome of the optic disc, especially sarcoidosis and 2) cases of chronic optic disc pallor associated with progressive central visual loss. Peripapillary depigmentation of the surrounding retina is often present in these two clinical situations.⁵⁻¹⁰ [Figure 6]



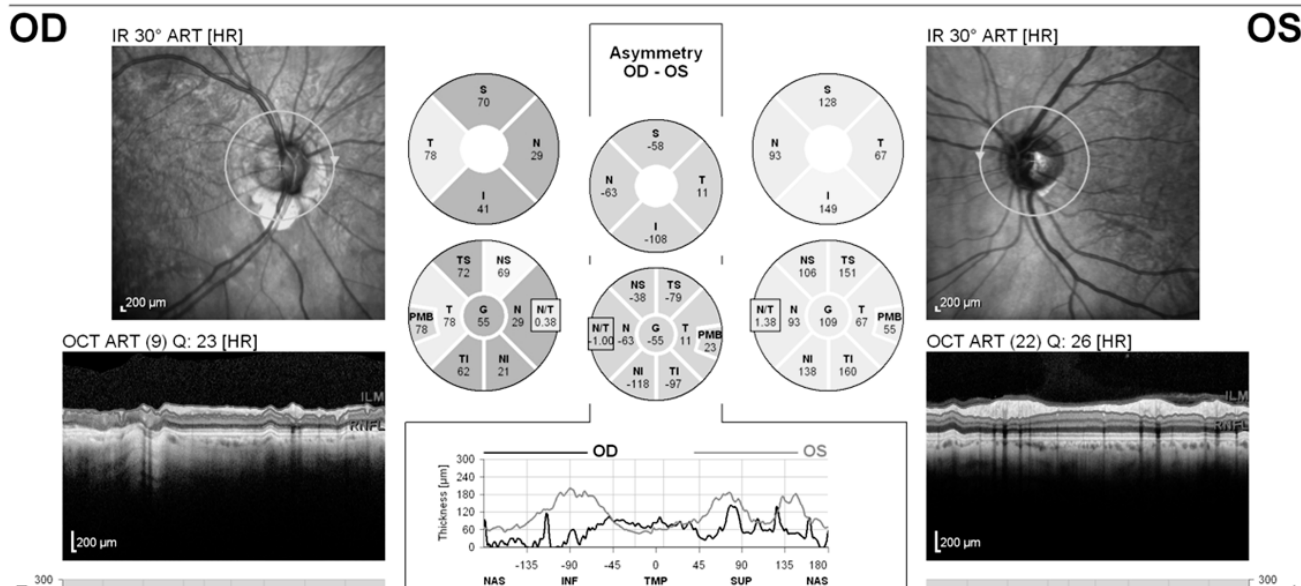


Figure 6, upper left, diffuse optic disc pallor with peripapillary retinal pigment abnormality in a patient who lost vision slowly from 20/25 to 20/200 over four years. Upper right image demonstrates the vitreous traction at the margins of the optic disc. Lower image demonstrates the retinal nerve fiber layer thickening except in the papillo-macular bundle where the traction has increased the thickness.

CME ANSWERS

1. e
2. a
3. b

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GENETIC MANIPULATION FOR INHERITED NEURODEGENERATIVE DISEASES – MYTH OR REALITY?

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LEARNING OBJECTIVES

1. Describe the main gene therapy paradigms for human disease
2. Critically appraise the advances made in developing effective gene delivery systems
3. Discuss the concepts underpinning germline genome editing and the possible applications to the treatment of inherited neurodegenerative diseases

CME QUESTIONS

1. True/False: The adeno-associated virus (AAV) is a commonly used viral vector for human gene therapy trials.
2. True/False: Clinical trials for LHON based on allotopic gene expression are currently ongoing for patients carrying the m.3460A>G, m.11778A>G, and m.14484T>C mtDNA mutations.
3. True/False: Optogenetics is an experimental tool that involves the introduction of photosensitive ion channels in the cell membrane of neurones to make them responsive to a light stimulus.
4. True/False: Mitochondrial-targeted nucleases can selectively decrease the level of mutant mtDNA molecules in a cell.
5. True/False: Pronuclear transfer and metaphase II spindle transfer could be used to prevent the maternal transmission of homoplasmic mtDNA mutations.

KEYWORDS

1. Gene Therapy
2. Mitochondrial Diseases
3. Neurodegenerative Diseases
4. Optogenetics
5. Viral Vector

I. INTRODUCTION

The genetic revolution of the past 25 years has transformed our understanding of the genetic basis of human neurodegenerative diseases.¹ The causative genes for a large number of well-recognised clinical entities have been identified and the pace of discovery will only accelerate further as next-generation whole-genome sequencing becomes routinely available to clinicians. In addition to classical monogenetic diseases with high penetrance, it is now clear that the majority of common late-onset neurodegenerative disorders are heavily determined by a complex cluster of genetic variants, each contributing to the overall risk of developing overt clinical disease, and in some cases having a synergistic deleterious interaction with environmental triggers.^{2,3} Unfortunately, the significant advances made in deciphering the genetic factors that contribute to the underlying neuropathological process have so far resulted in limited therapeutic benefits for patients. A number of factors have contributed to this frustrating translational gap and the challenges that remain are daunting. This review will provide a critical overview of genetic strategies that are being pioneered to halt or reverse disease progression in inherited neurodegenerative diseases. This field of research covers a vast area and only the most promising treatment paradigms will be discussed with a particular focus on inherited eye diseases, which have paved the way for innovative gene therapy paradigms, and mitochondrial diseases, which are currently generating a lot of debate centred on the bioethics of germline manipulation.

II. THE BURDEN OF DISEASE

Rare genetic diseases affect about 7% of the general population and over 7,000 distinct clinical syndromes have been described with the majority (80-90%) being due to single gene defects (<http://www.nihr.ac.uk/about/rare-diseases-translational-research-collaboration.htm>, accessed on 8 September 2015). The prevalence of monogenic neurological diseases has been estimated at 1 in 1,100 in a recent epidemiological study, but when late-onset neurodegenerative disorders, such as Alzheimer disease and Parkinson disease, are included, this figure increases to a staggering 1 in 400 of the general population.⁴ This group of disorders is not only an important cause of chronic morbidity and personal suffering, but it further magnifies the socioeconomic impact of an ageing population by exerting additional stress on already stretched national

health services. Treatment remains largely supportive and so far, conventional pharmacological approaches aimed at neuroprotection have failed to deliver game-changing disease modifying drugs. To palliate for these inadequacies, genetic manipulation seems an obvious solution as a radical means of correcting the primary pathological process that contributes to neuronal dysfunction and disease progression.

III. GENE THERAPY PARADIGMS

Gene therapy is a *priori* perfectly suited for “single gene” neurological disorders, but some additional criteria need to be fulfilled, namely: (i) there must be a relatively clear understanding of the pathways contributing to neuronal loss to ensure selection of the most appropriate therapeutic strategy; (ii) the natural history of the disease must be clearly defined and it must afford practical windows of opportunity for intervention; (iii) the tissue or organ system to be targeted must be relatively accessible; and (iv) the specific cells in question must be amenable to efficient transfection with a suitably designed gene vector.^{5,6}

Genetic diseases caused by recessive null mutations represent the most straightforward group as the replacement of the missing wild-type protein should prove effective in rescuing the disease phenotype.⁷ Gene therapy for autosomal dominant disorders can be more challenging if the mechanism is not due to haploinsufficiency, but secondary to a gain-of-function mutant allele that produces an aberrant protein with dominant negative properties.⁸ The mutant protein can either interfere with the wild-type protein to block its normal function or it can have a direct toxic effect on specific cellular processes. In this scenario, simply increasing the production of the wild-type protein with a gene therapy replacement approach will fail to reverse the negative effect of a dominant gain-of-function mutation. The most logical strategy is to block the expression of the mutant messenger RNA (mRNA) transcript and supplement the cell with a wild-type copy of the gene if required.⁹ This suppression and replacement approach is technically more complex as it requires a delicate balance of gene expression to be achieved. The main experimental paradigms for gene silencing are based on the use of antisense oligonucleotides, ribozymes or RNA interference (RNAi).¹⁰⁻¹⁴

If the causative gene for a rare monogenetic disease has not been identified or the mode of inheritance is complex as in late-onset neurodegenerative diseases, gene therapy can still be contemplated as a treatment strategy.¹⁵ The approach in these situations involve transfecting the cell with gene constructs that upregulate the expression of trophic factors, which in turn serve to rescue neuronal cells from impending death or at least prolong their survival. These blanket neuroprotective strategies could also be used to supplement more targeted gene therapy in monogenic diseases and conceptually, these could provide a synergistic

beneficial effect. A completely novel approach for neurodegenerative diseases is optogenetics, which involves the introduction of light-sensitive protein sensors into neurones making them functionally photosensitive.^{16,17} Ion channel proteins of the channelrhodopsin, halorhodopsin and archaerhodopsins families are able to confer these unique properties by modulating neuronal membrane potential and the balance between depolarized and hyperpolarized states. Optogenetics is being used not only to convert non-photosensitive retinal cells into artificial photoreceptors, but also to deliberately switch on and off specific central nervous system pathways in an attempt to circumvent the damaged circuitry in anatomically diseased areas.^{16,17}

IV. GENE DELIVERY SYSTEMS

The success of gene therapy is contingent upon an effective delivery system and various vectors have been developed to deliver the genetic construct, which is more commonly DNA, but sometimes RNA.¹⁸ The use of non-viral vectors has obvious safety advantages as they are devoid of potential immunogenic and neoplastic side effects for the human recipient. Most of these strategies revolve around the use of liposomes and nanoparticles to package the genetic material within a cationic lipid or polymer protective shell.¹⁹ However, these non-viral delivery systems have limited cargo capacity and therapeutic gene expression is usually low and transient, precluding a sustained therapeutic effect. The favoured alternative is a modified virus that has a natural tropism for the central nervous system and with the ability to integrate genetic material into the host cell's nuclear genome to achieve more prolonged gene expression (**Table 1**). The most commonly used viral vector in human clinical trials, especially for ocular gene therapy, is the adeno-associated virus (AAV).^{20,21} There is now long-term safety data for these recombinant vectors and reassuringly, no major concerns have been raised. AAV vectors are also able to efficiently transduce non-dividing cells, which make them particularly attractive for neuronal populations. A wide variety of AAV serotypes have been genetically engineered by altering the proteins on the outer shell (capsid) and the DNA sequence. These genetic modifications not only confer specific cellular tropism, but they also influence the onset and the intensity of transgene expression. AAV serotype 2 (AAV2) has a natural predilection for retinal cell types and it can induce prolonged levels of gene expression, potentially maximising the intended therapeutic effect. Despite their versatility, AAV vectors have a number of disadvantages including a limited transgene capacity (4.5 kb) and the risk of being rapidly eliminated by the humoral immune response in patients who have previously been exposed to the virus and possessing high circulating levels of neutralising antibodies.^{20,21} As an alternative, lentiviral vectors have gained increasing popularity for central nervous system disorders because of their larger transgene capacity and

the lack of a host immunological response.²²⁻²⁴ Besides the intrinsic properties of the viral carrier, another fundamental aspect of vector design is the use of an appropriate promoter sequence that can efficiently drive the expression of the transgene within the target cell. Depending on the therapeutic aims, the viral vector can be tailor-made with additional promoter elements that titrates the level of gene expression or even limits its action to specific cell types.

V. RETINAL NEURODEGENERATIVE DISEASES

The eye represents a target organ of choice for gene therapy as it is easily accessible and rather advantageously, it is an immunologically protected space.⁵ It is therefore hardly surprising that inherited retinal diseases have led the way both in terms of pioneering the clinical application of gene therapy and the refinement of the protocols for achieving efficient gene delivery *in vivo*. Advances in minimally-invasive intraocular surgery have also made it possible for ophthalmic surgeons to safely access various retinal layers providing a direct route for the delivery of the gene therapy vector. We will now review some key examples of neurodegenerative disease affecting the retinal pigment epithelium (RPE), photoreceptors, and retinal ganglion cells (RGCs) to illustrate some of the groundbreaking innovations that have been achieved to establish gene therapy as a viable treatment option for a broad range of ocular disorders.

5.1 CORRECTING GENE EXPRESSION

Leber congenital amaurosis (LCA) is a severe form of inherited blindness that affects at least 1 in 50,000 children.^{25,26} It is genetically heterogeneous and so far, 17 disease-causing genes have been identified that account for about half all diagnosed cases. One group of patients harbour recessive mutations in the *RPE65* (RPE-specific protein 65 kDa) gene, which encodes for a retinoid isomerase that is expressed almost exclusively within the RPE layer.^{27,28} This specific isomerase is a key component of the visual cycle as it converts all-*trans* retinoid to 11-*cis* retinal for the regeneration of visual pigment after exposure to light. LCA associated with *RPE65* is a complex disease in which vision loss results from two pathological mechanisms – dysfunction and degeneration of photoreceptors.^{25,26} The accumulation of all-*trans* retinyl esters has a toxic effect, causing progressive degeneration of both rod and cone photoreceptors, and resulting in profound visual impairment by early adulthood.²⁹ As the disease process is secondary to a lack of the wild-type protein, gene therapy aimed at augmenting *RPE65* gene expression was an obvious therapeutic target. Several pre-clinical studies were initiated worldwide that substantiated this approach, in particular the seminal study by Jean Bennett and colleagues who in 2001 showed that a subretinal injection of an AAV2 vector containing *RPE65* cDNA could restore visual function in three mutant *RPE65*^{-/-} Briard dogs within three months of them being treated.^{30,31} Additional work in murine models and the establishment of Good

Manufacturing Practice (GMP) for the production of viral vectors led to launch of four independent clinical trials for *RPE65*-LCA in the United States (US) and in Europe. The initial reports confirmed the safety of injecting a bolus of an AAV2-*RPE65* vector in the subretinal space, although some investigators caution against the fluid bleb involving the fovea to minimise the iatrogenic loss of foveal cones and secondary retinal thinning.³²⁻³⁵ All the studies showed a modest improvement in a number of visual parameters within the first month of treatment, probably due to the partial reconstitution of the canonical retinoid cycle within the RPE, and some patients performed better in a subjective test of visual mobility. The visual benefit persisted for at least three years, but there was ongoing loss of photoreceptors in the treated retina at the same rate as that of the untreated retina, and on longer periods of follow-up, the comparative improvement in retinal function was lost altogether.³⁶⁻³⁸ A number of limitations have been identified from this first wave of human clinical trials that will need to be addressed if a more robust and prolonged treatment response is to be achieved. It is clear that the earlier treatment is initiated the better in terms of photoreceptor rescue, and more efficient transduction of the outer retina will be essential to deliver a more substantial augmentation of *RPE65* and sustain the visual cycle.³⁹ Finally, although haploinsufficiency is considered to be a major factor driving retinal degeneration in LCA, correcting *RPE65* gene expression on its own might not be sufficient and additional neuroprotective strategies might have to be provided concurrently.

Another form of inherited retinal degeneration where significant progress has been achieved recently is choroideremia, which has an estimated prevalence of 1 in 50,000.⁴⁰ It is an X-linked disorder caused by null mutations in the *CHM* gene and the lack of the encoded Rab escort protein-1 (REP1) protein accounts for the neurodegenerative process.^{41,42} Loss of night vision begins in the first decade of life and there is gradual loss of peripheral vision leading to legal blindness by the fifth decade of life. The pathological hallmark of choroideremia is the progressive degeneration of the choriocapillaris, the RPE and the outer retina. Patchy areas of chorioretinal atrophy begin in the mid-periphery of the fundus and the foveal region is spared until the end stages of the disease, affording an attractive window of opportunity for therapeutic intervention.⁴⁰ Nearly all reported cases of choroideremia have been attributed to functionally null *CHM* mutations and because the gene has a relatively small protein coding sequence (1.9 kb), it can easily be packaged in an AAV delivery vector. Based on promising pre-clinical work that confirmed the effectiveness and safety of an AAV-based strategy for delivering the *CHM* cDNA encoding REP1, Robert MacLaren and colleagues initiated a first-in-man gene therapy trial that recruited six male patients with choroideremia and good central visual acuity of 6/6 or better.⁴³⁻⁴⁵ Although further work is needed, including longer periods of follow-up, the initial results 6 months

post-surgery showed improved rod and cone function based on microperimetry and visual acuity tests.⁴⁵ As for LCA caused by *RPE65* mutations, this choroideremia trial further confirms the huge potential of ocular gene therapy, which could be extended in due course to more common retinal neurodegenerative diseases such as age-related macular degeneration.

The encouraging results obtained for LCA and choroideremia have led to a major surge in interest from industry and increased collaborations with academic groups to fast-track development pipelines. More efficient replacement vectors are currently being developed for a broad range of inherited genetic diseases including other genetic forms of LCA besides *RPE-65*, recessive forms of Stargardt disease caused by *ABCA4* mutations, and achromatopsia secondary to *CNGB3* deficiency.⁷ A number of research groups worldwide are also actively working on the development of AAV2-based gene therapy treatments for patients with inherited optic neuropathies.⁴⁶ The two most advanced research programmes are for recessive forms of Wolfram syndrome secondary to *WFS1* mutations, and for autosomal dominant optic atrophy (DOA) caused by *OPA1* mutations that result in haploinsufficiency.⁴⁷⁻⁵⁰ Compared with gaining access to RPE cells and photoreceptors, retinal ganglion cells form the innermost layer of the retina, which obviates the need for a vitrectomy or direct physical manipulation of the retina. The ability to deliver the gene therapy vector with a minimally-invasive intravitreal injection procedure provides several advantages, in particular a much lower risk of iatrogenic complications and a faster recovery time for the patient. Unlike inherited retinal diseases, gene therapy vectors for DOA and Wolfram syndrome are still in preclinical phases of development and a number of technical limitations have been encountered that will need to be resolved, in particular RGC transfection efficiency and achieving the optimal gene replacement dosage.⁵¹ The latter point is only starting to be fully appreciated as it became apparent that supraphysiological levels of *OPA1* can, in fact, have a detrimental effect on RGC function, at least in the mouse model that was studied (G. Lenaers, personal communication).⁵²

5.2 ALLOTOPIC GENE EXPRESSION

Leber hereditary optic neuropathy is a mitochondrial DNA (mtDNA) genetic disorder characterised by bilateral severe visual loss secondary to the primary loss of retinal ganglion cells (RGCs) within the inner retina.^{53,54} The visual prognosis is poor with the majority of patients remaining legally blind with visual acuities worse than 6/60.⁵⁵ About 90% of cases are due to one of three mtDNA point mutations (m.3460G>A, m.11778G>A, and m.14484T>C), which affect key complex I subunits of the mitochondrial respiratory chain, resulting in reduced ATP production and increased levels of reactive oxygen species (ROS).^{56,57} There is currently no treatment that has been conclusively shown to reverse the rapid loss of RGCs in the acute phase of LHON and the management of

this disorder remains largely supportive.⁵⁸ The m.11778G>A mutation accounts for 60-70% of cases worldwide and gene therapy is being actively pursued as a therapeutic option for this inherited form of mitochondrial blindness. The two main treatment paradigms are allotopic gene expression and the enhancement of neuronal survival with various trophic factors.

Mitochondria have a double-membrane structure and this physical barrier represents a major challenge for direct gene therapy in LHON. An elegant solution to this problem is allotopic gene expression, which involves transfecting a modified version of the replacement gene into the nuclear genome.^{59,60} The modified protein that is produced has a specific targeting sequence that allows for its efficient import into the mitochondrial compartment. Proof-of-concept was first demonstrated in mutant LHON cybrids with the preferred viral vector being AAV2.^{32,33} The ability to rescue RGCs and improve visual function was subsequently demonstrated in rodent LHON models expressing a mutant form of the ND4 complex I subunit and replicating the pathological consequences of the m.11778G>A mutation.^{61,62} These promising *in vitro* and *in vivo* studies have paved the way for the first clinical trials of allotopic gene expression for patients with LHON harbouring this pathogenic mtDNA mutation (NCT02064569 and NCT02161380). There is still some debate whether the imported wild-type ND4 subunit does integrate into complex I of the mitochondrial respiratory chain to produce a stable and biochemically active unit within the inner mitochondrial membrane.⁶³ The results of the ongoing LHON gene therapy trials will hopefully help to answer these controversies and more importantly, whether patients experience a functional visual benefit using the gene delivery vectors that have been engineered to correct for the m.11778G>A mutation.

A complementary and possibly synergistic approach to replacing the defective complex I subunit in LHON is to protect RGCs against the deleterious downstream consequences of disturbed mitochondrial function. Increased ROS levels are considered to be a major factor driving the apoptotic loss of RGCs in LHON.⁶⁴ Superoxide dismutase is a key mediator of the cell's antioxidant defence mechanism and conceptually, increasing the activity of this ROS scavenger should have a beneficial impact on neuronal survival under unfavourable cellular conditions. This principle was demonstrated convincingly in m.11778G>A LHON cybrids with allotopic expression of the *SOD2* gene.⁶⁵ The increased expression of superoxide dismutase resulted in increased cell survival, and future work is now needed to determine whether consolidating antioxidant defences within RGCs could magnify the therapeutic potential of correcting for the mutant complex I subunit in patients with LHON. A radically different strategy is based on the xenotopic expression of Ndi1, an alternative NADH oxidase expressed in yeast (*saccharomyces cerevisiae*) mitochondria.^{66,67} Ndi1 is a versatile enzyme that can bypass a malfunctioning complex I to restore

downstream electron transfer whilst at the same time suppressing ROS overproduction. Successful rescue of optic nerve degeneration was achieved using the yeast Ndi1 gene in a rat model of LHON that involved injection of rotenone-loaded microspheres into the optic layer of the rat superior colliculus.⁶⁸

5.3 ENHANCING NEURONAL SURVIVAL

The correction of the underlying protein deficiency in monogenetic diseases is a logical treatment strategy that has moved beyond the proof-of-concept stage. However, despite the major advances in genomic medicine, the aetiology of a number of rare or ultra-rare genetic syndromes still remain undefined, and the genetic determinants for late-onset, sporadic neurodegenerative diseases such as Parkinson disease have not been sufficiently clarified to allow specific genetic risk factors to be targeted.⁶⁹ Even if the primary genetic trigger or sequence of cellular events that cause neuronal loss have not been defined, gene therapy could still prove a useful tool by enhancing the local expression of neuroprotective molecules that have consistently proven efficacious in pre-clinical studies. Once more, basic research on retinal dystrophies have paved the way with the identification of several neurotrophic factors, for example ciliary neurotrophic factor (CNTF), glial-cell derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF), which seem to arrest the pathological process irrespective of the genetic subtype.⁷⁰⁻⁷² Neurotrophic factors can diffuse away from the cell from which they are secreted and this important property can be used to extend their therapeutic range, especially for central nervous system disorders. This neuroprotective treatment paradigm still needs to be refined, but encouraging preliminary results have been obtained for Parkinson disease with neurturin (NRTN), a structural and functional analogue of GDNF that protects dopaminergic neurones.^{73,74} In a double-blind phase 2 trial, 58 patients with advanced Parkinson disease were randomly assigned, in a 2:1 ratio, to receive either a bilateral injection of AAV2-NRTN into the putamen or sham surgery.⁷⁵ The primary endpoint was the change from baseline to 12 months in the motor subscore of the unified Parkinson disease rating scale. The treatment was well tolerated and although the primary endpoint did not reach statistical significance, positive results were obtained in a subgroup of patients that had been assessed for up to 18 months. Histopathological analysis performed on the brains of two patients who were treated with AAV2-NRTN suggested a possible delay in the transport of neurturin from the putamen to the substantia nigra because of a severely degenerated nigrostriatal tract. To address these possible study limitations, a new clinical trial is currently underway to determine whether direct transgene delivery to the substantia nigra, in addition to a higher dose injected into the putamen, will prove beneficial to patients with advanced Parkinson disease when assessed over a longer follow-up period.

5.4 OPTOGENETICS

Optogenetics is a novel technique that involves imparting light-sensitivity onto neurones by transfecting them with bacterial opsin genes encoding for specific ion channel proteins.^{76,77} The opening of these channels is modulated by light and the flux of ions across cell membranes creates an action potential, analogous to a neurone discharging. The attraction of optogenetics for inherited retinal diseases lies in the structured relay system that exists with the mammalian retina, and disorders affecting the outer retina lend themselves particularly well to visual restoration using this technique. (**Figure 1**). If there is complete degeneration of the photoreceptor layer, one approach is to render RGCs or bipolar cells light sensitive.⁷⁸ The advantage of targeting bipolar cells is that they are able to generate RGC responses that are physiologically closer to natural activity patterns. A number of studies have shown the efficacy of this method in restoring photosensory responses and visually evoked neural activity in mouse models of retinitis pigmentosa, and rather encouragingly, the treated blind mice showed improved locomotor behaviours.⁷⁹⁻⁸² Optogenetics is in an early stage of development and in addition to achieving a sufficient level of transfection, better targeting of transgene expression to specific retinal cells needs to be achieved to avoid unwanted retinal pathways from being activated. Another factor that needs to be considered is the intensity of light and wavelength needed to produce sufficient activation of the opsin-encoded ion channels, but without causing long-term retinal phototoxicity.⁷⁸ The patient will be expected to wear a prosthetic device that delivers the light stimulus to the retina and newer opsin channels with greater photosensitivity are being developed that do not require stimulation with the more damaging blue light spectrum.

The potential applications of optogenetics extend far beyond inherited retinal diseases as the ability to selectively modulate neuronal function could be used to treat central nervous system disorders caused by an imbalance between inhibitory and excitatory pathways.^{16,83} The basal ganglia contain sophisticated neural networks that regulate motor planning and two main pathways with opposing actions have been described.⁸⁴ According to this classical model, activation of the 'direct' pathway facilitates movement whereas activation of the 'indirect' pathway inhibits movement. The motor dysfunction in patients with Parkinson disease is thought to arise due to a progressive weakening of the direct pathway, driven by the loss of dopamine-secreting nigrostriatal neurones. In a landmark paper, *Anatol Kreitzer and colleagues* tested this hypothesis in a mouse model of Parkinson disease with optogenic manipulation.⁸⁴ A recombinant AAV1 virus was used to deliver channelrhodopsin-2 and selectively target specific neuronal populations within the basal ganglia. Remarkably, activation of the direct pathway completely rescued deficits in freezing, bradykinesia and locomotor initiation in the mutant mice. Although still in its infancy,

these exciting findings have opened up a whole new avenue of translational research for Parkinson disease and other neurodegenerative disorders.⁸⁵

VI. MITOCHONDRIAL NEURODEGENERATIVE DISEASES

6.1 MITOCHONDRIAL GENETICS

Mitochondria are ubiquitous organelles present in every nucleated cell in the human body. A unique feature of mitochondria is that they contain their own genetic material in the form of a double-stranded circular DNA molecule, which is about 16,569 base pairs long.^{86,87} Mitochondrial DNA is a very high-copy number genome with 2 to 10 mtDNA molecules in each mitochondrion, and hundreds to thousands of mitochondria per cell depending on its overall metabolic expenditure. As a result, two situations can arise, namely homoplasmy or heteroplasmy. In the heteroplasmic state, two or more mtDNA variants are present at a specific nucleotide position, whereas in the homoplasmic, only one mitochondrial allele exists.⁸⁸ Due to its compact size, the mitochondrial genome has limited coding capacity for only 2 ribosomal RNAs, 22 transfer RNAs, and 13 essential subunits of the mitochondrial respiratory chain complexes.^{86,87} These encoded gene products are absolutely critical for survival as mitochondria provide for most of the cell's ATP requirements through oxidative phosphorylation. Nevertheless, it is important to remember that the majority of structural and accessory components required for normal mitochondrial function are encoded by the nuclear genome.⁸⁹ This synergistic nuclear-mitochondrial interaction explains why human disease can arise both from mutations in the mitochondrial genome (primary mtDNA disorders) and the nuclear genome (nuclear mitochondrial disorders).⁹⁰

Mitochondrial diseases are now recognised as a major cause of chronic morbidity and the minimum prevalence has been estimated at 1 in 5,000 in the general population.⁹¹ Reflecting the ubiquitous nature of mitochondria and their fundamental roles in energy production, patients with mitochondrial genetic disorders often manifest a heterogeneous combination of tissue and organ involvement, which can lead to significant diagnostic delays.^{86,87} Unlike LHON which tends to be monosymptomatic with no impact on life expectancy, a subset of patients harbouring more deleterious mtDNA mutations or nuclear genetic defects that result in severe mtDNA depletion can develop an aggressive disease course, frequently starting in early childhood, and characterised by irreversible encephalopathy, intractable epilepsy, liver failure and multisystem organ failure. The outcome of these mitochondrial syndromes is invariably fatal and in the absence of effective treatments, significant effort has been invested in developing tractable means of selectively eliminating these pathogenic mutations through germline genome editing, or in preventing the maternal transmission

of pathogenic mtDNA mutations from mother to child.⁹²

6.2 GERMLINE GENOME EDITING

There are about 2,300 women of childbearing age in the UK harbouring pathogenic mtDNA mutations and by using the national fertility rate, nearly 150 pregnancies per year could result in the birth of a child at high risk of developing severe mitochondrial disease.⁹³ Genetic counselling for prospective mothers harbouring heteroplasmic mtDNA mutations remains challenging as there can be rapid shifts in mitochondrial allele frequencies due to the "mitochondrial bottleneck" operating in the early stages of oocyte development.⁹⁴⁻⁹⁶ As the majority of mtDNA mutations cause disease when the level of heteroplasmy exceeds 70-80%, preimplantation genetic diagnosis (PGD) could be used to select the woman's embryo carrying the lowest mutant load, and therefore most likely to result in a healthy child.⁹⁷ However, there is only limited clinical experience in the use of PGD for mitochondrial diseases and there is always the risk that the mutation load detected in biopsied blastomeres or trophectoderm does not accurately represent the entire embryo, or more importantly, the level in the tissue most at risk from a particular mtDNA mutation.⁹⁸ To circumvent these difficulties, several research groups worldwide are working on mitochondrial-targeted nucleases that have been engineered to selectively eliminate mutated mtDNA molecules.⁹⁹⁻¹⁰¹

The principle is straightforward and it makes use of the differences in restriction sites created by the mtDNA mutation (**Figure 2**). Zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) are able to recognise these altered DNA sequences and they create double-strand breaks that effectively eliminate the mutated mtDNA molecules.¹⁰²⁻¹⁰⁶ The ability to shift the level of heteroplasmy could be used to reduce the overall mutant load in the oocyte of a woman carrying a known pathogenic mtDNA mutation to subthreshold level, thereby eliminating the risk of her child developing overt mitochondrial disease. The use of ZFNs or TALENs as a reproductive tool for manipulating levels of heteroplasmy is still in early stages of development and a number of technical difficulties need to be resolved.⁹⁹⁻¹⁰¹ There are still issues about the best way of delivering these nucleases to the mitochondrial matrix and safety concerns need to be addressed further due to the possibility of deleterious off-target effects in the nuclear genome. Germline genome editing, namely with the CRISPR/Cas9 system, could also be used to correct for pathogenic mutations within the nuclear genome.¹⁰⁷⁻¹⁰⁹ This technology is attracting significant interest (and debate) not only within the scientific community, but also within the wider public, as genetic manipulation of the germline and experimentation on early human embryos raises a number of important ethical and legal considerations.¹¹⁰⁻¹¹²

6.3 MITOCHONDRIAL REPLACEMENT

The elimination of mutated mtDNA molecules to shift the level of heteroplasmy to subthreshold level is an attractive strategy to prevent a biochemical deficit and rescue the cellular phenotype. However, in some mitochondrial diseases, such as LHON, the majority of carriers harbour homoplasmic mtDNA mutations and a different experimental strategy is needed to prevent the transmission of a pathogenic mtDNA mutation from mother to child.^{56,57} Two related *in vitro* fertilisation (IVF) techniques have been developed that involves transferring the parental nuclear genetic material into a donor cytoplasm containing a normal wild-type mtDNA population (**Figure 3**).¹¹³⁻¹¹⁵ There is minimal carryover of mutant mtDNA (< 2%) with pronuclear transfer and metaphase II spindle transfer, and both methods have been shown to be compatible with normal embryonic development and the birth of healthy offspring in a nonhuman primate model. Although encouraging, further work is needed to explore the safety implications of these IVF techniques for embryo development, including the concerns that have been raised about epigenetic abnormalities and the possibility of nuclear-mitochondrial genetic mismatch leading to unforeseen negative consequences.^{116,117}

If mitochondrial replacement is adopted for the prevention of mitochondrial disease, the child's entire genetic make-up will be derived from the biological parents except for the 37 mitochondrial genes inherited from the female donor oocyte.¹¹⁸ However, mitochondrial replacement carries important long-term implications as it involves germline manipulation transmissible to future generations.¹¹⁹ There is, understandably, fierce debate on this topic and a comprehensive public consultation exercise involving all the major stakeholders was initiated in the United Kingdom to discuss not on the scientific merits, but the possible ramifications to society as a whole. The Nuffield Council on Bioethics has concluded that mitochondrial replacement might be appropriate within a strictly regulated research environment, and with the prospective parents being fully informed about the potential risks, both real and theoretical.¹²⁰ In February 2015, both Houses of Parliament in the United Kingdom have voted strongly in favour of mitochondrial donation to prevent the maternal transmission of mitochondrial disease (<http://www.parliament.uk/business/news/2015/february/lords-mitochondrial-donation-si/>, accessed on 8 September 2015). The clinical application is expected to begin within the next two years and if approved, this procedure will be closely monitored by the Human Fertilisation and Embryology Authority (HFEA, UK).

VII. CONCLUSION

The launch of the Human Genome Project in 1990 was a seminal moment in the history of science and it started a rapid expansion in technology that continues unabated today. More recently, the availability of whole-exome and whole-genome sequencing in routine clinical practice has accelerated gene discovery and the genetic basis for the vast majority of monogenic diseases will likely be uncovered within the next 5-10 years. There are still limited treatments for most inherited neurodegenerative disorders and the next crucial step now is to translate this genomic revolution into tangible benefits for patients and their families. Gene therapy has had many setbacks over the years, but this field of research has matured, and there is now a much better understanding of gene delivery systems and the pathological pathways that could be manipulated to minimise disease burden. There is a still long way to go as the development of gene therapy for the central nervous system is far more challenging than for inherited retinal diseases, which benefit from the eye's relative ease of access and immune privilege. Germline genome editing is an exciting technological development that has the potential of preventing the transmission of both nuclear and mitochondrial DNA mutations from mother to child, but safety issues need to be rigorously addressed before it can be considered for clinical application. There is also the need for a wider debate within society about the ethical, moral and legal implications of manipulating the germline in human embryos, and the framework that will need to be put in place to avoid any misuse. Genetic manipulation for inherited neurodegenerative diseases is certainly not a myth, but a considerable amount of work is still needed before it becomes a reality.

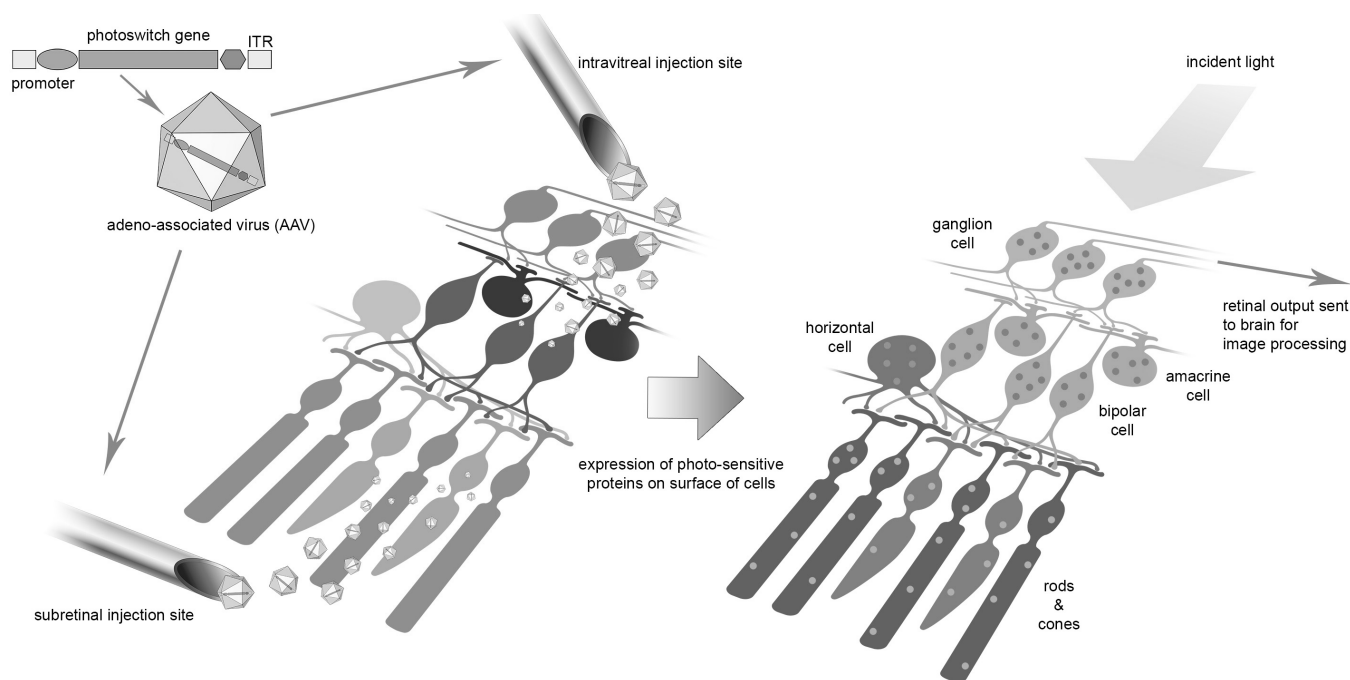
Table 1. Viral delivery systems for the treatment of neurodegenerative diseases

Characteristics	Adeno-associated virus	Adenovirus	Retrovirus	Lentivirus	Herpes Simplex Virus
Wild-type virus	Single-stranded DNA (4.7 kb)	Double-stranded linear DNA (36 kb)	Diploid positive strand RNA (9.2 kb)	Diploid positive strand RNA (9.2 kb)	Double-stranded linear DNA (152 kb)
Maximum insert size	4.5 KB	7.5 KB	8.0 KB	8.0 KB	20-40 KB
Achievable titre (per ml)	High ($>10^{12}$)	High ($>10^{11}$)	Low ($>10^8$)	Low ($>10^8$)	High ($>10^9$)
Infectivity	Broad	Broad	Dividing cells	Broad	Broad
Chromosomal integration	No ¹	No	Yes	Yes	No
Transgene expression	Long (months to years)	Short (days to weeks)	Long (months to years)	Long (months to years)	Short (days to weeks)
Latency in host cells	No	Yes	No	No	Yes
Pre-existing immunity	Yes	Yes	Unlikely	Unlikely ²	Yes
Host immunological response	Minimal	Extensive	Minimal	None	Moderate
Potential <i>in vivo</i> risks	Insertional mutagenesis ¹	Inflammatory response	Insertional mutagenesis	Insertional mutagenesis	Inflammatory response

1 Some integration occurs, but at low frequency. The risk of insertional mutagenesis is minimal compared with other viral vectors.

2 Except perhaps in HIV-infected patients.

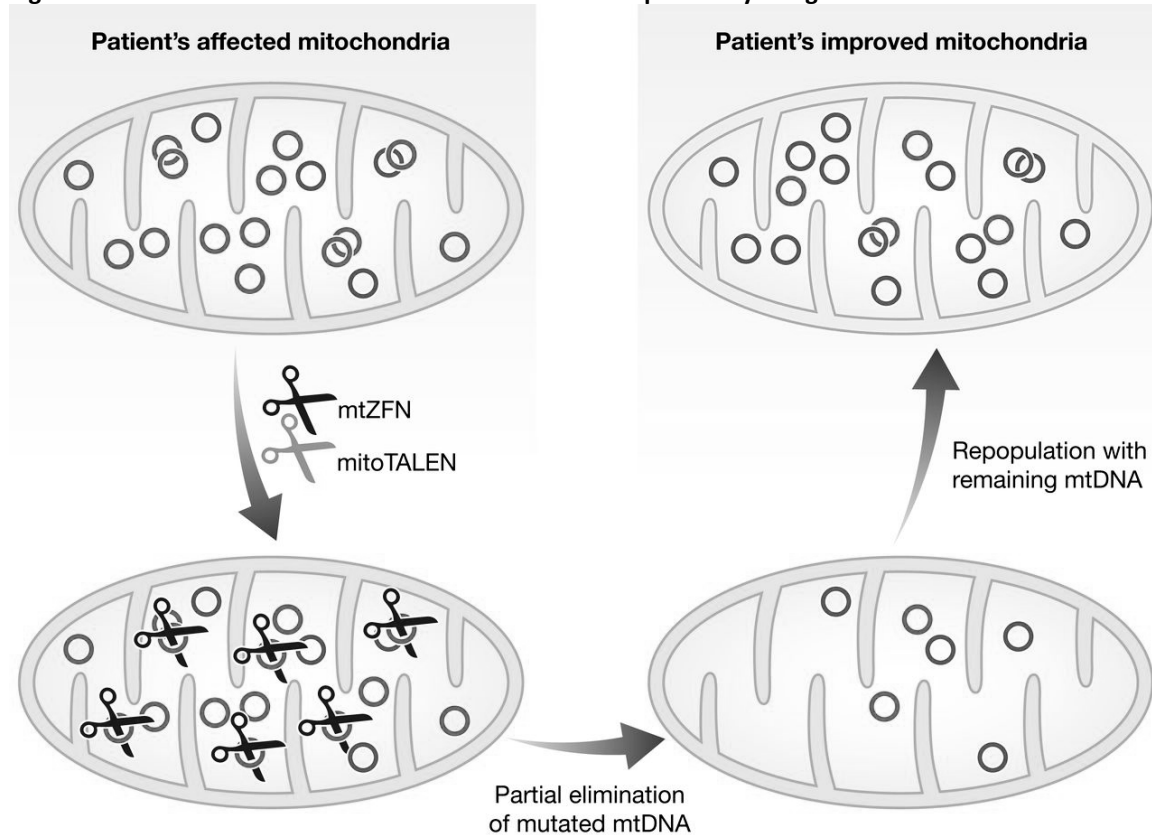
Figure 1. Therapeutic application of optogenetics to retinal neurodegenerative diseases



The gene construct encodes for a photosensitive channel protein belonging to the microbial opsin family and the preferred delivery system is an AAV vector due to its natural tropism for retinal cells. An intravitreal injection is sufficient when the inner retina is being targeted whereas delivery of the viral vector into the subretinal space is usually needed to achieve sufficient transfection of outer retinal cells. Cell-specific promoters can be used to limit the expression of the photoswitch gene to specific retinal

cell types. The selective expression of opsin proteins is represented by different coloured dots in the right figure panel. When stimulated by light of a certain wavelength, the protein channel opens, allowing the redistribution of ions across the cell membrane. The resultant depolarisation or hyperpolarisation of the retinal cells results in the transmission of the visual impulse to the occipital cortex via the optic nerve. Adapted from Francis et al., 2013.⁷⁷

Figure 2. Elimination of mutated mtDNA molecules with specifically designed mitochondrial nucleases

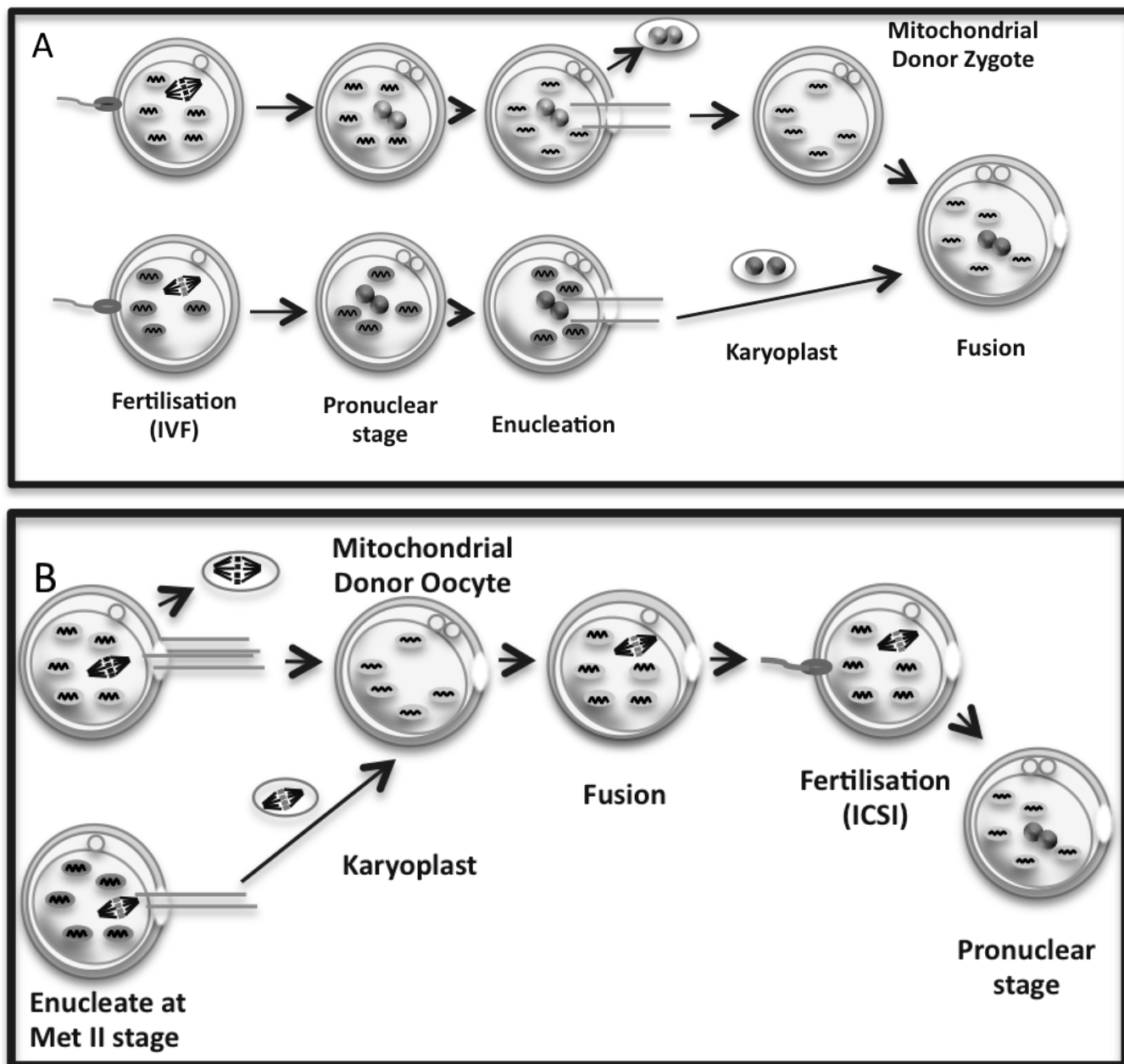


Zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) first need to be targeted to the

mitochondrial matrix compartment where they can physically interact with mtDNA molecules. There are a number of possible strategies, including transfecting the cell with plasmid vectors, the use of viral vectors to deliver the gene construct, or direct injection of mRNA encoding for the nuclease. The use of transiently expressed RNA in oocytes or one-cell embryos circumvents the disadvantages of exogenous DNA administration in the germline, which remains a cause of concern with other mitochondrial replacement techniques such as pronuclear transfer and metaphase II spindle transfer. ZFNs and TALENs can be designed to recognise specific DNA sequences and

they have the ability to create double-strand breaks that eliminate mutated mtDNA molecules. There is a transient reduction in mtDNA copy number, but the remaining mtDNA molecules are able to proliferate, repopulating the mitochondria with a higher proportion of the wild-type species. The end result is a beneficial reduction in the cell's overall mutant load and an improved bioenergetic profile. Adapted from Moraes, 2014.¹⁰⁰

Figure 3. IVF methods to prevent the maternal transmission of mtDNA mutations



[A] Pronuclear transfer. An embryo is created via conventional IVF using the father's sperm and the mother's oocyte, the latter carrying a homoplasmic mtDNA mutation (red mitochondria). After fertilisation has taken place, the parental pronuclei (red circles) are removed from the single-cell embryo and they are then transferred into a mitochondrial donor zygote harbouring only wild-type mtDNA (green mitochondria).

[B] Metaphase II spindle transfer. The maternal spindle is a structural unit that packages the mother's nuclear DNA in the unfertilised oocyte. In this alternative approach, the intended mother's metaphase II spindle is transferred into a mitochondrial donor oocyte, and this is then followed by intracytoplasmic sperm injection (ICSI) fertilisation (<http://blog.wellcome.ac.uk/2012/01/20/a-good-concept-science-mitochondrial-dna/>, accessed on 8 September 2015).

CME ANSWERS

1. True
2. False
3. True
4. True
5. True

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CIRCLE OF HELL: DIAGNOSING AND MANAGING STEROID-DEPENDENT OPTIC NEUROPATHIES (with apologies to Dante Alighieri)

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LEARNING OBJECTIVES

1. Describe the diagnostic criteria for chronic relapsing inflammatory optic neuropathy (CRION)
2. Distinguish CRION from other related optic neuropathies
3. Practice better management of CRION

CME QUESTIONS

1. Which of the following would be unusual for CRION?
 - a. Spontaneous recovery
 - b. Severe visual loss of 20/200 or worse
 - c. Pain
 - d. Bilaterality
2. Which of the following are not used for treating CRION?
 - a. Corticosteroids
 - b. Gamma-interferon
 - c. Rituximab
 - d. Mycophenolate
3. A patient with new-onset optic neuritis in the right eye had optic neuritis in the left eye one year ago and remained at hand-motions. The likelihood that they actually have CRION is greater than if they had recovered.
 - a. True
 - b. False

KEYWORDS

1. Chronic Relapsing Inflammatory Optic Neuropathy
2. Optic Neuritis
3. Immunosuppressives
4. Decision Analysis

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.

BACKGROUND

DIFFERENTIAL DIAGNOSIS

While semantically CRION requires both chronicity based on a relapse, ontologically the patient who has a single episode of optic neuritis that does not improve may actually have CRION that has not yet declared itself by relapsing. This could be considered CRION *forme fruste*, and it is currently impossible to make that diagnosis in the absence of follow-up. For the purpose of this syllabus, the distinction between CRION proven by relapse and potential CRION will be unavoidably blurred, at least until there is a valid biomarker.

There are several disorders that overlap in some way 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 has 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), now called *neuromyelitis optica spectrum disorder (NMOSD)*,¹ is diagnosed on clinical and radiological criteria. The 2006 criteria used clinical findings of 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. The 2015 criteria¹ are more complex, and distinguish NMOSD with and without antibodies to aquaporin 4. They also broaden the clinical and radiological requirements. Without an adequately sensitive and specific biomarker, it is difficult to definitively state that antibody-negative NMOSD is truly different from other clinically similar syndromes or whether it represents a different manifestation of the same underlying pathophysiology.

A typical case of CRION may have optic neuritis and MRI non-diagnostic for multiple sclerosis, but not have the spinal cord disease nor the presence of anti-aquaporin 4 antibodies. Given that there are occasional cases of CRION which can become positive for those antibodies, there is clearly overlap in the diagnosis of CRION and NMOSD.² 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 became aquaporin 4 antibody-positive because of the generation of antibodies as part of the response to inflammation involving astrocytes in the optic nerve.

There are many other inflammatory disorders of the central nervous system that are steroid responsive and can recrudescence 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. The following useful case definition has been suggested:³

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 Plant³)

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 literature³ and one out of France with 20 cases of CRION within a larger population of 62 cases of relapsing optic neuritis.⁴ 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

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 immunosuppressive agents 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 immunology point of view, there is little pathophysiological data besides that based on differential responses to various immunomodulatory agents. In one case managed by the author, the patient also had vitiligo, the autoimmune nature of which was evidenced by an improvement when he was placed on azathioprine for his CRION. This clinical picture overlaps with other immune disorders associated with vitiligo and optic nerve involvement, such as Vogt-Koyanagi-Harada disease, and partly overlaps a reported case of optic neuritis-only NMO and vitiligo⁵. Whether there are shared and stimulatory antigenic or co-antigenic molecules among optic nerve and melanocytes is unclear.

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.⁶

DECISION ANALYSIS CAN HELP GUIDE WHO TO TREAT AND HOW

Rocks and hard places, Scylla and Charybdis, the Devil and the deep blue sea – all of these are shorthand for the quandary that clinicians face when they see a patient with apparent optic neuritis who may actually have CRION. The problem is that forgoing early institution of aggressive treatment in a patient who needs it may result in permanent visual loss, while using potent immunosuppressive agents to treat a patient who does not require them may result in needless adverse effects and even death. This section describes the standard approach to management and an alternative strategy based on decision analysis.

STANDARD TEACHING FOR MANAGING CRION

The standard approach to diagnosing CRION is to first 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 a unilateral optic neuropathy of subacute onset in an age group that suggests idiopathic or multiple sclerosis-related optic neuritis, with no other ocular or systemic history or findings, the risk of CRION or related diseases is low, and standard protocols for diagnosis and treatment can be followed.

On the other hand, if there are red flags such as bilateral optic nerve involvement, non-Caucasian ancestry, or simultaneous involvement of other central nervous system structures such as the cervical spinal cord, then the decision-making becomes more complex. In most cases, the consideration of CRION is raised when the patient does not recover vision after the initial episode or the visual loss continues to progress over time.

The standard teaching is that under these circumstances, a workup for other optic neuropathy should be done, including MRI of the anterior visual pathways if not previously performed, laboratory studies 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-¹⁸FDG) should be performed. If there is 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 below should be considered.

A DECISION ANALYTICAL APPROACH FOR MANAGING CRION

The problem with standard teaching is that CRION is frequently recognized late in the course of the disease, often when irreversible visual loss has occurred in one or both eyes. A critical issue is that the reliance on laboratory testing or clinical course to diagnose CRION may impede early diagnosis. Clearly, patients with optic neuritis who have high-risk characteristics such as Asian heritage or a history of poor vision after a previous episode should

undergo rapid advancement of treatment, especially when there was poor response to high-dose intravenous corticosteroids. The question is how to quantify the risk and not over- or under-treat patients.

Instead, techniques of medical decision making can be used to guide management. A straightforward approach is a decision tree (Figure), which reflects a linear combination of probabilities and costs, the latter being either quality-adjusted life years (QALY's), dollar costs, or both.

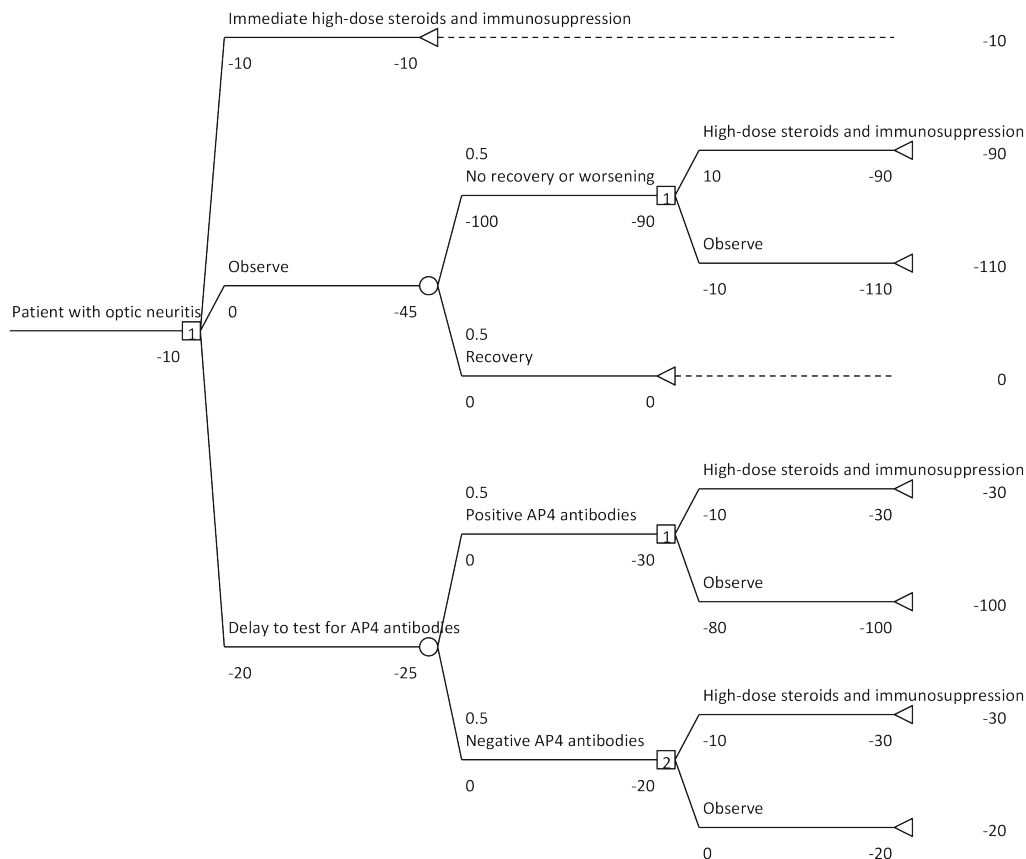


Figure. Example of a decision tree outlining possible approaches to a patient with apparent optic neuritis who may be harboring a more serious diagnosis such as CRION or NMOSD. The costs in the diagram are QALY's, and are purely illustrative, i.e. not based on published data.

If appropriately designed and based on valid data, such a decision tree can help guide management in the setting of imperfect information. The difficulties stem from inadequate data. The following are examples of areas for which there is insufficient quantitative knowledge:

1. How well does aggressive therapy increase the likelihood of a patient with CRION retaining good vision?
2. How much does a delay in aggressive therapy decrease the likelihood of a patient with CRION retaining good vision?
3. How much does a poor outcome in a previous episode of presumed optic neuritis increase the likelihood that a patient actually has CRION?

4. What is the incidence of CRION in patients of various ages, ethnic groups, and other demographic factors?

Because of this lack of information, a pragmatic approach can also be used, as discussed below. It reflects assumptions and intuition that are better captured in a formal decision analysis.

DEFINITIVE THERAPY IS MORE IMPORTANT THAN DEFINITIVE DIAGNOSIS

There is a tide in the affairs of men.
Which, taken at the flood, leads on to fortune;
Omitted, all the voyage of their life
Is bound in shallows and in miseries.

Julius Caesar, Act 4.

The most important issue in treating CRION is instituting powerful immunosuppression in the right patients at the right time. It is less important to rapidly determine whether there is underlying systemic disease, with some exceptions, discussed below. The neuro-ophthalmologist has the crucial opportunity to make a presumptive diagnosis of CRION early, before permanent visual loss ensues, but only if aware of the possibility.

There are two common scenarios for becoming aware of CRION. The first is when patients with apparent idiopathic optic neuritis are treated with corticosteroids from first symptom or sign at high intravenous doses (e.g. methylprednisolone 1 gm per day for three days) followed by oral prednisone at 1 mg/kg/day, and at the decrease or cessation of corticosteroids there is a relapse. In this case, rapid reinstatement of high-dose corticosteroids followed by either a much slower taper or the addition of other immunosuppressive agents will save vision. In some cases, the interval before the relapse may be several days or weeks after corticosteroids are stopped.

In the second scenario, there is little or no recovery of vision after an episode of apparent idiopathic optic neuritis, whether treated with corticosteroids or not. In this case, it is impossible to tell at that time whether this is CRION or simply optic neuritis that did not improve for other reasons. Some practitioners may choose to perform a corticosteroid trial in these patients when significant disc pallor and loss of the retinal nerve fiber layer on OCT has not yet ensued. Whether a trial is elected or not, the subsequent occurrence of a second episode of apparent optic neuritis in the same or opposite eye should be a warning sign that it should be treated aggressively. This is a high-risk situation, in that it is already clear that the optic neuritis in the first eye was atypical. At the very least, high-dose intravenous steroids should be used, the taper should be slow, and the threshold for adding other immunosuppressive agents should be very low.

DEFINITIVE DIAGNOSIS

Whichever of the above two scenarios is operative, the critical issue is the provisional diagnosis of CRION and the institution of immunosuppressive therapy. At the early stages it is less important to distinguish CRION from the other atypical optic neuritides mentioned in the Differential Diagnosis section (above) than to make sure the patient does not have permanent visual loss. The few exceptions relate to diseases that are either poorly responsive to corticosteroids or may worsen with corticosteroids, as listed in the following Table.

Disease	Reason to diagnose early
Fungal disease, usually from adjacent sinus	Corticosteroids may cause rapid spread, especially <i>Aspergillus</i> species.
Tuberculosis involvement of optic nerve	Corticosteroids may activate in lungs or elsewhere
Wegener granulomatosis	May require cyclophosphamide or rituximab for treatment
Rheumatoid disease	May possibly respond better with tumor necrosis alpha antagonists as immunosuppressive agents.

The other reason to attempt a definitive diagnosis after initial treatment is that it may help in detecting, monitoring, and treating involvement of other organs, e.g. the lungs in sarcoidosis or the kidneys in Wegener disease or polyarteritis nodosa.

SUBSEQUENT THERAPY

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 are no randomized clinical trials to guide selection nor even general agreement on which work best.

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,⁷ 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 they may exacerbate the problem.⁸

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 al⁹ and using Greenberg et al,¹⁰ was developed for NMO (now NMOSD), 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

THE ART AND SCIENCE OF THE TAPER

HOW SLOW CAN YOU GO?

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.

The frequently stereotyped nature of the breakthrough during the steroid taper can also be used to assess the efficacy of additional immunosuppressives. Assuming identical rates of tapering, e.g. 1 mg every 4 weeks, then a breakthrough at 7 mg with and without azathioprine suggests that the latter is not efficacious. Alternatives should then be tried, and the same approach can be used.

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.

WHAT NEXT?

No practice is big enough and no practitioner has enough patients to make perfectly reasoned decisions in an uncommon disease such as CRION. 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. At present, n of 1 studies are currently considered acceptable for finding the best management for patients with CRION. However, there are alternatives.

The simplest approach is the use of a registry, ideally involving all neuro-ophthalmologists who are interested in contributing. A standardized reporting form, approval by an institutional review board, and an agreement for how analysis will be carried out would be enough to improve several-fold the quality of clinical data for CRION.

A second approach is a registry randomized by center. This means that different centers would agree to follow standard management algorithms for all patients under their care, but with different algorithms. This would yield data about relative advantages and disadvantages of various approaches.

A third approach is a large simple trial for CRION, similar to what has been done by the Pediatric Eye Disease Investigator Group (PEDIG) and the Diabetic Retinopathy Clinical Research Network (DRCRnet). Inclusion criteria would be broad, and data collection and endpoints would have to be very simple, or otherwise such a trial would be too unwieldy.

SUMMARY

CRION is difficult to diagnose and harder to manage. At the same time, it is an irreversibly blinding disease that is a leading cause of frustration for both neuro-ophthalmologists and patients. Like many other neuro-ophthalmic diseases, the pathophysiology is unclear. Yet an even greater problem is the lack of accurate quantitative information about the disease and how best to treat it. Although classic randomized clinical trials are unlikely to be practical in this rare disease, there are other strategies that could be used to generate useful information. For now, the best strategy is to focus on early recognition and rapid aggressive treatment, even without definitive diagnosis, especially in patients who have already declared themselves to have a poor outcome from a previous episode.

CME ANSWERS

1. a
2. b
3. a

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NMO: WHAT YOU NEED TO KNOW

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LEARNING OBJECTIVES

1. Identify clinical presentations and new diagnostic criteria for NMO Spectrum Disorder with or without NMO-IgG positivity
2. Recognize that early diagnosis and institution of appropriate immunomodulating agents are crucial to reduce disability with NMOSD
3. Explain available treatment options for acute exacerbations and long-term disease modification

CME QUESTIONS

1. True/False: The diagnosis of 'NMO Spectrum Disorder with NMO-IgG positivity requires a clinical episode of either optic neuritis or transverse myelitis.
2. True/False: Ancillary data such as OCT and VEPs are not included in the formal diagnostic criteria for NMOSD.
3. True/False: NMO is typically a monophasic illness.
4. True/False: NMO-IgG serostatus correlates with risk of relapsing disease.
5. True/False: NMO-IgG titer corresponds to disease severity.
6. True/False: Anti-MOG antibodies are found in 15-40% of patients with NMOSD without NMO-IgG positivity.
7. True/False: Some therapies that are indicated for MS may worsen the clinical course in NMO.

KEYWORDS

1. Neuromyelitis Optica Spectrum Disorder
2. Optic Neuritis
3. Myelitis
4. Anti-aquaporin-4 Antibodies

INTRODUCTION

Neuromyelitis optica (NMO) is an antibody-mediated inflammatory disease of the central nervous system with a predilection for the optic nerves, spinal cord, and certain brain regions.¹ While NMO was previously considered to be

a variant of multiple sclerosis (MS), it is now known to have distinct clinical, pathological and immunological features. The identification of NMO-IgG, a pathogenic antibody against aquaporin-4 (AQP4), delineated NMO from MS.^{2,3} Early, accurate diagnosis of NMO permits treatment with appropriate acute and long-term immunosuppressive agents that are critical to mitigate the risk of disability associated with this disease. The distinct pathogenesis of NMO relates to aquaporin-4 autoimmunity and complement-mediated tissue injury. Better understanding of this pathophysiology has laid the foundation for targeted efforts to develop novel, disease-specific treatments. In this review, we discuss the revised diagnostic criteria for NMO, review evidence supporting the use of available treatments for acute episodes and long-term disease modification, and highlight key emerging immunotherapies.

CLINICAL PRESENTATION

Until the diagnostic criteria were revised in 2015, the definitive diagnosis of NMO had required the presence of optic neuritis *and* transverse myelitis.⁴ These syndromes may occur either simultaneously or sequentially, separated by days to several years. Additional supporting evidence for the diagnosis of NMO had included a spinal MRI showing longitudinally extensive transverse myelitis, the absence of brain lesions characteristic of MS, and/or NMO-IgG seropositivity. These 2006 criteria, written just 2 years after the discovery of NMO-IgG, were established in order to include NMO-IgG serostatus as a supporting (but not core) diagnostic feature. In addition, these criteria acknowledged that certain brain lesions may occur with NMO, most often in the dorsal brainstem and hypothalamus.

Because of growing recognition of the specificity of the NMO-IgG assay, the concept of NMO spectrum disorders (NMOSD) was introduced in 2007 to describe clinically limited forms of the disease with NMO-IgG seropositivity.⁵ In 2015, 9 years after publication of the previous diagnostic criteria, the formal criteria were further updated to reflect the diagnostic importance of NMO-IgG serostatus in other clinical situations, beyond the limited forms of isolated transverse myelitis or optic neuritis (Table 1).⁶

In the proposed modern nomenclature, the term NMO is subsumed by the term NMOSD, stratified according to NMO-IgG serostatus. The diagnosis of '*NMOSD without NMO-IgG positivity*' requires at least 1 episode of optic neuritis, transverse myelitis, or an area postrema

Table 1. 2015 Diagnostic Criteria for NMOSD⁶

Diagnostic criteria for NMOSD with AQP4-IgG
<ol style="list-style-type: none"> 1. At least 1 core clinical characteristic (see below) 2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) 3. Exclusion of alternative diagnoses
Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
<ol style="list-style-type: none"> 1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements: <ol style="list-style-type: none"> a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome b. Dissemination in space (2 or more different core clinical characteristics) c. Fulfillment of additional MRI requirements, as applicable 2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable 3. Exclusion of alternative diagnoses
Core clinical characteristics
<ol style="list-style-type: none"> 1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions
Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status
<ol style="list-style-type: none"> 1. Acute optic neuritis: requires brain MRI showing <ol style="list-style-type: none"> (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium enhancing lesion extending over 1/2 optic nerve length or involving optic chiasm 2. Acute myelitis: requires associated intramedullary MRI lesion extending over >2 contiguous segments (LETM) OR >2 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis. 3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions 4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

syndrome; and a second episode that is either another one of these core criteria or else a brainstem, diencephalic, or other cerebral syndrome. In contrast, '*NMOSD with NMO-IgG positivity*' can be diagnosed in the setting of *any* of the 6 clinical criteria. As of 2015, therefore, it is now possible to diagnose NMOSD in a patient that has had *neither* optic neuritis nor myelitis (in essence, this version of the condition represents what I call "Non-M, Non-O NMO").

Several clinical and diagnostic features that suggest NMOSD should prompt clinicians to test for NMO-IgG serostatus in order to establish the diagnosis. NMO-related transverse myelitis is characterized by a longitudinally extensive lesion that extends over 3 or more vertebral segments and can lead to severe disability with limited recovery. The optic neuritis associated with NMO is often characterized by severe vision loss, poor visual recovery, simultaneous or rapidly sequential bilateral involvement of both eyes, chiasmal lesions, and severe retinal nerve fiber layer loss demonstrated using optical coherence tomography (OCT).⁷⁻⁹ Other neurologic manifestations of NMO, relating

to lesions in the brainstem and diencephalon, include refractory hiccups, nausea and vomiting, respiratory failure, and disorders of arousal.^{10,11} Ancillary tests, such as OCT or visual evoked potentials, are not formally included in the diagnostic criteria for NMOSD due to lack of evidence, specificity, or reliability.⁶

NMOSD can co-exist with autoimmune conditions such as systemic lupus erythematosus, Sjögren's syndrome, and myasthenia gravis.¹²⁻¹⁴ NMO-IgG testing should therefore be considered when optic neuritis or transverse myelitis occurs in patients where these diagnoses are established or suspected. Case reports of NMOSD coexisting with cancer suggest that the disease may occasionally be a paraneoplastic immune phenomenon.¹⁵

The worldwide prevalence of NMO ranges from 0.5 to 4.4 cases per 100,000.¹⁶ It is relatively rare in the United States and European countries, with a prevalence that is 50-100 times lower than that of MS.^{17,18} In people of Asian or African descent, however, the prevalence of NMO is

only 2-4 times lower than the prevalence of MS, primarily because MS is less common in these populations. The disease is 3-7 times more common in women than men,¹⁶ and the typical age of onset is about one decade later than MS (median age 33-46 vs 28-31 in MS).^{16, 18} Although NMO was originally thought to represent a monophasic illness,¹ in fact a relapsing course is much more common, occurring in approximately 90% of patients.¹² The median time to first relapse ranges from 5 to 12 months, but relapses may occur even after 10 years or more.^{16, 19} Older age at disease onset is associated with poorer outcomes.²⁰ The mortality directly associated with NMO ranges from 7 to 30%, mostly attributed to neurogenic respiratory failure, but these rates are drawn from an era with less effective immunosuppressive treatment.²⁰⁻²²

IMMUNOPATHOGENESIS

The target antigen of NMO-IgG is AQP4, a cell-membrane water channel protein that is expressed predominantly at astrocytic end-feet forming the blood-brain barrier, as well as in subpial and subependymal regions.³ Although AQP4 is also expressed in human tissues outside the CNS, NMO-IgG-mediated pathology outside the CNS is rare. Several factors contribute to NMO's predilection for involving the optic nerves and spinal cord, including the absence of protective membrane complement regulators at astrocytic end-feet as well as the composition of AQP4 heterotetramer subunits in these regions.^{23, 24} Binding of NMO-IgG to AQP4 causes astrocytic injury through antibody-dependent cell-mediated cytotoxicity and activation of the complement pathway. These signaling pathways attract inflammatory cells including T and B lymphocytes, macrophages, neutrophils, and eosinophils.²⁵ Downregulation of AQP4 channels and glutamate transporters disrupts cellular water and glutamate homeostasis.²⁶ Injury to oligodendrocytes and resulting demyelination are thus the downstream effects of a complex cascade of immune responses.²⁵

Several assays exist to identify NMO-IgG in patients with suspected NMO, but the sensitivity of these tests varies greatly.²⁷ Recombinant human AQP4-based assays are more sensitive than the original mouse tissue-based indirect immunofluorescence (IIF) NMO-IgG assay.²⁸ The most sensitive recombinant human assay is the quantitative fluorescence-activated cell-sorting assay (FACS), followed by the transfected cell-based assay (CBA), the enzyme-linked immunosorbent assay (ELISA), and the immunoprecipitation assay (IPA).^{28, 29} When a patient with suspected NMO has negative serology, it is often helpful to use a more sensitive method to test serum and/or test CSF.³⁰ The new criteria suggest that the cell-based assays (FACS or CBA) are the optimal tests to employ, with pooled analyses showing 76.7% sensitivity and 0.1% false-positive rate among control MS patients.

NMO-IgG seropositivity confers a higher risk of relapsing disease compared to NMO-IgG seronegativity.^{31, 32} Among

NMO patients, however, the quantified NMO-IgG titer typically does not correlate with disease severity.³³⁻³⁵ At this time, therefore, there is no established clinical utility in repeated assessment of serum titers in an individual seropositive patient.

SERONEGATIVE NMO AND ANTI-MOG ANTIBODIES

Even with the most sensitive assays, many patients with a typical NMO phenotype may test negative for NMO-IgG.⁶ These patients are thought to have seronegative NMO, which may represent either false negative testing (i.e. incomplete sensitivity) or a separate disease entity that shares its clinical phenotype with seropositive NMO. Recently, antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) have been identified in 15-40% of NMO-IgG-seronegative patients with a clinical diagnosis of NMO or NMOSD.³⁶⁻³⁹ This subset of patients seems to have a better prognosis and is more likely to have a monophasic course than patients with NMO-IgG antibodies or those who are seronegative for both antibodies. Larger series of patients will be required to develop a better understanding of the full spectrum of anti-MOG syndrome. In addition, it should be noted that the testing for anti-MOG antibodies is still not commercially available as a diagnostic tool. The pathogenic mechanism of MOG antibody remains unclear; animal passive transfer experiments are hampered by differences in human and rodent MOG structure.⁴⁰

CURRENT THERAPIES

Although no masked, randomized treatment trials have been completed, available retrospective and open-label uncontrolled data permit several tentative conclusions about the use of immunomodulating therapies for acute attacks and prevention of future relapses (Table 1 and Table 2).⁴¹

ACUTE TREATMENTS

Any acute exacerbation of confirmed or suspected NMOSD should ideally be treated promptly with high-dose intravenous corticosteroids for 3 to 5 days.⁴² A corticosteroid taper for several months may be considered. Plasma exchange (PLEX) is often recommended for severe attacks, either concomitantly or immediately following a course of glucocorticoids.⁴³ Its use is supported by results of a randomized, sham-controlled double-masked clinical trial in 22 patients with demyelinating disease, including only 2 with definite NMO.⁴⁴ Retrospective studies have also shown that PLEX in combination with glucocorticoids is superior to glucocorticoids alone with respect to final visual outcome in patients with NMO.^{45, 46} Complications occur in about 4% of patients.⁴⁷

Table 2. Available and emerging therapies for NMOSD

Immunotherapy		Mechanism of action	Regimen
Available	Glucocorticoids	Pleiotropic effects (anti-inflammatory and immunosuppressive)	Pulse methylprednisolone 1 g IV daily, for 3-5 days
	Plasmapheresis	Removal of pathogenic antibodies, cytokines, complement	1-1.5 plasma volumes every other day, typically 5 exchanges
	Intravenous immunoglobulin (IVIg)	Blockade of immune complex binding; neutralization of pathogenic antibodies, cytokines, chemokines	Total dose 2 g/kg IV over 3-5 days
	Azathioprine (AZA)	DNA intercalation, inhibition of <i>de novo</i> purine synthesis	2-3 mg/kg PO daily
	Mycophenolate mofetil (MMF)	Inhibition of inosine monophosphate dehydrogenase (<i>de novo</i> guanosine synthesis)	Total daily dose of 750-3000 mg PO (typically 1000 mg PO mg twice daily)
	Rituximab (RTX)	Depletion of B-cells and plasmablasts (Anti-CD20 chimeric monoclonal antibody)	Typically 1 g IV on day 1 and day 14, repeat every 6 months
Emerging	Eculizumab	Prevention of cleavage of complement C5 (Anti-CD5 humanized monoclonal antibody)	600 mg IV weekly for 4 weeks, 900 mg in week 5, then 900 mg every 2 weeks
	Tocilizumab	IL-6 receptor blockade (Anti-IL-6 receptor humanized monoclonal antibody)	6 mg/kg IV every 4-6 weeks
	Aquaporumab	Competition with NMO-IgG for AQP4 binding (Anti-AQP4 human monoclonal antibody)	In development

Treatment with intravenous immunoglobulin (IVIg) was evaluated in a small retrospective study of 11 patients with NMO who failed to respond to corticosteroids with or without PLEX.⁴⁸ Five patients improved, suggesting that IVIg may have a role in treating acute exacerbations when PLEX is unavailable. Mild adverse effects include headache, nausea, and constitutional symptoms, while rare serious adverse reactions include thromboembolic events.⁴⁹

A purified C1-esterase inhibitor (Cinryze®), in combination with high dose corticosteroids, was assessed in an open-label study of 10 patients with acute optic neuritis or transverse myelitis associated with NMO. Dual therapy including the C1-esterase inhibitor proved safe. Only two patients in the study required escalation to plasmapheresis and all but one patient returned to their pre-attack

disability level.⁵⁰ Controlled clinical studies of this agent have not been completed.

LONG-TERM DISEASE MODIFYING TREATMENTS

Several immunosuppressive agents have been accepted as long-term disease modifying treatment for patients with NMOSD, based upon expert opinion, retrospective studies, and prospective open label series (Table 2).^{41, 51} These include azathioprine, mycophenolate mofetil, and rituximab. Other medications that have also been used, less commonly, include methotrexate, mitoxantrone, and cyclophosphamide.

Azathioprine, often administered in combination with prednisone, was the first agent to show efficacy in preventing NMO relapses.⁵² Reported reductions in the absolute annualized relapse rate (ARR) range from 0.4 to

1.6.^{51, 53-55} The most frequent side effects include elevated transaminases, leukopenia, and recurrent infections. In addition, it appears to slightly increase the incidence of lymphoma, although the base rate of lymphoma is higher in patients with autoimmune conditions and the incidence that can be definitively attributed to treatment with agents such as azathioprine is not known.^{53, 56}

Treatment with mycophenolate mofetil is supported by three retrospective studies showing reduction of absolute relapse rate by 0.7-2.3.^{51, 55, 57} The most common adverse reactions are gastrointestinal symptoms, photosensitivity, recurrent infections, and bone marrow toxicity.⁵¹

Rituximab is a murine/human chimeric monoclonal antibody targeting CD20 expressed on the surface of B cells and plasmablasts. Rituximab has demonstrated greater efficacy than other first-line medications, with ARR reduction of 0.9-2.6.^{51, 55, 58} It also produces fewer significant adverse effects, which include infusion-related flu-like reactions and infections.^{33, 51, 55, 59} The estimated risk of progressive multifocal leukoencephalopathy is 1:25,000 according to data from patients with rheumatoid arthritis treated with rituximab;⁶⁰ there have been no case reports of the infection in patients with NMOSD.

CONTRAINDICATED AGENTS

Several disease-modifying agents frequently used for treatment of MS, including interferon-beta (IFN-β),⁶¹⁻⁶⁴ natalizumab,⁶⁵⁻⁶⁷ and fingolimod,⁶⁸ may have a deleterious effect on the relapse rate in NMOSD patients. This phenomenon likely reflects the different immunobiology of these conditions, emphasizing the importance of accurate diagnosis to guide optimal treatment decisions.

DURATION OF IMMUNOSUPPRESSION

Given that the course of NMOSD can be unpredictable and that there are no reliable biomarkers for ongoing disease activity, recommendations regarding the optimal duration of preventative treatment have not been established. Some authors propose continuing therapy for 5 years after the last clinical relapse.⁶⁹ The decision to limit the duration of therapy is motivated by an attempt to offset risks of long-term toxicity, particularly malignancies and severe opportunistic infections.⁷⁰

EMERGING THERAPIES

Several agents that are currently approved for other autoimmune disorders are currently under clinical investigation for therapeutic use in NMOSD. Eculizumab, a humanized monoclonal antibody that neutralizes complement component C5, was found to reduce ARR in NMO-IgG seropositive patients,⁷¹ but carries a risk of infectious complications such as meningococcal sepsis. Tocilizumab, a humanized monoclonal antibody that

antagonizes the interleukin-6 (IL-6) receptor, has also shown promising results in unblinded case reports and small case series. It reduced ARR in 10 NMO-IgG seropositive patients who had been refractory to rituximab.^{72, 73} Its full safety profile in NMOSD patients needs further investigation. Aquaporin-4 is a synthetic non-pathogenic IgG that competes with NMO-IgG for aquaporin-4 binding and is currently in preclinical development.⁷⁴

CONCLUSION

Optimal management of patients with NMOSD requires effective treatment of acute attacks, reduction of relapses using immunomodulating therapies, symptomatic treatment, and rehabilitation. There is a growing evidence base to support the use of various immunosuppressive treatments in the acute and chronic stages of the disease in order to mitigate long-term disability. There are many open questions regarding the optimal treatment of NMOSD, particularly regarding drug efficacy comparisons and duration of treatment.⁷⁵ Future research is needed to elucidate the mechanisms of seropositive and seronegative NMOSD, identify biomarkers that correlate with disease activity, and develop highly specific, targeted treatment strategies that improve outcomes for these patients.

ACKNOWLEDGMENT

I am grateful to Drs. Ivana Vodopivec and Marcelo Matiello for their insightful discussions on this topic. Portions of this syllabus are modified with permission from Vodopivec I, Matiello M, Prasad S. Treatment of Neuromyelitis Optica. *Semin Ophthalmol* 2105; 26:476-83.

CME ANSWERS

1. False
2. True
3. False
4. True
5. False
6. True
7. True

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North American Neuro-Ophthalmology Society

42nd Annual Meeting

February 27 – March 3, 2016

JW Starr Pass Marriott • Tucson, Arizona

PLATFORM SESSION I

Monday, February 29, 2016 • 5:00 pm - 7:00 pm

Moderators: Rudrani Banik, MD and Marc Dinkin, MD

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**Please note that all abstracts are published as submitted.*

Monday, February 29, 5:00 - 5:15 pm

Efficacy for Remyelination and Safety of Anti-LINGO-1 Monoclonal Antibody (BIIB033) in Acute Optic Neuritis: Results from the RENEW Study

Laura Balcer¹, Steven Galetta¹, Oscar Fernandez², Orhan Aktas³, Tjalf Ziemssen⁴, Ludo Vanopdenbosch⁵, Helmut Butzkueven⁶, Focke Ziemssen⁷, Luca Massacesi⁸, Yi Chai⁹, Lei Xu⁹, Stefanie Freeman¹⁰, Diego Cadavid¹¹

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Introduction:

Anti-LINGO-1 is a monoclonal antibody antagonist of LINGO-1, an oligodendrocyte differentiation and myelination suppressor. RENEW (NCT01721161) aimed to determine the efficacy and safety of anti-LINGO-1 for CNS remyelination.

Methods:

Subjects with a first unilateral acute optic neuritis episode were treated with high-dose steroids and randomized to 100 mg/kg anti-LINGO-1 IV or placebo every 4 weeks. Nerve conduction latency recovery using full-field visual evoked potential (FF-VEP) in the affected eye over time versus unaffected eye at baseline was used to assess remyelination (pre-specified primary endpoint). Retinal neuroprotection was studied by measuring the thickness of the retinal nerve fiber and ganglion cell layers using spectral-domain optical coherence tomography (SD-OCT) and change in low-contrast letter acuity (LCLA). Patient-reported outcomes (PRO) were also assessed. Between-treatment comparisons were evaluated by ANCOVA and mixed-effect model repeated measure in subjects who completed the study and did not miss >1 study dose or receive MS modifying therapy (pre-specified per-protocol population; n=69/82 subjects randomized). Safety/tolerability were evaluated in those who received ≥1 study dose and included adverse event (AE) and clinical laboratory result assessments.

Results:

Anti-LINGO-1-treated subjects (n=33) showed improved FF-VEP latency recovery versus placebo (n=36): mean (95% confidence interval) -7.55ms (-15.12 to 0.01) at Week 24 ($P=0.05$); -9.13ms (-16.11 to -2.14; $P=0.01$) at Week 32. 54% of anti-LINGO-1 subjects had normal/near normal latency at Week 24 (affected eye FF-VEP latency ≤10% worse than the fellow eye) versus 27% of the placebo group ($P=0.04$). Additional subgroup analyses and PRO data will be presented. No treatment differences were observed in SD-OCT and LCLA. 34/41 in each group experienced any AE, serious AEs (SAE) occurred in 2 placebo and 5 anti-LINGO-1 subjects, with treatment-related SAEs reported in 3 subjects.

Conclusions:

Improvement in FF-VEP latency is consistent with the first evidence of remyelination in a Phase 2 trial. Anti-LINGO-1 was generally well tolerated.

References: None

Keywords: Optic Nerve Trauma And Treatment, Visual Fields, Demyelinating Disease, Neuro-Ophth & Systemic Disease, Optic Neuropathy

Financial Disclosures: This study was supported by Biogen (Cambridge, MA, USA). LB has received consulting fees from Biogen for work related to visual outcome measures for the RENEW trial. SG has received consulting fees from Biogen for work related to visual outcome measures for the RENEW trial. OF has received consulting/advisor fees and research support from Biogen. OA has received advisor fees/honoraria and research support from Biogen, and was a Principal Investigator in the RENEW trial. TZ has received consulting fees and research support from Biogen, and was a Principal Investigator in the RENEW trial. LV has received consulting/advisor fees/honoraria from Biogen, and was a Principal Investigator in the RENEW trial. HB has received consulting/advisor fees/honoraria and research support from Biogen, and was a Principal Investigator in the RENEW trial. FZ was a Principal Investigator in the RENEW trial. LM has received educational grants and research support from Biogen, and was a Principal Investigator in the RENEW trial. YC, LX, SF and DC are employees of and stockholders in Biogen. Writing support was provided by Excel Scientific Solutions (Horsham, UK) and funded by Biogen.

Grant Support: None.

Monday, February 29, 5:15 - 5:30 pm

The Idiopathic Intracranial Hypertension Treatment Trial: Outcomes from Months 6 - 12

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Introduction:

Our goal was to determine whether the beneficial effects of acetazolamide (ACZ) in improving vision continues from months 6 to 12 in participants of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).

Methods:

In the IIHTT, after 6 months of a weight management program and either placebo or maximally tolerated ACZ, subjects transitioned from study drug to ACZ unless their papilledema resolved. The main outcome was the change in MD from Month 6 to Month 12 in the study eye, groups based on treatment at study entry and after 6 mos. – 1) ACZ to ACZ n = 34, 2) placebo to ACZ n = 35, 3) ACZ to no treatment n = 20, and 4) placebo to no treatment n = 12.

Results:

The placebo subjects in group 4 improved 0.86 dB, p = 0.04 at 12 mos. The other three groups improved 0.35 to 0.41 dB PMD. Mean improvements in papilledema grade also occurred in all groups but most markedly in the group that exchanged placebo for ACZ (0.91 Frisén grade units, p <0.001). QoL scores and headache disability, improved also with a large and significant improvement in the group that transitioned from placebo to ACZ. Significant weight change occurred in those transitioning from placebo to ACZ who lost about 6 pounds (p = 0.02) while those tapered off acetazolamide gained about 6 pounds (p = 0.03).

Conclusions:

Improvements in MD continued from month 6 to month 12 of the IIHTT in all treatment groups. This effect was most marked and significant in the placebo group tapered off study drug. Significantly beneficial effects of ACZ on papilledema grade and QoL increased from month 6 to 12. Adding ACZ to the placebo group subjects significantly improved their quality of life.

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Keywords: Idiopathic Intracranial Hypertension, Perimetry, Visual Fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Monday, February 29, 5:30 - 5:45 pm

The Relationship of Vision and Quality of Life (QOL) in Patients with Pediatric Primary Brain Tumors (PBT)

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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 QOL.¹ Visual dysfunction and impaired vision-related QOL (VR-QOL) are often not recognized in children because of examination difficulty and lack of awareness.

Methods:

We evaluated visual impairment and its effects on QOL in an ongoing quality improvement project. Patients ≤18 yo, ≥6 months from diagnosis of primary brain tumor, excluding primary intrinsic anterior visual pathway tumors, underwent neuro-ophthalmologic examination. Health-related QOL (HR-QOL) questionnaires, using PedsQL Brain Tumor Module,² were obtained from patients and parents. VR-QOL questionnaires, using CVFQ (Children's visual function questionnaire)³ in children <8yo, and EYE-Q⁴ in children 8-18yo, were obtained. Demographic data, driving status, schooling, and use of low-vision aids were recorded.

Results:

43 patients were evaluated. Astrocytomas (9/43) and craniopharyngiomas (9/43) were the most common tumors. Diagnosis was made at 6.6years (range 0.2-17), Mean age at examination was 11.7 years (IQ range 8.8-15.6). 3/43 patients (7%) were legally blind; 12/43(28%) were visually impaired. Eye-Q median score was 4.275(IQ range 3.925-4.750). Eye-Q score decreased 0.14 with every 0.1 increase in logMAR visual acuity [p<0.001]. Average Eye-Q score for legally blind patients was 1.4; for non-legally blind patients 4.35[p=0.003]. Cognitive HR-QOL scores decreased 1.2 for every 0.1 increase in logMAR visual acuity [p=0.06].

Conclusions:

Pediatric PBT patients' vision, HR-QOL, and VR-QOL are often severely affected, even when the PBT is considered "cured". Visual acuity is correlated with VR-QOL. Number of treatment modalities used was not associated with lower QOL. Systematic neuro-ophthalmologic examinations in pediatric PBT patients may improve long-term visual outcomes and QOL through earlier interventions.

References:

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Keywords: Tumors, Pediatric Neuro-Ophthalmology

Financial Disclosures: This study was supported in part by a departmental grant (Department of Ophthalmology) from Research to Prevent Blindness, Inc., New York, NY, and by Core Grant P30-EY06360 (Department of Ophthalmology) from the National Institutes of Health, Bethesda, MD.

Grant Support: None.

Monday, February 29, 5:45 - 6:00 pm

Pupillary Light Reaction in Pre-Clinical Alzheimer's Disease vs. Normal Aging Controls

Gregory P. Van Stavern¹, Ying-Bo Shui, Ling Bei, Julie Huecker, Mae Gordon, Fang Bai

Washington University in St. Louis, St. Louis, MO, USA

Introduction:

Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive deficits and visual dysfunction. Neural biomarkers such as PET-PiB imaging and CSF ABeta levels are predictive of future development of AD but are expensive and cumbersome. There is increasing interest in using ocular biomarkers as a surrogate for disease activity in AD¹. Several studies have shown that the pupillary light response (PLR) can differentiate AD patients from healthy controls^{2,3}. However, many of these studies assessed the PLR in established AD, and failed to control for systemic diseases and medications which affect the PLR. The PLR in pre-clinical AD remains poorly studied.

Methods:

Subjects were recruited from our institution's Alzheimer's Disease Research Center. All subjects completed PET-PiB imaging, cerebrospinal fluid analysis and at least 1 neuropsychiatric assessment and had clinical dementia rating (CDR) of 0. Subjects were divided into a biomarker + and – group. Subjects with systemic disease or drugs known to affect the PLR were excluded. Pupillometry was performed by using the NeuroOptics PLR-200 Pupillometer.

Results:

59 participants were recruited, 24 biomarker + and 35 biomarker-. All PLR parameters were assessed. Comparisons between groups were analyzed using SAS V9.3. Subjects + for ABeta had significantly reduced constriction percentage compared with ABeta – subjects, $p=0.03$. None of the other pupillometry parameters showed a significant difference between groups. Males showed reduced maximal constriction ($p=0.03$) and reduced average constriction velocity ($p=0.007$) compared with females.

Conclusions:

Constriction percentage was significantly reduced in the ABeta+ group compared with the ABeta-, but no other significant differences were found. This suggests that reduced cholinergic tone may alter the PLR in pre-clinical AD, but this effect may be small at the earliest stages of the disease. We found significant gender differences in PLR in the biomarker + and – groups.

References: None.

Keywords: Pupillometry, Alzheimer's Disease, Ocular Biomarkers

Financial Disclosures: The authors had no disclosures.

Grant Support: 1. Frost S, Martins RN, Kanagasingam Y. Ocular biomarkers for early detection of Alzheimer's disease. *J Alzheimers Dis* 2010;22:1-16 2. Fotiou DF, Brozou CG, Haidich AB et al. Pupil reaction to light in Alzheimer's disease: evaluation of pupil size changes and mobility. *Aging Clin Exp Res* 2007;19:364-371 3. Prettyman R, Bitsios P, Szabadi E. Altered pupillary size and darkness and light reflexes in v disease. *J Neurol Neurosurg Psychiatry* 1997;62:665-668.

Monday, February 29, 6:00 - 6:15 pm

A New Complementary Video Head Impulse Test Paradigm to Elicit Anti-Compensatory Saccades as an Indicator of Peripheral Vestibular Function

Konrad P. Weber^{4,5}, Hamish G. MacDougall¹, Leigh A. McGarvie², G. Michael Halmagyi², Stephen J. Rogers¹, Leonardo Manzari³, Ann M. Burgess¹, Ian S. Curthoys¹

¹*School of Psychology, University of Sydney, Sydney, Australia*, ²*Department of Neurology, Royal Prince Alfred Hospital, Sydney, Australia*, ³*MSA ENT Academy Center, Cassino, Italy*, ⁴*Department of Ophthalmology, University Hospital Zürich, Zürich, Switzerland*, ⁵*Department of Neurology, University Hospital Zürich, Zürich, Switzerland*

Introduction:

The conventional head impulse test paradigm (HIMP) elicits catch-up saccades as a sign of vestibular loss. The new suppression head impulse paradigm (SHIMP) is designed to elicit catch-up saccades as an indicator of vestibular function. During this new complementary paradigm, the subject is asked to follow a head-fixed target, which is rotating with the head, rather than to fixate an earth-fixed target as in HIMP.

Methods:

The saccadic patterns in response to the SHIMP and HIMP paradigms, as well as the gain of the vestibulo-ocular reflex (VOR) were quantified with the video head impulse test (vHIT). Five patients with unilateral vestibular loss (UVL) and five patients with bilateral vestibular loss (BVL) were compared to six normal subjects.

Results:

VOR gains correlated closely ($R^2=0.97$) with slightly lower SHIMP than HIMP gains (mean gain difference 0.06 ± 0.05 SD, $p < 0.001$). However, the resulting catch-up saccade patterns in the two paradigms were complementary: While HIMP elicited compensatory saccades mainly in patients, SHIMP elicited anti-compensatory saccades in normals, but only few in BVL patients. To the affected side UVL patients produced mostly covert saccades during HIMP, but mainly overt saccades during SHIMP.

Conclusions:

The new SHIMP paradigm produced closely correlating VOR gains with slight, but significant VOR suppression compared to SHIMP. While the appearance of compensatory saccades during conventional HIMP indicates vestibular loss, the anti-compensatory saccades during SHIMP indicate vestibular function. In UVL patients SHIMP elicits mainly overt saccades to the affected side, thus facilitating VOR gain measurements. The new complementary SHIMP paradigm is equally simple to explain to patients as the HIMP paradigm, while the results are complementary.

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1. MacDougall HG, McGarvie LA, Halmagyi GM, Curthoys IS, Weber KP. The video Head Impulse Test (vHIT) detects vertical semicircular canal dysfunction. PLoS One 2013, 8(4), e61488, 2013.
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Keywords: Diagnostic Tests, Ocular Manifestations Of Vestibular Disorders, Vestibular, Video Head Impulse Test, Vestibulo-Ocular Reflex

Financial Disclosures: GMH, ISC, HGM, LAM, KPW act as unpaid consultants and have received funding for travel and free equipment for beta testing from GN Otometrics. However, the study was conducted with a custom-built, non-commercial prototype and the authors have no commercial interest in video head impulse systems. LM, SJR and AMB report no disclosures.

Grant Support: Garnett Passe and Rodney Williams Memorial Foundation, the National Health and Medical Research Council Australia (Grant 632746 and 1046826), the Betty and David Koetser Foundation for Brain Research and the Forschungskredit of the University of Zurich.

Monday, February 29, 6:15 - 6:30 pm

***En Face* and Raster SD-OCT Imaging of Retinal and Choroidal Folds in Papilledema**

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Introduction:

The purpose of this study was to demonstrate how *en face*/raster SD-OCT imaging of the optic disc and retina in papilledema can be used to detect and characterize the patterns of folds and wrinkles in papilledema.

Methods:

Masked reviewers evaluated 125 patients with papilledema from the IIH Treatment Trial(IIHTT). We compared the relative sensitivity of *en face*/raster SD-OCT to fundus photographs in identifying retinal and choroidal folds at baseline. Using a standardized protocol, folds were characterized by type, frequency, location, pattern and spatial wavelength. The relationship between the presence and types of folds and a number of structural and functional parameters were examined.

Results:

We identified several types of folds: peripapillary wrinkles(PPW), retinal folds(RF), choroidal folds(CF). SD-OCT was more sensitive than fundus photos in identifying folds. The frequency, with photos was 26%,19%, and 1% respectively; with SD-OCT was 46%,47%, and 10%.. At least one type of fold was present in 41% of eyes with photos and 73% with SD-OCT. Each type of fold has a distinctive pattern, location and spatial wavelength that reflects the biomechanical stress and strain, material (tissue layer) properties and structural geometry of the optic nerve head(ONH) and retina. Parameters that reflect the severity of papilledema (e.g.RNFL, disc volume, Frisén scale) were associated with PPW/RF whereas anterior deformation in the shape of the eye-wall was associated with CF/RF. These associations were statistically significant. Folds were not associated with baseline vision.

Conclusions:

The interactive features of the SD-OCT using *en face* and raster imaging enhances our ability to identify and characterize folds compared to fundus photos. Retinal and choroidal folds are common in papilledema. Folds in papilledema are the biomechanical expressions of stress/strain on the ONH and load-bearing structures (sclera, lamina) induced by intracranial hypertension; they are products of a complex interaction between the degree of papilledema and anterior deformation of the load-bearing structures.

References:

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4. Sibony PA, Kupersmith MJ, Feldon SE et al. Retinal and choroidal folds in papilledema. *Invest Ophthalmol Vis Sci* 2015. 56:5670-5680

Keywords: OCT, Papilledema, Choroidal Retinal Folds, Optic Nerve, Intracranial Hypertension

Financial Disclosures: The authors had no disclosures.

Grant Support: This report is supported in part by U10 EY017281-01A1, U10 EY017387-01A1, 3U10EY017281-01A1S1, RO1 EY023279, Unrestricted Grant from Research to Prevent Blindness.

Monday, February 29, 6:30 - 6:45 pm

Abnormal Integration of Audiovisual Spatial Information in Amblyopia

Michael D. Richards^{1,2,3}, Herbert C. Goltz^{2,3,4}, Agnes M.F. Wong^{1,2,3,4}

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Introduction:

Perception of our environment involves combining information from multiple senses by a process termed multisensory integration. This process is evident in illusions like the McGurk effect, which juxtapose subtly incongruous auditory and visual stimuli to reveal the bias in the neurological networks underlying perception. Interestingly, studies using the McGurk effect show that patients with unilateral amblyopia integrate auditory and visual speech information in an abnormal way. It is unknown, however, whether this abnormality is specific to speech, or whether it reflects a more general failure of multisensory integration in amblyopia. To address this question, we used another illusion – the ventriloquism effect – to examine integration of non-speech audiovisual information. The ventriloquism effect is known to obey the maximum likelihood estimate (MLE) model of optimal combination in normal adults, and thus provides a predictive model to evaluate performance in amblyopia.

Methods:

All experiments were done in an acoustic chamber under binocular viewing conditions. Adults with amblyopia (n=8) and normal controls (n=17) performed spatial localization of auditory clicks, visual Gaussian blobs (5 sizes), and combined audiovisual stimuli in a 2-alternative forced choice paradigm. Localization precision and bias for each click, blob, and click-blob pair was estimated from the fitted psychometric functions. Performance was compared to predictions from the MLE model.

Results:

Unlike normal controls, patients with unilateral amblyopia did not combine auditory and visual information as predicted by the MLE model when viewing binocularly ($p = 0.003$). Auditory spatial information was over-valued in amblyopia.

Conclusions:

Integration of audiovisual spatial information in amblyopia does not obey the MLE model of optimal combination. This suggests that normal visual experience may be required for the development of robust audiovisual integration, and points to a lifelong impact of pediatric sensory disturbances on perception.

References: None.

Keywords: Amblyopia, Multisensory Integration, Higher Visual Functions, Psychophysics

Financial Disclosures: The authors had no disclosures.

Grant Support: This study was supported by grants MOP 106663 from the Canadian Institutes of Health Research (CIHR), Leaders Opportunity Fund from the Canada Foundation for Innovation (CFI), the John and Melinda Thompson Endowment Fund in Vision Neurosciences, the Vision Science Research Program at the University of Toronto, and the Department of Ophthalmology and Vision Sciences at The Hospital for Sick Children.

Monday, February 29, 6:45 - 7:00 pm

Quantitative MRI Criteria for Optic Pathway Enlargement in Children with Neurofibromatosis Type 1

Robert A. Avery^{1,2}, Awais Mansoor², Rabia Idress³, Roger J. Packer¹, Marius G. Linguraru¹

¹Children's Hospital of Philadelphia, Philadelphia, PA, USA, ²Children's National Medical Center, Washington, DC, USA, ³George Washington University School of Medicine, Washington, DC, USA

Introduction:

Children with Neurofibromatosis type 1 (NF1) frequently develop optic pathway gliomas (OPGs), low grade tumors of the anterior visual pathway (AVP) which include the optic nerve, chiasm and tract. The diagnosis of an OPG is frequently based upon enlargement of these structures, yet a quantitative MRI criterion of enlargement does not exist. We introduce quantitative size thresholds for enlargement of the AVP.

Methods:

Children 0.3-18.6 years of age who underwent high resolution T1-weighted cube MRI and did not have other acquired, systemic or genetic conditions (other than NF1) that could alter their AVP, were eligible for inclusion. Diameter, volume and length of AVP structures were calculated from reconstructed MRI images. Values above the 95th percentile from the control subjects were considered the threshold for defining an abnormally large AVP measure.

Results:

One-hundred eighty-six children (controls = 82; NF1noOPG = 54; NF1+OPG = 50) met inclusion criteria. NF1noOPG and NF1+OPG subjects demonstrated greater maximum optic nerve diameter and volume, optic chiasm volume and total brain volume compared to controls (P <0.05, all comparisons). Total brain volume, rather than age, predicted optic nerve and chiasm volume in controls (P <0.05). Applying the 95th percentile threshold to all NF1 subjects, the maximum optic nerve diameter (4.0 mm) and AVP volumes resulted in few false positive errors (specificity >80%, all comparisons).

Conclusions:

Quantitative reference values for AVP enlargement will enhance development of objective diagnostic criteria for OPGs secondary to NF1.

References: None.

Keywords: Neuroimaging, Tumors, Pediatric Neuro-Ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: National Eye Institute K23-EY022673, and The Gilbert Family Neurofibromatosis Institute.

North American Neuro-Ophthalmology Society

42nd Annual Meeting

February 27 – March 3, 2016
JW Starr Pass Marriott • Tucson, Arizona

Program Schedule

TUESDAY, MARCH 1, 2016

6:00 am - 6:45 am	Yoga Class	San Ignacio
6:30 am - 5:30 pm	Registration/Help Desk	Arizona Foyer
6:30 am - 7:30 am	Breakfast	Arizona Ballroom
6:30 am - 12:15 pm	Exhibits	Arizona Ballroom
6:30 am - 7:30 am	JNO Editorial Board Meeting	San Pedro
7:30 am - 12:00 pm	SCIENTIFIC PLATFORM PRESENTATIONS: SESSION II [3.75 CME]	Tucson Ballroom
9:15 am - 9:30 am	Update: The Journal of Neuro-Ophthalmology <i>Lanning Kline, MD, Editor-in-Chief & Jason Roberts, PhD, Managing Editor</i>	Tucson Ballroom
9:30 am - 10:00 am	Coffee Break	Arizona Ballroom
12:00 pm - 6:00 pm	Free Afternoon/Optional Excursions	
12:15 pm - 5:00 pm	Kartchner Caverns	Depart from Starr Circle Terrace
12:30 pm - 4:30 pm	Desert Horseback Trail Ride	Depart from Starr Circle Terrace
12:30 pm - 5:30 pm	Arizona Sonora Desert Museum	Depart from Starr Circle Terrace
1:00 pm - 6:00 pm	NANOS Golf Tournament	Starr Pass Golf Club
6:00 pm - 9:30 pm	Poster Session II: Scientific Advancements in Neuro-Ophthalmology	Arizona Ballroom

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



North American Neuro-Ophthalmology Society

42nd Annual Meeting

February 27 – March 3, 2016
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PLATFORM SESSION II

Tuesday, March 1, 2016 • 7:30 am - 12:00 pm

Moderators: Madhu Agarwal, MD and Timothy McCulley, MD – before the break

Moderators: Beau B. Bruce, MD, PhD and Heather Moss, MD, PhD – after the break

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**Please note that all abstracts are published as submitted.*

Tuesday, March 1, 7:30 - 7:45 am

Handheld Ocular Fundus Photography in Acute Subarachnoid Hemorrhage (SAH): The FOTO-ICU Study

Philip S. Garza¹, Caroline Fajoles-Vasseneix¹, Lindsay Clough¹, Kevin R. Sitko¹, Prem Kandiah^{2,3}, Nancy J. Newman^{1,2,3}, Valérie Biousse^{1,2}, Owen B. Samuels^{3,2}, Beau B. Bruce^{1,2,4}

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³Department of Neurological Surgery, Emory University, Atlanta, GA, USA, ⁴Department of Epidemiology, Emory University, Atlanta, GA, USA

Introduction:

Intraocular hemorrhage (IOH) among SAH patients (Terson syndrome) has been suggested as a risk factor for poor clinical outcomes, but this association remains debated.^{1,2,3} Our goal was to assess IOH's prevalence and to evaluate its association with ICU length of stay (LOS) and in-hospital morbidity/mortality.

Methods:

Patients admitted to our neurosurgical ICU from 9/2014-7/2015 with a primary diagnosis of acute SAH were included. Bedside handheld mydriatic fundus photography was performed early after admission (median=1.5 days, IQR=1-3) and intermittently throughout the hospitalization. Fundus photographs were reviewed for IOH. Poor outcome was defined as death, care withdrawal, or discharge Glasgow Outcome Score ≤ 3 . Multivariable logistic and Cox models were used to evaluate associations between IOH and poor outcome/LOS, controlling for age, sex, race, APACHE II score, Hunt & Hess score, respiratory failure at ICU admission, and aneurysmal etiology.

Results:

79 consecutive SAH patients were enrolled (mean age: 54 [SD=13], 50 [63%] women, and 53 [67%] aneurysmal). 13/79 (16%) had Hunt & Hess >3 . 20/79 (25%) had IOH, and 11/20 (55%) had a poor outcome vs. 19/59 (32%) without IOH ($p=0.07$). Median ICU LOS was longer for patients with IOH (18 vs. 11 days, $p=0.01$). Multivariable logistic regression found that male sex, higher APACHE II, and aneurysmal etiology, but not IOH (OR=1.1, 95% CI=0.2-5.5), were associated with poor outcome. Cox modeling did not support a significant association between IOH and ICU LOS (median increased LOS: 4-5 days; $p=0.13$), although male sex, aneurysmal etiology, and higher Hunt & Hess and APACHE II were associated with longer ICU LOS.

Conclusions:

IOH is associated with markers of disease severity in patients with SAH, but does not appear to add prognostic information beyond that of known risk factors. Routine ophthalmologic examination for SAH in the ICU appears unwarranted and can be deferred until the patient is stable or has visual complaints.

References:

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Keywords: High Intracranial Pressure/Headache, Neuro-Ophth & Systemic Disease, Retina, Stroke, Vascular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: This work was supported in part by an unrestricted departmental grant (Department of Ophthalmology) from Research to Prevent Blindness, Inc., New York. Mr. Garza receives research support from the Emory Eye Center Research to Prevent Blindness Pilot Grant and from the NIH/NCATS (TL1-TR000456-08) via the Atlanta Clinical and Translational Science Institute (ACTSI). Dr. Bruce receives research support from the NIH/NINDS (R01-NS089694).

Tuesday, March 1, 7:45 - 8:00 am

Neuroprotective Effects of ST266 in Experimental Optic Neuritis

Kenneth S. Shindler¹, Reas S Khan¹, Kimberly Dine¹, Larry Brown²

¹University of Pennsylvania/Ophthalmology, Philadelphia, PA, USA, ²Stemnion, Inc., Pittsburgh, PA, USA

Introduction:

Optic neuritis, demyelinating optic nerve inflammation, often occurs in multiple sclerosis (MS) patients. Loss of retinal ganglion cells (RGCs) and their axons also occurs in optic neuritis, and correlates with permanent vision loss. ST266 is a novel biologic mixture of growth factors and cytokines secreted from Amnion-derived Multipotent Progenitor (AMP) cells, that exhibits anti-inflammatory and neuroprotective properties in a variety of disease models. The ability of ST266 to suppress optic neuritis in the EAE model of MS was examined.

Methods:

C57/BL6 EAE mice, induced by immunization with myelin oligodendroglial glycoprotein peptide, were treated daily with one drop (6uL) of ST266 intranasally beginning before or after onset of optic neuritis. Visual function was assessed by optokinetic responses (OKR) at baseline, then weekly until sacrifice 6 weeks post-immunization. Retinas and optic nerves were isolated. RGCs were immunolabeled with Brn3a and counted. Inflammation, demyelination and axonal loss were quantified by staining of optic nerve sections.

Results:

Progressive decreases in OKR occurred in vehicle-treated EAE mice, along with significant RGC loss, consistent with prior studies showing onset of optic neuritis 12-15 days post-immunization. Daily intranasal ST266 treatment beginning on day 0 (day of immunization), 15, 22, or 30, significantly reduced the level of vision loss, and treatment from day 0 or day 15 attenuated RGC loss. ST266 also decreased the degree of demyelination and axonal loss, and reduced inflammation, in the optic nerve.

Conclusions:

ST266 treatment attenuates RGC loss, preserves OKR responses, and reduces demyelination and axonal loss during experimental optic neuritis. ST266 exerts effects with treatment initiated before and after disease onset, suggesting it may be useful as a preventative or abortive therapy. Results suggest ST266 is a potential treatment for optic neuritis that warrants further study. Furthermore, potent effects seen after intranasal administration suggest this may be a novel drug delivery method for optic neuritis.

References: None.

Keywords: Optic Neuritis, Neuroprotection, Retinal Ganglion Cell, Multiple Sclerosis

Financial Disclosures: KS Shindler has received payment for serving on the scientific advisory board for Stemnion, Inc, who produces the ST266 drug used in these studies. L Brown is employed full time by Stemnion. Stemnion provided the ST266 drug for these studies.

Grant Support: NIH Grant EY019014 Research to Prevent Blindness and the F. M. Kirby Foundation.

Tuesday, March 1, 8:00 - 8:15 am

Change in Peripapillary Bruch's Membrane Shape Can Be Detected 1 Hour After Lowering of Intracranial Pressure by Lumbar Puncture

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Introduction:

While papilledema is an indicator of increased intracranial pressure(ICP) in patients with idiopathic intracranial hypertension(IIH), it takes several days to develop and resolve and does not correlate with immediate changes in ICP. Prior studies have shown that there is a change in the shape of peripapillary Bruch's membrane opening (pBMO) in patients with papilledema weeks after ICP-lowering interventions. The objective of this study was to determine whether change in pBMO shape can be detected in patients with and without IIH within one hour after ICP lowering by lumbar puncture (LP).

Methods:

30 degree nasal-temporal ocular coherence tomography(OCT) B-scans were obtained within one hour before and after LP in 34 eyes from 18 patients(age 23-86, 83% female, ICP[opening pressure] 10-55 cm H2O). pBMO shape was defined on each image using 16 equidistant points. Geometric morphometric analysis was used to identify shape-defining features (principal components [PCs]) in the image set. Generalized estimating equation models, accounting for within-subject correlations, were used to identify PCs that were associated with chronic ICP (comparing pre-LP images between eyes) and/or acute ICP changes (comparing pre- and post-LP images within eyes).

Results:

PCs 1,2,3 and 4 accounted for 76%, 18%, 2% and 2% of the pBMO shape variations, respectively. PC 1 magnitude on pre-LP images was associated with ICP ($p < 0.0005$). PC 3 and 4 magnitudes changed within eyes after LP ($p = 0.034$, $p = 0.049$). For each of PCs 1, 3, and 4, lower ICP corresponded with a more posterior position of the pBMO.

Conclusions:

Our geometric morphometric analysis confirms an association between pBMO shape and chronic ICP. Furthermore, we demonstrate consistent changes in pBMO shape within 1 hour of lowering ICP. This suggests that pBMO shape may be a useful marker for acute ICP changes. Further study is needed to determine how pBMO shape changes relate to clinical markers of papilledema.

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Keywords: IIH, Papilledema, ICP, OCT

Financial Disclosures: The authors had no disclosures.

Grant Support: Sybil B. Harrington Award from Research to Prevent Blindness, NIH grant P30 EY01792, NIH grant K23 EY024345, Illinois Society for Prevention of Blindness Research Grant.

Tuesday, March 1, 8:15 - 8:30 am

Demographic, Systemic and Ocular Features of Non-Arteritic Anterior Ischemic Optic Neuropathy in a Large US Claims Beneficiary Database

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Introduction:

The etiology of non-arteritic ischemic optic neuropathy (NAION), the most common acute neuropathy in older adults, is poorly understood. We assessed demographic, systemic and ocular factors associated with NAION to gain insight into the pathogenesis of the disease.

Methods:

Claims data in a nationwide managed care network between 2001-2014 were examined for beneficiaries between the ages of 40-75 years with no history of NAION to identify new cases of NAION. All subjects were under ophthalmic surveillance and were required to have a confirmatory code for NAION in at least one subsequent visit. Multivariable Cox regression modeling was used to generate adjusted Hazard Ratios (HR) and 95% confidence intervals (CI) to assess the relation between demographic, systemic and ocular features, and the risk of developing NAION.

Results:

There were 1,381,477 eligible enrollees, 0.1% (N=977) of whom were diagnosed with NAION. Mean age \pm SD for NAION at index date was 64.0 \pm 9.2 years versus 58.4 \pm 9.4 years for other beneficiaries. After adjustment for confounding factors, each additional year older was associated with a 2% increased risk of NAION (HR=1.02;95% CI:1.01-1.03). Females were 36% less likely than males to develop NAION (HR=0.64;CI:0.55-0.74). Compared with Caucasians, Latinos had a 46% decreased hazard of developing NAION (HR=0.54;CI:0.36-0.82), while African ancestry was not related to NAION (HR=0.91;95%CI:0.72-1.15). Systemic features associated with NAION included systemic hypertension (HR=1.62;95%CI:1.26-2.07) and hypercoagulable states (HR=2.46;95%CI:1.51-4.00). Diabetes was not associated with NAION, unless there was end organ involvement, which produced a 27% increased hazard of NAION (HR=1.27;95%CI:1.01-1.59). Ocular features associated with NAION were age-related macular degeneration (HR=1.29;95%CI:1.08-1.54) and retinal vein occlusion (HR=3.94;9%CI:3.11-4.99).

Conclusions:

This is the first large scale population survey of NAION. This study revealed gender, race and systemic disease factors that influence the risk of developing NAION. This data can motivate new investigations to explore the pathogenesis of NAION.

References: None.

Keywords: NAION, Risk Factors, Optic Neuropathy, Patient Database

Financial Disclosures: The authors had no disclosures.

Grant Support: Joshua D. Stein, MD MS has support from an RPB (Physician Scientist Award).

Tuesday, March 1, 8:30 - 8:45 am

The Effect of Pupillary Dilation on Strabismus Measurements in Adults

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Introduction:

Pupillary dilation can significantly alter strabismus measurements in pediatric patients. This study aims to determine if pupillary dilation affects strabismus measurements in adults.

Methods:

Patients aged 18 years and older with strabismus were eligible. Each underwent standard evaluation of motility, stereopsis, and ocular alignment with alternate prism cover test by a certified orthoptist. After pupillary dilation with phenylephrine 2.5% and tropicamide 1%, ocular alignment was re-measured in primary gaze at 6 m and 1/3m (with and without +3.00 lens) by a second, masked orthoptist.

Results:

Fifty-six patients (59% women, age range: 19-92, mean age: 51.6 years) were enrolled with the following deviations in primary gaze before dilation: esodeviation (n=14, range 1-52, mean 15.7 PD), exodeviation (n=4, range 2-20, mean 10.9 PD), mixed vertical/esodeviation (n=11, ET: range 2-45, mean 13.1 PD; HT: range 1-25, mean 6.4 PD), mixed vertical/exodeviation (n= 14, XT: range 2-55, mean 16.6 PD; HT: range 2-10, mean 5.3 PD), vertical deviation (n=13, range 1-20, mean 5.7 PD). For horizontal misalignments, the mean change in PD after dilation was 1.65 at distance (95% CI +/- 0.77, p=0.99), 4.33 at near (95% CI +/- 1.47, p=0.77), and 3.51 at near with +3.00 add (95% CI +/- 1.17, p=0.95). For vertical measurements the change was 0.76 at distance (95% CI +/- 0.31, p=0.99), 1.33 at near (95% CI +/- 0.53, p=0.99), and 1.16 at near with +3.00 (95% CI +/- 0.67, p=0.99). Significant change was observed in those aged 18-39 (mean 9.59, 95%CI +/-3.90, p=0.0023), but not after +3.00 add was used (mean 4.41, 95%CI +/- 5.75, p=0.64).

Conclusions:

Pupil dilation does not affect distance strabismus measurements in adults. Measurements at near are significantly different in non-presbyopic adults, but this can be mitigated by +3.00 lenses.

References: None.

Keywords: Strabismus, Dilation, Pupil

Financial Disclosures: The authors had no disclosures.

Grant Support: Research to Prevent Blindness, New York, NY.

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Introduction:

Over a century ago, German ophthalmologist Hermann Wilbrand studied human optic chiasms and reported that inferonasal crossing fibers within the chiasm curved anteriorly into the contralateral optic nerve. This anatomic bend ("Wilbrand's knee") is classically cited as the explanation for the contralateral superotemporal visual field defect that may appear when a lesion affects the optic nerve at its junction with the chiasm (the so-called "junctional scotoma"). More recent reports have called into question the existence of Wilbrand's knee or suggested that it may simply be an artifact of monocular enucleation, partly because no evidence of Wilbrand's knee could be found in monkey optic chiasms.

Methods:

Four human optic chiasms (obtained from cadaver donors with normal pre-mortem vision) and three monkey chiasms were fixed and thin sectioned (40 µm), then examined using a novel imaging technology that takes advantage of the observation that light will reflect/scatter off of well-defined linear structures (i.e., axons) in a predictable manner based on their orientation. Using this technique, tissue structures oriented in different directions can be clearly distinguished, allowing tractography similar to DTI MRI but with a 10- to 100-fold higher resolution.

Results:

In all four human optic chiasms (three axial sections and one coronal section), thin fiber tracts consistent with those Wilbrand had described were observed. No such tracts were found in the three monkey chiasms (two axial sections and one coronal section).

Conclusions:

Wilbrand's knee exists in humans but is not present in monkeys, which may explain conflicting reports in the literature regarding its existence.

References:

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Keywords: Neuroimaging, Visual Fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, March 1, 9:00 - 9:15 am

Cranio-Spinal CSF Redistribution Before and Following Lumbar Puncture in Patients with Idiopathic Intracranial Hypertension

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Introduction:

The physiologic effect of lumbar puncture (LP) in idiopathic intracranial hypertension (IIH) has not been adequately studied and automated quantitation of cerebrospinal fluid (CSF) volumes by MRI is lacking. We characterized the physiologic effect of LP by determining the change of cranio-spinal CSF redistribution before and after LP. To achieve this aim, we developed a new automated method for delineating spinal CSF spaces.

Methods:

The study subjects consists of 8 young overweight women with newly-diagnosed untreated IIH (Age 29±5.9 years, BMI 34±6.7). Research cranio-spinal MRIs were performed immediately before and immediately after the diagnostic LP to establish IIH (opening pressure 33±9.1 cm water). MR imaging included T1W MPRAGE and T2W SPACE sequences of the brain and 2 separate T2W SPACE sequences covering the upper and lower portions of the spinal canal. Cranio-spinal CSF volumes prior and following LP were compared to the amount of CSF withdrawn.

Results:

LP results in reduced spinal CSF volume localized near the region of the LP without change in cranial CSF volume. Spinal CSF and cord volumetric automated measurements were highly reproducible with mean variability of less than 1%, -0.7±1.4%, -0.7±1.0%, respectively. The pre-to-post CSF withdrawal differences in the cranio-spinal CSF volumes were consistently smaller and strongly correlated with the CSF amounts removed (R=0.86, p=0.006). The smaller measured pre-to-post LP CSF differences compared to the CSF amount withdrawn can be reconciled assuming a net CSF formation of 0.41±0.18ml/min.

Conclusions:

Despite the high intracranial pressure, the drop in intracranial pressure from LP in IIH is related to the immediate increase in spinal canal compliance from CSF removal near the spinal region of the LP without change in cranial CSF volume. Our findings enhance the understanding of the CSF flow dynamics of LP in IIH, and the automated method developed permit future longitudinal studies to assess cranio-spinal CSF in IIH patients.

References: None.

Keywords: Idiopathic Intracranial Hypertension, Lumbar Puncture, Cerebral Spinal Fluid, MRI

Financial Disclosures: The authors had no disclosures.

Grant Support: Funded by NANOS pilot grant.

Tuesday, March 1, 10:00 - 10:15 am

Glucagon Like Peptide-1 (GLP-1) Reduces Cerebrospinal Fluid Secretion and Intracranial Pressure: A Novel Treatment for Idiopathic Intracranial Hypertension?

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²Neurology Department, University Hospitals Birmingham NHS Trust, Birmingham, United Kingdom, ³Danish Headache Center, Clinic of Neurology, Rigshospitalet-Glostrup, University of Copenhagen, Glostrup, United Kingdom

Introduction:

Introduction: To investigate whether the gut neuropeptide, Exendin-4, a glucagon like peptide-1 (GLP-1) receptor agonist (currently used to treat diabetes and obesity), would be able to modulate CSF secretion at the choroid plexus and subsequently reduce ICP.

Methods:

Methods: GLP-1 receptor mRNA, protein levels and localisation were assessed by quantitative PCR, western blot and immunohistochemistry respectively, with and without Exendin-4 treatment. Activation of the receptor was evaluated using a cAMP immunoassay and Na⁺ K⁺ ATPase activity was measured to assess CSF secretion. The effect of Exendin-4 on ICP was assessed in adult rats.

Results:

Results: We demonstrated that GLP-1 receptor mRNA and protein were detected in the choroid plexus and was localised to the cytoplasm and apical surface of the epithelial cells. Following Exendin-4 treatment, GLP-1 receptor mRNA (3.40 ± 0.78 fold, $P < 0.05$) and protein levels (0.92 ± 0.05 , $P < 0.05$) were increased compared to baseline (1.00 ± 0.20 fold and 0.59 ± 0.06 respectively). Evaluation of the downstream signalling pathway on primary choroid plexus epithelial cells identified a 2.14 ± 0.61 fold increase in cAMP after Exendin-4 treatment ($P < 0.01$). Exendin-4 also significantly reduced Na⁺ K⁺ ATPase activity, a marker of CSF secretion ($39.3 \pm 9.4\%$ of control; $P < 0.05$). Finally, *in vivo* ICP recording in adult rats demonstrated that Exendin-4 significantly reduced ICP ($41.7 \pm 5.0\%$ reduction from baseline $P < 0.0001$).

Conclusions:

Conclusions: We demonstrate that Exendin-4 reduces CSF secretion by the choroid plexus and ICP in rats. Repurposing existing GLP-1 drugs may represent a novel therapeutic strategy for conditions of raised ICP such as idiopathic intracranial hypertension. Additionally, GLP-1 therapy promotes significant weight loss which would be advantageous in idiopathic intracranial hypertension.

References: None.

Keywords: Idiopathic Intracranial Hypertension, Glucagon Like Peptide 1, Intracranial Pressure, Choroid Plexus, Cerebrospinal Fluid Secretion

Financial Disclosures: The authors had no disclosures.

Grant Support: Dr Alexandra Sinclair is funded by an NIHR Clinician Scientist Fellowship (NIHR-CS-011-028) and by the Medical Research Council, UK (MR/K015184/1). This work was supported by the West Midlands Neuroscience Teaching and Research Fund.

Tuesday, March 1, 10:15 - 10:30 am

Recombinant AAV2 Containing the Wild-Type ND4 Gene (rAAV2/2-ND4) is an Experimental Gene Therapy for Vision Loss in LHON Due to the ND4 Mitochondrial Mutation: Phase I/IIa Safety Investigation Results and Upcoming Pivotal Phase III Efficacy Studies

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Introduction:

Allotopic expression of the wild-type ND4 gene delivered by a rAAV2/2 vector through intra-vitreous injection is an experimental therapy for vision loss in patients with ND4 LHON.

Methods:

An open-label Phase I/IIa safety study included patients with vision loss due to ND4 LHON. Four dose escalation cohorts and an extension cohort were comprised of 3 patients each. Patients received a single intra-vitreous injection of rAAV2/2-ND4 in their worse seeing eye. Primary outcome was the occurrence of adverse events (AE). Secondary outcomes included immune response to AAV2 and evaluation of visual function

Results:

Fifteen patients were included. Average duration of vision loss was 5.9 years (0.62-22.2) at treatment. Mean LogMAR acuity of the injected eye at study entry was 2.25 (1.10-3.01). Follow-up includes the 2 week visit of the extension (last) cohort. Thirteen of 15 patients experienced an AE. A total of 57 AEs were documented; 24 considered related to GS010 and 13 considered related to procedures. No GS010-related, unexpected AE occurred. One serious AE unrelated to GS010 or procedures occurred. The most common ocular AEs were inflammation and IOP elevation. All AEs were mild except 2 moderate IOP elevations and one severe event each of anterior chamber and vitreous inflammation. Ocular side effects are improving or resolved with standard therapy and no visual sequelae occurred. Typical immune responses to AAV2 were observed and no relationship between anti-AAV2 antibody levels (IgG, neutralizing antibodies) and ocular inflammation was noted. At 24 weeks post-injection some patients were noted to have a trend of effect on visual acuity, color vision and contrast sensitivity in the treated eye.

Conclusions:

Intra-vitreous injection of rAAV2/2-ND4 is safe and encouraging trends on vision testing are noted. Dose selection is completed for the pivotal Phase III trials RESCUE and REVERSE which will include patients with vision loss up for to 1 year

References: None.

Keywords: Optic Neuropathy, Genetic Disease

Financial Disclosure: Catherine Vignal, MD, Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts and Fondation Rothschild Principal Investigator of CLIN 01(Consultant for GenSight-Biologics *); Scott Uretsky MD, GenSight-Biologics* (GenSight-Biologics* employee); Nitza Thomasson, PhD, GenSight-Biologics *(GenSight-Biologics* employee); Celine Bouquet, PhD, GenSight Biologics*(GenSight Biologics* employee); Anne Galy, PhD, GenSight-Biologics *(GenSight-Biologics *employee); Jean-Philippe Combal PharmD PhD, GenSight-Biologics*, (GenSight-Biologics* employee), Serge Fitoussi, MD, MSc, GenSight-Biologics* (GenSight-Biologics* employee); Jose Alain Sahel, MD, Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts and Institut de la Vision (GenSight-Biologics* Share Holder and Consultant) *Gensight -Biologics is the sponsor of the CLIN 01 study and sponsor of the development of Recombinant AAV2 Containing the Wild-Type ND4 Gene (rAAV2/2-ND4). All other authors had no financial disclosures.

Grant Support: None.

Tuesday, March 1, 10:30 - 10:45 am

Light Evoked Retinal Activation is Metabolically Coupled to Increases in Human Retinal, Choroidal and Optic Nerve Head Blood Flow Measured Simultaneously by Laser Speckle Flowgraphy

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Introduction:

Our purpose was to develop a light-induced metabolic stress test for use in disorders of the retina and optic nerve. The direct relationship between neural activation and blood flow is well known and forms the basis for quantitative, functional imaging of the brain. Neurovascular coupling to light stimuli has also been described for the retinal vasculature. Laser speckle flowgraphy provides a means to quantify light-induced changes in retinal, choroidal, and optic nerve head circulations simultaneously throughout the cardiac cycle.

Methods:

10 healthy subjects (mean age 39; range 18 to 61 years old; 4 males and 6 females) were studied using laser speckle flowgraphy (LSFG-NAVI device, Softcare Co. LTC, Fukuoka, Japan). After two baseline blood flow measurements were made, a 10Hz flickering light stimulus with 50% duty cycle and 145,96 cd/m² of luminance was given using a portable, wireless LED array, while recording blood flow. The white light-induced blood flow response of the right eye was measured in the first experiment while the consensual blood flow response of the left eye was recorded in the second experiment. Blood pressure and intraocular pressure were measured before, during and after each 30-second light stimulus.

Results:

A significant increase in flicker-induced blood flow was found in the stimulated eye in 3 vascular beds simultaneously measured: retina; 35.3%±6.5, choroid; 16.1%±3.3, and optic nerve head; 12.5%±4.8. The consensual effect was significantly lower in the non-stimulated eye and was mainly explained by an increase in systemic blood pressure.

Conclusions:

Our results show that the retina, choroid, and optic nerve head adjust their blood flow to the metabolic demands in a coordinated way, and the lack of response in the non-stimulated eye suggests a local response. Laser speckle flowgraphy measurement of light-induced neurovascular coupling has potential for use as a metabolic stress test of the retina and optic nerve in health and disease.

References: None.

Keywords: Neurovascular Coupling, Laser Speckle, Optic Nerve Flow, Retinal Blood Flow, Choroidal Blood Flow

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, March 1, 10:45 - 11:00 am

A Novel Approach to Measuring Peripapillary Retinal Perfusion in Papilledema: A Pilot Study Using Optical Coherence Tomography Angiography

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Introduction:

The utility of Optical Coherence Tomography Angiography (OCTA) in imaging perfused radial peripapillary capillaries (RPCs) has been demonstrated.¹ The purpose of this pilot study was to assess the density of perfused RPCs in subjects with papilledema and normals.

Methods:

Subjects were prospectively recruited from a single institution. Peripapillary 4.5x4.5mm scans were obtained in each subject using a 70-kHz, 840nm wavelength spectral OCT system (Avanti RTVue-XR, Optovue, Fremont, CA). The split-spectrum amplitude decorrelation angiography (SSADA) algorithm was used to identify perfused RPCs. A customized algorithm was applied to perform vessel skeletonization and generate a color-coded capillary perfusion density (CPD) map. The algorithm also calculated mean whole en face and peripapillary CPD within a 0.75 mm width ring surrounding the nerve. We performed qualitative analysis of CPD maps and quantitative analysis of whole en face and peripapillary CPD values in papilledema and normal patients. Statistical analysis was performed using a two-tailed student t-test.

Results:

Images from 13 subjects with papilledema and 13 normals were included. Qualitative analysis of whole en face CPD maps revealed dense RPC networks in normals, and patchy areas of decreased capillary density in papilledema subjects. Quantitative analysis of whole en face CPD was not statistically significant. In contrast, mean peripapillary CPD values were decreased in papilledema (59.1%) compared to normals (63.1%). (P=0.001). Subgroup analysis of Frisén² low (0-II) and high (III-V) grade papilledema revealed decreases of 5.9% (P<0.01) and 8.1% (P=0.01), respectively, compared to normals.

Conclusions:

Mean peripapillary CPD was decreased in papilledema subjects compared to normals, as measured by OCTA. This finding may suggest reduced flow from vascular congestion at the peripapillary region. These vascular changes may be useful in the understanding of structural and functional relationships in papilledema.

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2. Frisén, Swelling of the optic nerve head: a staging scheme, Journal of Neurology, Neurosurgery, and Psychiatry, 45, 13-18, 1982.

Keywords: OCT Angiography, Ocular Imaging, Papilledema, Retinal Perfusion, IIH

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, March 1, 11:00 - 11:15 am

The Effect of Red Light Exposure on the Pre-existing Melanopsin-Driven Post-illumination Pupil Response

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Introduction:

Intrinsically photosensitive retinal ganglion cells (ipRGCs), the specific sub-group of retinal ganglion cells that mediate the pupillary light reflex, contain a bistable photo-pigment called melanopsin. The activation of melanopsin drives a persistent firing of ipRGCs resulting in a sustained pupil constriction after the offset of light stimulation (post-illumination pupil response, PIPR). It has been proposed that after activation by blue light, activated melanopsin is converted back to its resting state by long wavelength light exposure, a putative mechanism of melanopsin chromophore recovery in vivo. We tested this hypothesis by investigating whether red light attenuates the ongoing post-illumination pupil response (PIPR) induced by melanopsin-activating blue light.

Methods:

Pupillary light responses were tested using “Blue + Red” double flashes and “Blue only” single flash stimuli in 10 visually normal subjects (mean age 31.8 years, range 20-57 years). For “Blue + Red” conditions, PIPR was induced with an intense blue flash, immediately followed by experimental red light exposure of variable intensity and duration (Experiment 1) or 9 s after the offset of the blue flash (Experiment 2). For “Blue only” conditions, only the PIPR-inducing blue stimuli were presented (reference condition). PIPR was defined as the mean pupil size from 10 to 30 seconds (Experiment 1) or 25 to 60 seconds (Experiment 2) after the offset of blue light stimuli.

Results:

PIPR from “Blue + Red” conditions did not differ significantly from those of “Blue only” conditions ($p=0.551$) in Experiment 1. They also did not differ in Experiment 2 ($p=0.413$).

Conclusions:

Red light exposure does not alter the trajectory of PIPR induced by blue light. This finding does not support the hypothesis that long wavelength light reverses activated melanopsin; rather it lends support to the hypothesis that the spectral distributions of stimuli driving the forward and backward reactions of melanopsin may be similar.

References: None.

Keywords: Pupil Light Reflex, Chromatic Pupillometry, Melanopsin, Post-Illumination Pupil Response

Financial Disclosures: The authors had no disclosures.

Grant Support: Supported by the Canada Foundation for Innovation, John and Melinda Thompson Endowment Fund for Vision Neuroscience, and the Department of Ophthalmology and Vision Sciences at The Hospital for Sick Children.

Tuesday, March 1, 11:15 - 11:30 am

Experimental Anterior Ischemic Optic Neuropathy in Diabetic Mice Exhibited Severe Retinal Swelling and Subretinal Fluid Accumulation Acutely and More Severe Thinning Chronically

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Introduction:

Non-arteritic ischemic optic neuropathy (AION) is the most common acute optic neuropathy in those older than 50¹⁻² and is associated with post-ischemic inflammation and oligodendrocyte dysfunction and degeneration.³⁻⁸ Diabetes mellitus (DM) is one of the most common vascular risk factors and leads to vascular changes, inflammation, and neuron loss.⁷ We studied the contribution of elevated glucose in experimental AION and assessed retinal and inflammatory changes.

Methods:

We induced photochemical thrombosis model of AION³⁻⁸ in STZ-induced chronically diabetic C57BL/6 mice (N = 43) and performed optical coherence tomography (OCT), fluorescence angiography (FA), and immunohistochemical and morphometric analyses of anti-Iba-1 antibody stain (activated microglia). Statistical analysis was performed using SPSS.

Results:

We measured post-ischemic swelling one-day after AION using OCT and found there was significant swelling of the ganglion cell complex (GCC: RNFL+GCL+IPL) and increased total retinal thickness ($P < 0.01$) in animals with or without DM, which was associated with increased Iba-1⁺ staining at the optic nerve head and microglial activation. There was more subretinal fluid accumulation in the DM-AION eyes compared with non-DM AION eyes, and the subretinal fluid was more prominent further away from the optic nerve head. In the DM mice, there was no correlation between serum glucose level and the severity of swelling. There was greater GCC thinning in DM mice at week-1 (DM: $79.2 \pm 1.2 \mu\text{m}$, non-DM: $97.6 \pm 11.2 \mu\text{m}$, $P = 0.096$) and at week-4 (DM: $66.6 \pm 2.9 \mu\text{m}$, non-DM: $74.7 \pm 3.5 \mu\text{m}$, $P = 0.2$).

Conclusions:

After AION, there was post-ischemic inflammation and microglial activation, which was similar in diabetic- and non-diabetic mice, but diabetes was associated with greater swelling and subretinal fluid one day after ischemia and greater thinning four weeks later.

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Keywords: Optic Neuropathy (AION), Diagnostic Tests (OCT)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, March 1, 11:30 - 11:45 am

Change in the Deflection of the Neural Canal Opening Away from the Vitreous and Towards the Retrobulbar Space as an Indicator of Treatment Efficacy of Optic Nerve Sheath Fenestration and Non-surgical Treatment for Idiopathic Intracranial Hypertension (IIH)

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Introduction:

Our purpose was to determine if change in the displacement of Bruch's basement membrane (BM) surrounding the neural canal of the optic disc could reveal surgical and medical treatment efficacy of IIH. We also sought to determine if BM displacement was independent of reductions in optic nerve volume.

Methods:

The displacement of Bruch's membrane surrounding the neural canal of the optic disc was quantified from OCT scans of the optic disc using shape analysis before and after treatment of papilledema. 39 patients treated with maximum tolerated acetazolamide+diet (ACZ+diet) were compared to 34 patients treated with placebo+diet (PL+diet) from the OCT substudy of the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT). 6 patients not enrolled in the IIHTT were treated with optic nerve sheath fenestration (ONSF). The 2nd principal component coefficient from the shape analysis reflected the BM anterior/posterior displacement; more negative values reflected anterior displacement towards the vitreous and more positive values reflecting a posterior displacement away from the vitreous (-3.0 to +3.0). Disc volume was determined by segmentation analysis of the OCT disc volume scan.

Results:

There was a statistically significant posterior deformation of Bruch's membrane layer after treatment for both the ACZ+diet group (+0.87±1.2) and the eye receiving ONSF (+1.59±1.5). There was no significant change in displacement of BM in either the PL+diet group (+0.03±.83) or the fellow eye not receiving ONSF (+.14±1.0). Disc volume decreased significantly in all groups.

Conclusions:

Displacement of Bruch's membrane at the optic nerve head reflects the translaminar pressure differential between the retrolaminar and intraocular fluid compartments and appears to be a biomarker of successful treatment of raised intracranial pressure. Unexpectedly, reduction in disc volume did not correlate with BM displacement, implying two independent mechanisms for improvement.

References:

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Keywords: IIH, OCT, Neural Canal, Optic Nerve Sheath Fenestration, Papilledema

Financial Disclosures: Randy Kardon MD PhD, grant funding from NEI, and VAMona Garvin PhD, grant funding from NEI, and VAMatthew Thurtell MBBS MSc grant funding from NEI, and VAMichael Wall MD, grant funding from NEI, and VA

Grant Support: NIH U10 EY017281-01A1, NIH U10 EY017387-01A1, NIH 3U10EY017281-01A1S1, VA Rehab R&D C9251-C, NIH R01 EY023279, NIH Clinical Trial: NCT01003639

Tuesday, March 1, 11:45 am - 12:00 pm

The Localization and Patterns of Dyschromatopsia: A Study of Prosopagnosic Subjects

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Introduction:

Dyschromatopsia can accompany acquired prosopagnosia, but given the structural variety of the latter, it is not clear which lesions are associated with colour impairments, or whether these impairments also occur with developmental prosopagnosia. In addition, whether the impairment selectively affects specific regions of colour space is uncertain, given conflicting reports in prior single cases.

Methods:

We investigated hue discrimination in a cohort of 12 subjects with acquired prosopagnosia and 9 with developmental prosopagnosia, along with 42 matched controls, using the Farnsworth-Munsell 100-hue test. Behavioural results were subjected to a Fourier analysis, and neuroimaging to a lesion overlap analysis.

Results:

We found impaired hue discrimination in 6 subjects with acquired prosopagnosia, 5 with bilateral and one with a unilateral occipitotemporal lesion. Structural MRI analysis showed maximum overlap of lesions in the right and left lingual and fusiform gyri. Fourier analysis of their error scores showed tritanopic-like deficits and blue-green impairments, similar to tendencies displayed by the healthy controls. Three subjects also showed a novel fourth Fourier component, indicating additional peak deficits in purple and green-yellow regions. No subject with developmental prosopagnosia had impaired hue discrimination.

Conclusions:

In subjects with prosopagnosia, dyschromatopsia is limited to those with acquired lesions of the fusiform gyri, usually bilateral but sometimes unilateral. The dyschromatopsic deficit shows an accentuation of normal tritanopic-like tendencies, sometimes accompanied by anomalous deficits that do not correspond to traditional red-green axes.

References: None.

Keywords: Hue Discrimination, Face Recognition, Prosopagnosia, Fusiform Gyrus

Financial Disclosures: The authors had no disclosures.

Grant Support: This work was supported by CIHR operating grant MOP-102567 to JB. JB was supported by a Canada Research Chair and the Marianne Koerner Chair in Brain Diseases. BD was supported by grants from the Economic and Social Research Council (UK) (RES-062-23-2426) and the Hitchcock Foundation. SC was supported by National Eye Institute award F32 EY023479-02.



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Poster Session II: Scientific Advancements in Neuro-Ophthalmology

Tuesday, March 1, 2016 • 6:00 pm - 9:30 pm

Authors will be standing by their posters during the following times:

Odd-Numbered Posters: 6:45 pm - 7:30 pm

Even-Numbered Posters: 7:30 pm - 8:15 pm

**Please note that all abstracts are published as submitted.*

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119	To Evaluate Changes in Retinal Nerve Fibre Layer and Ganglion Cell Layer on SD-OCT in Cases of Multiple Sclerosis and Optic Neuritis	Ganesh Pillay
120	Sensitive Assessment of Acute Optic Neuritis by a New Digital Flicker Test	Gorm Pihl-Jensen
121	Factors Associated with Papilledema in Children with Hydrocephalus	Haeng Jin Lee
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126	Neural Cell Adhesion Molecules in Acute Optic Neuritis: Relation to Clinical and Paraclinical Findings	Jette L. Frederiksen
127	Radiographic and Systemic Prognosticators of Visual Acuity After Indirect Traumatic Optic Neuropathy	Joanna H. Queen
128	Optic Atrophy in Classical Methylmalonic Acidemia	Joyce N. Mbekeani
129	Structure-Function Analysis in Chiasmal Compression Helps Predict Visual Prognosis	Juthamat Witthayaweerasak
130	Effect of Intraocular Pressure on Optic Nerve Structure and Function in Adults with Optic Nerve Head Drusen	Kaitlyn W. Nolan
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132	Long-Term Evolution Optic Disc Drusen - 57 Year Follow-Up	Lasse Malmqvist
133	Early Treatment with Levodopa Promotes Visual Improvement in Nonarteritic Anterior Ischemic Optic Neuropathy	Lenworth N. Johnson
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135	Correlation Between Stereopsis and Reverse Stereopsis: "Turn Upside-Down the Stereo"	Michael Dattilo
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140	A Photothrombotic Model of Optic Neuropathy Using Mesoporphyrin IX: Our Experience with Rats vs. Mice	Peggy Bouzika
141	The Photopic Negative Response as an Objective Measurement of Visual Function in Patients with Leber's Hereditary Optic Neuropathy	Rustum Karanjia
142	Neuro-Ophthalmic Manifestations of Costeff Syndrome	Ruth Huna-Baron
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144	Visual Outcomes of Diabetics and Prognostic Factors in Non -Arteritic Ischaemic Optic Neuropathy	Srilakshmi Sharma
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148	Clinical Features of Optic Neuritis in Patients Over 45 Years-Old	Thong Pham
149	Transcorneal Electrical Stimulation in Optic Neuropathies	Umur A. Kayabasi
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159	Headache Characteristics in Pediatric Patients with Definite Pseudotumor Cerebri Syndrome and Intracranial Hypertension	Ali G. Hamedani
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172	Comparison of the Surgical Treatment of Superior Oblique Palsy: Inferior Oblique Myectomy Versus Combined Contralateral Inferior Rectus Recession	Dean M. Cestari
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174	Hyperintense Optic Nerve Heads on Diffusion Weighted Imaging: Is This Sign Specific to Papilledema?	Christopher Terrill
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179	Prevalence of Thymoma in Ocular Myasthenia Gravis	Anthony J. Brune
180	Absence of Bacteria in the Temporal Arteries of Patients with Giant Cell Arteritis	Bradley J. Katz
181	Incidence and Evaluation of Third Nerve Palsy Using a Population-Based Method	Chengbo Fang
182	The CHOP Sign: Saccadic Correction With Horizontal Prism. A Novel Method to Identify Functional Monocular Vision Loss	David A. Clark
183	Risk Factors of Ischemic Optic Neuropathy in Korean Population	Gwang Rae Shin
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194	Retinal Nerve Fiber Layer Thickness in HTLV-1 Patients	Rabih Hage
195	Sabril Vision Study: Retinal Structure and Function in Adult Patients with Refractory Complex Partial Seizures (rCPS) Treated with Vigabatrin	Robert C. Sergott
196	Patterns of Change in Macular Thickness on OCT in Normal Pregnancy and Pregnancy Complicated by Hypertension: A Tool for Assessing Dynamic Function of the Microcirculation	Robert J. Herman
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198	Asymmetric Fundus Autofluorescence Findings in Parkinson's Disease	Umur A. Kayabasi
199	Visual Symptoms and Movement Disorders: Establishing a Neuro-ophthalmology Clinic Designed for Patients with Movement Disorders	Victoria S. Pelak
200	Pseudotumor Cerebri Secondary to Venous Sinus Occlusion	Kumudini Sharma
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202	Ocular Alignment After Bilateral Medial Rectus Recession in Esotropic Patients with Spinocerebellar Atrophy	Bo Young Chun
203	Capturing the Efferent Side of Vision in Multiple Sclerosis: New Data from a Digitized Rapid Number Naming Task	Clotilde Hainline
204	Exploring the Oculomotor Effects of Sustained-Release Fampridine in Multiple Sclerosis Patients with Gait Impairment.	Cristina Duque
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212	Stability of Human Binocular Alignment: A Video-Oculographic Luminance Study	Michael C. Brodsky
213	Pitfalls and Rewards for Implementing Emergent Bedside Oculomotor Testing in Patients with Acute Vestibular Syndrome	Oana Dumitrascu
214	Head Tilt Observation Study	Olga R. Rosenvald
215	Factors Influencing Success of Prisms in the Management of Diplopia From Various Causes	Shiming Luo
216	Screening for Thymoma in Suspected Ocular Myasthenia Gravis: A Retrospective Study	Sui H. Wong
217	The Ocular Motor Underpinnings of Rapid Number-Naming as a Sideline Performance Measure for Concussion	Todd E. Hudson
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221	FOTO-ED Phase III: What Happens When You Try to Teach Emergency Providers to Read Fundus Photographs?	Beau B. Bruce
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223	Optic Neuritis History Does Not Influence OCT Measurement in Long-Standing Secondary Progressive Multiple Sclerosis	Kimberly M. Wings
224	Peripapillary Subretinal Hemorrhage: Clinical and Ocular Coherence Tomography Findings in 5 Cases	Lola M. Grillo
225	The Utility of a Hand-Held, Non-Mydriatic Fundus Camera for the Detection of Optic Nerve Edema	Lulu Bursztyn
226	Morphometric Evaluation of Asymptomatic Optic Disc Elevation and Grade I Papilledema	Mack W. Savage
227	Optical Coherence Tomography Angiography and Anterior Ischemic Optic Neuropathy	Marie B. Rougier
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233	Optic Canal Temperature Change with Ultrasonic Drill Decompression of the Orbital Apex	Jessica R. Chang
234	Brave New World: 3D Printing of the Orbit for Anatomy, Pathology, Surgical Simulation	Remy R. Lobo
235	An Incomplete Awakening: Sleep-Induced Apraxia of Eyelid Opening	Sara N. Reggie
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Poster 117**Timing of Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) After Modern Cataract Extraction**

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Introduction:

To study the prevalence of non-arteritic anterior ischemic optic neuropathy (NAION) and its temporal relationship with modern cataract surgery.

Methods:

Retrospective and prospective, chart review and patient historical assessment. SETTING: Single tertiary care center.

All patients seen at The Wilmer Eye Institute between January 1, 2010 and December 31, 2014, with a documented episode of NAION were included in this study. Records were reviewed to identify which patients had previous cataract surgery during the 1-year period prior to developing an NAION. Patients with cataract surgery were reviewed and evaluated for differences in perioperative anesthesia, duration of surgery, and time interval between surgery and NAION onset.

Results:

188 patients were identified as having had an episode of NAION during the study period. Of these, 18 (9.6%) patients (22 eyes) had history of cataract extraction during the year subsequent to developing NAION. The median interval between cataract surgery and NAION was 173 days (range: 9-328 days). NAION occurred within 3 months, 3-6 months, 6-9 months, and 9-12 months after cataract surgery in 5 eyes (22.7%), 7 eyes (31.8%), 8 eyes (36.4%), and 2 eyes (9.1%) respectively (Figure 1). The temporal relationship between NAION onset and previous surgery was evaluated by using a chi-squared goodness of fit t-test to compare the observed with a uniform distribution across 3-month time interval, which suggested no significant temporal pattern ($P=0.28$).

Conclusions:

Our data suggest that there is no temporal relationship between modern cataract surgery and the occurrence of NAION.

References:

McCulley TJ, Lam BL, Feuer WJ. Nonarteritic Anterior Ischemic Optic Neuropathy and Surgery of the Anterior Segment: Temporal Relationship Analysis. Am J Ophthalmology, 136 (6), 1171-1172, 2003.

Keywords: NAION, Cataract Surgery

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 118

Getting Stoned From Being Too High: Accidental Discovery That Optic Disc Drusen May Arise From High Intracranial Pressure of Pseudotumor Cerebri / Idiopathic Intracranial Hypertension

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Introduction:

To evaluate the prevalence of optic disc drusen (ODD) in the setting of papilledema from pseudotumor cerebri/idiopathic intracranial hypertension (IIH), and to assess if the coexistence of both conditions may worsen the visual outcomes as compared with either condition alone.

Methods:

Observational retrospective review of 372 consecutive participants with ODD or resolved papilledema (rPAP) from IIH evaluated over a 25-year period. The prevalence of ODD among participants with rPAP was calculated. One eye from each of 372 participants was used to assess logMAR visual acuity and visual field mean deviation (MD) outcomes.

Results:

Participants included 170 ODD alone, 159 rPAP alone, and 43 combined ODD with rPAP (cODD-rPAP). The prevalence of ODD at 19% among eyes with rPAP alone and combined was almost 10 times greater and significantly higher ($P<0.001$) than the prevalence of ODD in the general population. Eyes with exposed drusen had significantly worse visual acuity at 0.14 logMAR as compared with eyes with buried drusen at 0.029 logMAR ($P=.025$). The visual field MD of eyes with exposed drusen at -9.88 dB was worse than buried drusen at -3.35 dB ($P<0.001$), rPAP at -4.80 dB ($P<0.001$), and rPAP with exposed drusen at -6.02 dB ($P=0.047$). Eyes with cODD-rPAP did not have worse visual acuity or visual fields than eyes with rPAP alone.

Conclusions:

The high prevalence of ODD with rPAP suggests a non-coincidental relationship, and that in some cases ODD may develop secondary to papilledema. Additionally, the presence of ODD in the setting of papilledema does not portend worse visual outcome. Our investigation supports the theory that conditions causing axonal distress, specifically optic disc edema (papilledema), may contribute to the formation of ODD.

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Keywords: Exposed Optic Disc Drusen, Idiopathic Intracranial Hypertension, Papilledema, Pseudotumor Cerebri, Vision Outcomes

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 119**To Evaluate Changes in Retinal Nerve Fibre Layer and Ganglion Cell Layer on SD-OCT in cases of Multiple Sclerosis and Optic Neuritis**

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Introduction:

To prospectively evaluate retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL) changes over 6 months in multiple sclerosis and optic neuritis patients and correlate them with visual functions and disability.

Methods:

Patients with multiple sclerosis without optic neuritis (MS, n=40 eyes), optic neuritis (ON, n= 58 eyes), Multiple sclerosis with optic neuritis (MS+ON, n=48 eyes), and disease-free controls (n=40 eyes) were included. All subjects underwent visual testing(VA), contrast sensitivity, colour vision, visual evoked response, retinal nerve fibre layer thickness (RNFL) and ganglion cell layer thickness (GCL) measurement using spectral domain optical coherence tomography (SD-OCT) at baseline and 6 months. Expanded disability status scale (EDSS) score was calculated for multiple sclerosis patients.

Results:

Compared to controls average RNFL thickness was reduced significantly in affected eyes of MS+ON($p<0.005$) unaffected fellow eye ($p<0.005$) and ON ($p<0.005$) but no significant difference was found in MS patients. Compared to controls GCL thickness was reduced significantly in eyes of MS+ON($p<0.005$), unaffected fellow eye($p<0.005$), ON ($p<0.005$) as well as MS patients ($p<0.005$). In MS patients GCL thickness correlated significantly with VA ($p=0.0032$), colour ($p<0.001$), EDSS ($p=0.0047$), VER amplitude ($p=0.0078$) and latency($p=0.0001$). Significant correlation of GCL was observed with VA($p=0.0042$), colour vision (<0.001) and contrast ($p=0.02$) in ON. GCL and RNFL loss in M.S+O.N and O.N patients and GCL loss in M.S patients over 6 months was significant as compared to age matched controls ($p<0.005$).

Conclusions:

Ganglion cell layer thickness may be a more sensitive marker of involvement in Multiple sclerosis and optic neuritis patients. Although eyes with history of optic neuritis demonstrate the greatest reduction in GCL thickness, MS non-ON eyes are also affected suggesting sub-clinical involvement causing chronic axonal loss in MS patients. Ganglion cell layer clinically correlated with EDSS and maybe used as a marker for disease progression.

References: None.

Keywords: SD-OCT, Ganglion Cell Layer Thickness, Visual Function, Optic Neuritis, Multiple Sclerosis

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 120

Sensitive Assessment of Acute Optic Neuritis by a New Digital Flicker Test

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Introduction:

ON is primarily a clinical diagnosis but clinical tests with increased sensitivity, and tests which predict MS risk in the ON patients, are needed. The Aulhorn flicker test was shown in the 1980's to effectively diagnose acute ON¹. The aim of this study was to examine the applicability of a new, digitalized version of the analog test for examination of acute optic neuritis (ON).

Methods:

A psychophysical test where the subjective brightness of a steady field has to be adjusted to that of a flickering field of randomized varying frequencies 0-60 Hz. Recorded luminances are then plotted against frequencies. The normal curve shows a light-enhancement at medium frequencies (Brücke-Bartley-effect (BBE)^{2,3}) whereas the ON curve is hypothesized to show darkness enhancement and a cancelled BBE at these frequencies. Visual acuity (VA, ETDRS) and flicker test measurements were obtained in acute ON patients (within 1 month of onset). 52 consecutively referred, untreated ON patients were included (bilateral symptoms in 5/52).

Results:

Mean logMAR VA was 0.52 (SD:0.58) and mean age 37.1 year (SD:11.2). The flicker test was performed 22 days (SD:15) following ON onset. 49 of 52 patients showed abnormal response (cancelled BBE, darkness enhancement) corresponding to 94.23 %. 20/52 patients were reexamined 3 months following ON onset where 7/20 showed normal response (1/20 in the acute phase) which may indicate a dynamic response of the flicker test at different time points following ON onset.

Conclusions:

Preliminary results indicate very good sensitivity of the digital flicker test in ON. Follow up of the ON patients, and a general MS patient population, may further provide evidence of an accurate and easy to use tool in diagnosing acute ON and signs of demyelinating disease in the visual pathway.

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Keywords: Optic Neuritis, Clinical Testing, Psychophysics, Demyelinating Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: The study was supported by the Danish Multiple Sclerosis Society.

Poster 121**Factors Associated with Papilledema in Children with Hydrocephalus**

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Introduction:

To report the factors associated with papilledema in children with hydrocephalus.

Methods:

The medical records of patients under 15 years old who were diagnosed with hydrocephalus and treated by ventricular drainage or ventriculo-peritoneal shunt operation from January 2005 to July 2015 were retrospectively reviewed. Factors including age, gender, etiology of hydrocephalus, duration of signs or symptoms, intracranial pressure (ICP) and presence of papilledema were investigated.

Results:

Thirty-eight patients were included. Their mean age was 5.5 ± 4.6 years and 19 patients (50%) showed papilledema. The mean age of patients without papilledema was 3.0 ± 3.3 years and 7.9 ± 4.4 years in patients with papilledema ($p=0.000$). The ICP was 19.8 ± 11.8 cmH₂O in patients without papilledema and 33.1 ± 9.3 cmH₂O in patients with papilledema ($p=0.000$). The mean duration of symptoms was 3.2 ± 4.5 months in patients without papilledema and 3.9 ± 4.4 months in patients with papilledema ($p=0.621$). The causes of hydrocephalus were tumor (50%), congenital anomaly (24%), hemorrhage (16%) and infection (10%). The groups with brain tumor had older age, higher intracranial pressure and showed papilledema more commonly than others.

Conclusions:

In patients with older age, higher intracranial pressure, and hydrocephalus induced by brain tumor, papilledema was more common. However, since there were 50% of patients without papilledema in children with hydrocephalus, the absence of papilledema does not ensure the absence of hydrocephalus, especially for younger patients.

References: None.

Keywords: Pediatric Neuro-Ophthalmology, High Intracranial Pressure/Headache

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 122**Postural Effects on Intraocular Pressure and Ocular Perfusion Pressure in Patients with Non-Arteritic Anterior Ischemic Optic Neuropathy**

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Introduction:

The aim of this study was to investigate postural effects on intraocular pressure (IOP) and ocular perfusion pressure (OPP) in patients with non-arteritic ischemic optic neuropathy (NAION).

Methods:

Twenty patients with unilateral NAION underwent IOP and blood pressure (BP) measurements 10 minutes after changing to each of the following positions sequentially: sitting, supine, right lateral decubitus position (LDP), supine, left LDP, and supine. IOP was measured using a rebound tonometer. OPP was calculated using formulas based on mean BP. The dependent LDP was defined as the position when the eye of interest (affected or unaffected eye) was placed on the dependent side in the LDP.

Results:

In both the affected and unaffected eye, mean IOP was significantly increased and OPP significantly reduced when changing position from sitting to supine (all $P < 0.05$), but inter-eye comparisons showed no statistical difference (all $P > 0.05$). The affected eye showed a higher IOP in the dependent LDP compared to the unaffected eye-dependent LDP ($P < 0.001$). Compared with the IOP of the unaffected eye, the mean IOP of the affected eye increased significantly ($+2.89 \pm 4.40$ versus $+0.65 \pm 3.14$ mmHg, respectively; $P = 0.003$), and the mean OPP decreased significantly (-6.67 ± 9.37 versus -4.94 ± 7.98 mmHg, respectively; $P = 0.022$) after changing from supine to dependent LDP.

Conclusions:

Postural change from supine to dependent LDP may significantly increase IOP and decrease OPP in the affected eye. Posture-induced IOP changes could be a predisposing factor for NAION development.

References: None.

Keywords: Optic Neuropathy, Vascular Disorders, Visual Fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 123

Risk Factors for Radiation-Induced Optic Neuropathy: A Case-Control Study

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Introduction:

Radiation-induced optic neuropathy (RION) is a rare complication of radiation therapy characterized by acute, painless vision loss many months after treatment. Various factors which appear to increase the risk of RION within determined safe-dosage thresholds have been described; however, these findings have been inconsistent and primarily based on descriptive case series.

Methods:

This study applied a case-control design to interrogate potential risk factors for RION. Patients with a diagnosis of RION established by ophthalmologic testing (n=14) were matched in a 2:1 ratio to controls according to maximum point dose to the affected optic nerve. Patient characteristics (age, gender, race, vascular risk factors, tumor profile) and treatment parameters (cumulative and fractionated dose volume and schedule) were analyzed for potential risk factors.

Results:

No significant association was found for diabetes (p=0.66, OR=1.84, 95% CI [0.35-9.61]) or hypertension (p=0.69, OR=1.3, 95% CI [0.35-4.8]). Odds ratios suggest hyperlipidemia may pose an increased risk (p=0.28, OR=2.31, 95% CI [0.56-9.48]), as may male gender (p=0.11, OR=2.85, 95% CI [0.77-10.57]). Age was not a significant risk factor (p=0.94, MD=1.04). A potentially increased risk was found for prior visual complaint (p=0.1, OR=3.04, 95% CI [0.78-11.81]) and tumor impingement of the optic nerve (p=0.95, OR=2.11, 95% CI [0.59-7.61]). Concurrent chemotherapy (p=0.74, OR=0.63, 95% CI [0.16-2.48]) and primary surgery (p=1, OR=0.86, 95% CI [0.23-3.23]) were not significant risk factors.

Conclusions:

More rigorously identifying risk factors for RION may decrease the incidence of this profound, irreversible outcome. Our study found a potential increased risk for male gender, hyperlipidemia, prior visual complaint, and tumor impingement of the optic nerve. While these individually may play some role, no single trait proved predictive when controlling for maximum radiation dose to the affected optic nerve, suggesting that radiation dose may be the overriding determinant.

References: None.

Keywords: Chemotherapy and Radiation Injury, Optic Neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: Supported by the Clinical and Translational Science Award (CTSA) program of the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH) under Award Numbers UL1 TR000448 and TL1 TR000449.

Poster 124**Number and Distribution of Causes of Optic Neuropathy in Patients Evaluated at a Tertiary Care Center**

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Introduction:

Optic nerve dysfunction is among the most common causes of vision loss in the industrialized world. The range of diseases that cause optic neuropathies is quite large, although the great majority of optic neuropathies are caused by a relatively small number of etiologies. The purpose of this study was to assess the total number and distribution of causes of optic neuropathies for patients who were evaluated at a tertiary care center, and to determine the frequency of patients who had optic neuropathies without identifiable cause despite current state-of-art diagnostic studies.

Methods:

A cross-sectional study of all patients who were evaluated by our Neuro-Ophthalmology service from July through October 2015 and found to have an optic neuropathy. For each patient, data was collected on the medical history, visual presentation, findings on neuro-ophthalmic examination, as well as the results of diagnostic studies that were obtained to search for an etiology. No diagnostic studies were performed that would not have otherwise been performed as part of our standard clinical evaluation.

Results:

A total of 165 patients were found to have an optic neuropathy. Of these patients, 41 (25%) had ischemic optic neuropathy, 30 (18%) had idiopathic intracranial hypertension, 23 (14%) had optic neuritis, and 8 (5%) had an identifiable genetic cause. In 15 (9%) patients, the etiology could not be determined. Of the 15 patients, 10 had bilateral optic nerve involvement.

Conclusions:

The most useful result of this study is the proportion of patients for whom an etiology of optic neuropathy could not be determined. This subgroup represents a potential target for future investigation, especially genetically, to identify new explanations for visual loss. The results of this ongoing study will be compared to results obtained in an identical way from other tertiary care centers around the world.

References: None.

Keywords: Optic Neuropathy, Ischemic Optic Neuropathy, Idiopathic Intracranial Hypertension, Optic Neuritis, Hereditary Optic Neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 125**Short Follow-Up Bias Confounds Estimates of the “Typical” Clinical Course of Susac Syndrome**

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Introduction:

The prevailing view regarding the clinical course of Susac syndrome (SS) is that it is generally monocyclic and shows spontaneous resolution within approximately 2 years. However, the duration of follow-up in existing case reports may be inadequate to judge the veracity of these assumptions.

Methods:

We identified all reported cases of SS between 1973 and October 2015. If the duration of follow-up was not explicitly stated, we calculated it based upon provided information regarding the initial symptoms, clinical course during observation, and submission date of the published report. A course of up to 24 months without subsequent relapses was labeled “monocyclic”, whereas a relapse beyond 24 months indicated a “polycyclic” course. We performed descriptive analyses of the duration of reported follow-up for all patients.

Results:

We identified 185 reports, in which a total of 416 individual cases of SS were reported. Of these, the duration of follow-up was determined in 258 cases. It ranged from 0.5 to 312 months. The mean (\pm SD) was 42.2 ± 53.2 months, but the distribution was positively skewed. The median duration of follow-up was only 24 months. Classification of the clinical course as monocyclic or polycyclic was possible in 109 cases. A polycyclic course (60 cases, 55%) was associated with longer follow-up period (median 66 vs. 42 months, $P < 0.001$).

Conclusions:

This analysis of all published cases of SS shows that the median reported follow-up period is only 24 months, which is too short to establish a true estimation of the long-term risk of relapsing disease. Short follow-up in published case reports creates an inherent bias toward the impression that SS is a monocyclic, self-limiting disease. A multicenter patient registry with long-term follow-up is essential to determine the true clinical course and risk of relapse.

References: None.

Keywords: Susac Syndrome, Clinical Course

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 126**Neural Cell Adhesion Molecules in Acute Optic Neuritis: Relation to Clinical and Paraclinical Findings**

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Introduction:

Acute optic neuritis (AON) is an inflammatory condition of the optic nerve presumably of autoimmune origin. More than 50 % develop multiple sclerosis (MS). AON patients were chosen to achieve a homogenous patient group in which complete diagnostic work up was performed within one month from onset. No studies have thus far investigated the levels of Neural Cell Adhesion Molecules (NCAM) in the CSF in AON to determine whether NCAM is associated with demographic and paraclinical findings suggestive of MS.

Methods:

We performed a prospective study of NCAM level in the CSF in 50 adults with AON, median age 32 (range 18 to 62) years and healthy controls. Associations between NCAM levels and age, gender, results of brain MRI at 3.0 Tesla and routinely measured biomarkers in the CSF in patients with AON were assessed.

Results:

The median level of NCAM in the CSF was 348 ng/ml in AON, compared to a mean value 412 +/- 109 ng/ml in healthy controls. There was no age and gender difference. There was neither significant association between NCAM and presence of elevated leucocyte count in the CSF, nor elevated IgG index, nor presence of oligoclonal IgG bands in the CSF. No significant association was found between brain MRI and NCAM level, but patients with a normal NCAM level tended to be more likely to also have a normal brain MRI (p=0.057, Fisher exact test). The results showed a trend towards increased NCAM and the presence of Gadolinium enhancing lesions on brain MRI albeit not significant.

Conclusions:

The study showed no significant association between NCAM level in the CSF and the results of routinely measured biomarkers in the CSF and brain MRI without and with Gadolinium DTPA in 50 consecutive patients with AON. In a follow up study we will examine whether NCAM levels predict development of MS.

References: None.

Keywords: Demyelinating Disease, Optic Neuropathy, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 127

Radiographic and Systemic Prognosticators of Visual Acuity After Indirect Traumatic Optic Neuropathy

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Introduction:

Indirect traumatic optic neuropathy (iTON) is a well-described cause of post-traumatic vision loss thought to result from shearing forces transmitted to the optic nerve in the optic canal in the absence of a canal fracture. Visual recovery is unpredictable. The purpose of this study is to identify characteristics of cranial computed tomography (CT) and systemic comorbidities that may predict visual outcomes in eyes with iTON.

Methods:

This study is a retrospective case series of patients with iTON treated initially at a large, urban trauma center with follow-up at an affiliated ophthalmology clinic. In addition to detailed cranial CT characteristics and demographics, systemic comorbidities, co-injuries, blood products administered, and intracranial pressure (ICP) along with other factors were gathered. LogMAR visual acuity (VA) at initial presentation and up to 12 months follow-up was also collected.

Results:

Thirteen patients met inclusion criteria; 11 men and 2 women with mean age of 35.2 years +/- 15.2. One (8%) patient received high-dose IV steroids at the time of injury. Mean initial VA was 1.6 +/- 1.0 logMAR and final VA was 1.2 logMAR +/- 1.1 at the final visit. Three NLP eyes from 2 patients at the final visit were also NLP at presentation. Of the 25 predictors analyzed, three were found to significantly influence visual outcomes. Patients with worse presenting VA and ICP bolt placement had worse final vision, while patients with systemic immune response syndrome had better final vision. Orbital fractures and intra- and/or extraconal emphysema and/or hemorrhage were not found to significantly affect visual outcome.

Conclusions:

In this small case series, initial visual acuity and need for ICP bolt placement predicts poorer visual recovery in patients with iTON. The relationship between SIRS and vision after iTON maybe due to high correlation between ICP bolt placement and SIRS. Further studies are needed to investigate.

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Keywords: Optic Nerve Trauma And Treatment, Optic Neuropathy, Trauma, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: National Eye Institute Vision Core Grant P30EY010608 Challenge Grant from Research to Prevent Blindness Hermann Eye Fund.

Poster 128

Optic Atrophy in Classical Methylmalonic Acidemia

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Introduction:

Methylmalonic acidemia (MMA) is an autosomal recessive, metabolic failure to process various amino acids and lipids. Classical MMA results in methylmalonyl CoA mutase deficiency, preventing the vitamin B12-dependent conversion of methylmalonyl CoA to succinyl CoA, required in Krebs cycle. Patients typically present in early infancy with lethargy and failure to thrive. Long-term complications include renal failure (CRF) and encephalopathy. Only 4 cases of optic atrophy (OA) have been reported. With improved survival of patients offered advanced treatment, OA needs to be identified so that prophylactic/therapeutic intervention, when available, can be incorporated into management protocols. The purpose of this study is to identify and determine the prevalence of OA in classical MMA.

Methods:

22 patients diagnosed and genetically confirmed to have classical MMA were assessed neuroophthalmically. Diagnosis of OA was determined by a combination of visual acuity, pupil reactions, optic nerve appearances, optical coherence tomography (OCT) and VEP. Ophthalmic and medical data were tabulated and associations determined using Mann-Whitney U, Kruskal-Wallis, Chi-squared and Fisher's exact tests. Statistical significance was set at $p < 0.05$. Patients with propionic acidemia and intracellular cobalamin metabolism disorders, which have similar clinical features, were excluded.

Results:

8 patients were female and 14, male. Age range was 7 to 27yrs (median=14;IQR=11-16).13(59%) patients had OA; 85% of these were bilateral. 6 (46.15%) reported decreased vision and 7(53.85%) were asymptomatic.12 patients had CRF (median=16;IQR=14.5-20). Age was not significantly associated with OA ($p=0.17$) but was significantly related to CRF ($p=0.0067$). Patients with OA were more likely to have CRF ($p=0.0058$).

Conclusions:

Optic atrophy is a frequent finding in classical MMA and commonly is bilateral and sub-clinical. A positive correlation with CRF, known to be associated with OA, suggests a causal relation or common pathogenesis. These findings have important management implications. Early and periodic ophthalmic assessments should be performed in all, including asymptomatic patients with classical MMA.

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Keywords: Optic Atrophy, Methylmalonic Acidemia, Chronic Renal Failure

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Structure-Function Analysis in Chiasmal Compression Helps Predict Visual Prognosis

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Introduction:

Sellar mass compression of optic chiasm is often an emergency, and there is a relative lack of data helping clinicians predict visual outcome. To address this problem, we performed structure-function correlation of automated perimetry and optical coherence tomography measurements after treatment of chiasmal lesion.

Methods:

We performed a retrospective, cross sectional study of >100 patients with sellar mass at one institution from 2003 to 2015 and analyzed clinical characteristics and chronic, post-operative (range 3m-16y) paired perimetry and optical coherence tomography (OCT) measurements of retinal nerve fiber layer (RNFL) and macular ganglion cell complex (GCC), which includes the ganglion cell and the inner plexiform layers. For statistical analysis, we used SPSS ver.20.

Results:

We performed *post-operative* structure-function correlation with 64 eyes in 33 patients. Despite the relatively good visual acuity (81% of eyes with 20/30 or better), persistent visual field loss was found in 61% (bi-temporal 42%, unilateral-temporal 18%). Retinal thinning as defined by OCT measurement at 5-percentile of normal was found in 45% of eyes per RNFL (mean 80.2±1.9 microns, 64 eyes) and in 55% of eyes per GCC (mean 69.5±1.5 microns, 62 eyes), consistent with irreversible retrograde degeneration. Using re-calculated visual field mean deviation and GCC (nasal=crossed, temporal=uncrossed), we best fit the structure-function correlation using formula: thickness = slope*10^{0.1*} (mean deviation in dB) + residual thickness.¹ The temporal-superior field had residual thickness of 43-microns and the temporal-inferior field, 48-microns, consistent with chiasmal compression from below. Using ROC analysis, nasal GCC ≥55-micron significantly predicted good temporal visual field outcome (mean deviation better than -10 dB)¹ (P<0.001, area under curve 0.914). The sensitivity and specificity using these criteria were 89.1% and 93.7%.

Conclusions:

Timely treatment of severe optic chiasm compression can often lead to good visual outcome. A GCC thickness of ≥55 micron correlated with good post-operative visual outcome.

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Keywords: Chiasmal Compression, Optical Coherence Tomography, Ganglion Cell Layer, Diagnostic Test, Visual Prognosis

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 130

Effect of Intraocular Pressure on Optic Nerve Structure and Function in Adults with Optic Nerve Head Drusen

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Introduction:

To determine whether the intraocular pressure (IOP) in patients with optic nerve head drusen (ONHD) correlates to the mean deviation (MD) on automated visual fields (VFs) and the mean retinal nerve fiber layer (RNFL) thickness on optical coherence tomography (OCT).

Methods:

This retrospective chart review included adults with ONHD from two academic medical centers. Inclusion criteria were age over 18, definitive diagnosis of ONHD, and a VF within 3 months of diagnosis. Exclusion criteria were unreliable VFs and comorbidities that could alter VF results. Data were collected from the initial visit associated with the diagnosis of ONHD. Age, IOP, location of drusen (i.e. surface vs. buried), method of diagnosis, mean RNFL thickness, and MD were recorded.

Results:

A total of 239 patients were identified. Of 97 patients, 154 eyes met inclusion criteria. Mean age was 40.4 years (range, 19-76 years). Average mean deviation was -5.2 dB (range, -27.15 to +0.32 dB). Mean IOP was 15.9 mmHg (range, 6-23 mmHg). Forty eyes (25.9%) underwent Spectralis™ RNFL measurement; mean RNFL thickness was 80.8 micrometers (range, 43-117 micrometers).

Unexpectedly, there was a significant association between lower IOP and worse MD ($p=0.05$), however after adjusting for age this finding is no longer significant ($p=0.12$). There was no statistically significant association between IOP and RNFL thickness ($p=0.61$) in this study.

Conclusions:

Some have proposed that lowering IOP in patients with ONHD may prevent progression of optic neuropathy.¹ To our knowledge, this is the first large-scale study to investigate whether a correlation between IOP and optic nerve structure and function exists in patients with ONHD. This study suggests that lowering IOP may not be beneficial in this disease, as higher IOPs are not associated with either a worse visual field deviation or a thinner RNFL in this group of patients.

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Keywords: Disc Drusen, Intraocular Pressure, Visual Fields, Ocular Imaging, Optic Nerve

Financial Disclosures: The authors had no disclosures.

Grant Support: Unrestricted grant from Research to Prevent Blindness, New York, New York.

Poster 131**Electrical Fields Direct Retinal Ganglion Cell Axon Growth**

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Introduction:

Restoration of vision in patients with advanced optic neuropathies such as glaucoma requires regenerating the optic nerve (ON). A major hurdle to ON regeneration was the lack of available retinal ganglion cells (RGCs). Now that advances in stem cell biology readily allow for the production of RGCs, the rate-limiting step to ON regeneration becomes directing axons of newly transplanted cells from the retina their distant targets. While much of the current efforts to address this problem attempt to recapitulate ON development, studies suggest that an exogenous signal is needed. The body has naturally occurring electrical currents and many tissue culture experiments have shown that cells grow directionally in an electrical field. The effects of an electrical field on RGC growth, however, have never been tested. This project addresses the question of whether electrical fields can be used to direct the growth of transplanted RGC axons.

Methods:

Retina was isolated from post-nasal mice and cultured in an electrotaxis apparatus. One hour after plating, retina was exposed to various electrical fields for 6 hours. Time-lapsed microscopy was performed to record neuron and neurite movement.

Results:

In control cultures, cells and axons migrated away from the explant edge indiscriminately. In contrast, explants exposed to a continuous electrical field of 50mV/mm demonstrated no neuron or axon migration from the explant edge facing the cathode. Numerous cells and neurites were seen moving away from the explant facing the anode. Quantification of these experiments revealed a decrease in the number of RGCs that migrated towards the cathode compared to the anode.

Conclusions:

These experiments demonstrate that RGCs and/or RGC axons migrate directionally in an electrical gradient. Although further experimentation is needed, these experiments suggest that there may be a potential role for electrical currents in facilitating ON regeneration and the restoration of vision in patients with advanced optic neuropathies.

References: None.

Keywords: Orbital/Ocular Pathology, Optic Neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 132**Long-Term Evolution of Optic Disc Drusen – 57 Year Follow-Up**

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Introduction:

Optic disc drusen (ODD) are hyaline deposits in the optic nerve head. The pathophysiology remains unknown, but the formation of ODD is probably based on alterations of axoplasmic transport in the optic nerve head. Long-term evolution of ODD anatomy and visual field defects in ODD patients is a key factor for learning more about the pathophysiology and prognosis of the condition. With a mean follow-up period of 57 years, this is the first study that evaluates optic disc anatomy and visual fields in patients with ODD over a life-span.

Methods:

Funduscopy pictures and visual fields from 7 ODD patients with known hereditary ODD were compared with 57 years between examinations. Digitalized quantification was used to assess progression of visual field defects examined by Goldmann perimetry.

Results:

Mean age at initial examination was 17.4 years. Mean age at follow-up examination was 73.9 years, resulting in a mean follow-up time of 56.7 years. When comparing funduscopy pictures from the initial and follow-up examinations, a minimal or non-existing change in ODD anatomy was seen in 12 out of 14 patients. However, there was a tendency towards more anatomical change in subjects younger at first examination. A 15.8% decrease in Goldmann visual field area (cm²) using digitalized quantification was found between initial and follow-up examination.

Conclusions:

Minimal or non-existing change in optic disc anatomy and visual fields in ODD patients oldest at the initial examination suggest that anatomical progression of ODD in patients with hereditary ODD happens primarily before adulthood and then ceases. A slow progression of visual field defects are seen throughout life, but mainly occurs in younger age.

References: None.

Keywords: Optic Disc Drusen, ODD, Visual Fields, Perimetry

Financial Disclosures: The authors had no disclosures.

Grant Support: This study was supported by Værn om Synet, Synoptik Fonden and Svend Helge Arvid Schrøder og Hustru Ketty Lydia Larsen Schrøders Fond.

Poster 133

Early Treatment with Levodopa Promotes Visual Improvement in Nonarteritic Anterior Ischemic Optic Neuropathy

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Introduction:

To determine the clinical effectiveness and potential neuroprotection of levodopa in improving visual acuity, visual field, and retinal nerve fiber layer (RNFL) thickness in eyes affected by NAION.

Methods:

Retrospective cohort study involving 59 eyes of 59 participants with NAION evaluated within 15 days of NAION onset. Participants received 25mg carbidopa/100mg levodopa three times daily with meals for 12 weeks (Levodopa group) or untreated (Control group). Best corrected visual acuity converted to logMAR, mean deviation (MD) threshold sensitivity on automated perimetry, and mean RNFL thickness on optical coherence tomography (OCT) were assessed. The primary outcome was the categorization of eyes into improved visual acuity (by 0.3 logMAR difference), worsened visual acuity (by 0.3 logMAR difference), or no change in visual acuity. The proportions in each category were compared between the Levodopa and Control groups.

Results:

Among participants with 20/60 or worse initial visual acuity, Levodopa-treated participants had significant improvement ($P < 0.0001$) in the mean change from initial to final logMAR visual acuity of -0.74 ± 0.56 (95% CI, -0.98 to -0.50), while the mean change for the Control group at -0.37 ± 1.09 (95% confidence interval estimate, -1.00 to $+0.26$) was not significant ($P = 0.23$). A significant difference between groups was observed ($P = 0.0086$) such that 18/23 (78%) in the Levodopa group improved and none got worse, as compared with 6/14 (43%) in the Control group improving while 3 (21%) worsened. The change in visual field MD and RNFL thickness on OCT showed no significant difference at $P = 0.23$ and $P = 0.75$, respectively. No levodopa treated participant had any adverse event from the levodopa.

Conclusions:

Treatment within 15 days of onset of NAION with levodopa improved central visual acuity by an average of 6 lines on Snellen acuity chart. Levodopa may promote neuroprotection of the maculopapular retinal ganglion cell fibers in NAION.

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Keywords: Levodopa, Nonarteritic Anterior Ischemic Optic Neuropathy NAION, Neuroprotection, Dopamine, Optic Nerve

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 134**Comparison of Critical Flicker-Fusion Threshold Between Patients with Either Demyelinating or Ischemic Optic Neuropathy**

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Introduction:

Critical flicker-fusion (CFF) threshold is the frequency at which a flickering light is indistinguishable from a steady, non-flickering light. CFF is a well-established test to show optic neuropathy due to demyelination and other causes. The purpose of this study was to compare CFF threshold results between patients with demyelinating disease and ischemic causes of optic neuropathy. We hypothesize that demyelinating disease would have a more profound and more consistent effect on CFF compared to ischemic disease.

Methods:

We performed a retrospective review for eyes with demyelinating or ischemic optic neuropathies. Multiple independent 2-sided T-tests and Z-tests were used to compare eyes with demyelinating optic neuropathy (Group 1) from ischemic optic neuropathy (Group 2). A multivariate linear regression was performed for the dependent variable CFF.

Results:

The mean CFF value for Group 1 (20.7 Hz) and Group 2 (24.3 Hz) were not significantly different from each other ($P=0.06$). However, both CFF values were significantly less than fellow eyes from these patients (30.9 Hz) with no optic neuropathy ($P<0.01$). Roughly 71% of Group 1 and 37% of Group 2 had a CFF value of <24 Hz ($P<0.01$). The strongest factors found to contribute to the CFF value were: the type of optic neuropathy, age, duration, vision, and mean deviation by automated perimetry. Within this model Group 1 contributed to usually a CFF about 8.2 Hz lower than Group 2 ($P<0.01$).

Conclusions:

The mean critical flicker fusion value in eyes with demyelinating vs. ischemic optic neuropathies approach a statistically significant difference. A large majority of eyes with demyelinating disease have a CFF <24 Hz compared to eyes with ischemic disease. The variable with the greatest impact on CFF in our model was having demyelinating optic neuropathy. CFF may be a useful adjunct in distinguishing between demyelinating from ischemic optic neuropathy when the diagnosis is uncertain.

References: None.

Keywords: Demyelinating Disease, Diagnostic Tests, Optic Neuropathy, Neuro-Ophth & Systemic Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 135

Correlation Between Stereopsis and Reverse Stereopsis: “Turn Upside-Down the Stereo”

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Introduction:

Stereopsis is a binocular phenomenon dependent on higher order visual processing. We previously reported that although stereopsis can reliably suggest a range of visual acuity (VA) in patients with no history of strabismus¹, it cannot be used to establish a given VA. Michael Brodsky, M.D.² suggested that reverse stereovision testing in patients with bitemporal hemianopias demonstrates absence of stereopsis. The goal of this study was to compare the results of stereopsis and reverse stereopsis in patients without visual field (VF) defects before testing Dr. Brodsky's hypothesis.

Methods:

Patients seen in a neuro-ophthalmic service over a 6 month period underwent a detailed examination, including polarized vectogram stereoacuity measurements (Titmus) and VF. Patients were first tested with the stereoacuity book upright (traditional stereoacuity, “TS”) and then with the stereoacuity book rotated 180 degrees (reverse stereoacuity, “RS”).

Results:

Of 495 patients tested, we included the 98 (median age, 45 years [13-79]) who had normal VF, no ocular misalignment, and >0 circles on TS. Among these 98 patients mean score was 7.8/9 circles correct on TS and 7.5/9 on RS [p-value 0.07, paired two-tailed t-test]. 26/98 patients (26.5%) scored higher on TS than on RS (average difference, 2.3 circles), 16 patients (16.3%) scored higher on RS than on TS (average difference, 2.0 circles), and 56 patients (57.1%) scored the same on both. 64/98 patients (65.3%) scored 9/9 circles correct on TS; of those 64, 54 (84.4%) scored 8/9 or 9/9 circles, 5 (7.8%) scored 7/9 circles, 2 scored 6/9, and 1 patient each scored 5/9, 3/9, and 2/9 on RS.

Conclusions:

In a patient population presenting for neuro-ophthalmology evaluation with normal VF and without strabismus, there is no difference in TS and RS testing. Therefore, any difference found in patients with homonymous or heteronymous VF defects may relate to the VF defect itself.

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Keywords: Stereopsis, Perimetry, Visual Acuity

Financial Disclosures: The authors had no disclosures.

Grant Support: Research to Prevent Blindness National Institute of Health: EY006360

Poster 136**Improved Visual Outcomes in Giant Cell Arteritis from Prior Use of Corticosteroids May Be Dose-Dependent**

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Introduction:

The literature suggests high-dose steroids have a protective effect in preserving vision in giant cell arteritis (GCA), however, the optimal dose has not been well elucidated. Clinical observation has noted that prior use of corticosteroids may result in less GCA-related visual dysfunction. Our hypothesis was that patients with corticosteroid use prior to visual dysfunction had a dose dependent benefit with improved visual outcomes in comparison to patients not on prior corticosteroids.

Methods:

A retrospective analysis was performed of GCA patients presenting to neuro-ophthalmology clinic between 2005-2013, all satisfying the 1990 ACR-GCA criteria. Patients were divided into two groups based upon whether they were on corticosteroids at the time of ocular manifestations or not. Data was collected from the most reliable baseline neuro-ophthalmic examination. Each eye was analyzed independently. Visual acuities were recorded using a modified LogMar scale. Visual fields were assessed by mean deviation and quadrants involved.

Results:

78 patients were analyzed (65% women, mean age 75 years), 69 of whom underwent temporal artery biopsy (84% positive). 13 patients (17%) were on corticosteroids at the time of visual manifestations. Those on greater doses of corticosteroids tended to have better visual acuity outcomes with a negative correlation between the LogMar scale and corticosteroid dose (spearman rho -0.31; P=0.002). This association remained in linear regression models when accounting for prior eye disease and aspirin use (p=0.019). There was also a positive correlation between visual field mean deviations and the corticosteroid dose (spearman rho 0.26; P=0.019), remaining when accounting for confounding aspirin use (p=0.024).

Conclusions:

Prior use of corticosteroids resulted in improved visual outcomes in GCA-related visual dysfunction. This appears to be a dose-dependent effect seems to be present as demonstrated in our analyses of the visual field mean deviations and visual acuity. Larger scale studies may provide supporting evidence for the optimal dose of steroids to protect from GCA-related vision loss.

References: None.

Keywords: Giant Cell Arteritis, Optic Neuropathy, Corticosteroid Use

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 137**Reconstructive and Destructive Process in Traumatic Injuries Optic Nerve After High Dose of Corticosteroids Use**

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Introduction:

The research on the possibilities of regeneration of the optic nerve turns attention by scientist for many decades. The aim was to activate regenerative processes in the optic nerve traumatic injury at high doses of corticosteroids.

Methods:

Six mature rabbits (group injured) males, weighing 3.5-4 kg Soviet Chinchilla breeds were used as an experimental model. Additionally, 6 rabbits (treated group) on the second day after the injury were treated using a / m administration of methylprednisolone 30 mg / kg for 3 days, then the dose is gradually reduced. The control group consisted of 15 intact rabbits. Both groups of animals injured removed from the experiment using the guillotine after 2 weeks. Cranial part of both eyes the optic nerve was morphological examined. As a control, use the appropriate structure of the control group.

Results:

There were manifested MNF, which MS consisted only of a few blades of myelin, that was expressly ordered in the study of ultrathin cross sections of the right optic nerve with an electron microscope in animals treated group. Young elongated mitochondria with dense matrix and ordered cristae were founded in axoplasm of MNF. The moderate amount of microtubule clearly structured and neurofilaments were indicated the recovery of backbone and conductivity of the neural fibers. The large nucleus with dispersed chromatin and multiple clear nucleoli shallow invagination of young mitochondria and clearly arranged tank granular endoplasmic reticulum detected in the cytoplasm of neurolemocytes. Many ribosomes situated on its surface. These morphological features are evidence of active electric utility and biosynthetic processes that occur in neurolemocytes. Nevertheless, it were present MNF with widespread MS else. There lamellar structure of myelin was disorder.

Conclusions:

Consequently, results showed reduce of microcirculation swelling and remyelination of MNF that improves of activation of damaged optic nerve regeneration by corticosteroids high doses at the 14th day.

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Keywords: Traumatic Injury Of The Optic Nerve, Regeneration, Remyelination, High Doses Of Corticosteroids, Microcirculation

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 138

Optic Coherent Tomography Shows Anatomical-Functional Correlation with Visual Function of Children with Optic Pathway Glioma

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Introduction:

To describe long term follow-up of children with optic pathway glioma (OPG) and to investigate the anatomical-functional correlation between optic nerve function and nerve fiber layer thickness (NFL) as measured by optical coherence tomography (OCT).

Methods:

Medical files of 62 children, 35 with neurofibromatosis-1 (NF-1) and 27 without NF-1, diagnosed with OPG and followed between 2003-2015, were reviewed for demographic, clinical and neuro-imaging data. The correlations between visual function and OCT measurements were analyzed.

Results:

Among 258 NF-1 patients, 35 had OPG detected by routine imaging. Nine of them performed OCT. In the non-NF1 group, all were symptomatic and diagnosed with OPG at a mean age of 3.6 year (5m-17years). Mean follow-up was 6 years. Among 27 non-NF-1 children, thirteen performed OCT exam, 10 had more than one exam. In both groups, gliomas involved the chiasm(32), optic nerve(27), optic tract(10) or combination. Two of the NF-1 group and ten in the non-NF-1 had deterioration of vision during the follow-up. Imaging showed enlarged mass and intraventricular hemorrhage in two, and no change in imaging of the others. Mean OCT measurements of the 17 and 23 eyes examined in the NF-1 and non-NF-1 respectively were 85u and 62u. At the end of the follow-up, poor vision was observed in 34% of non-NF-1 (8/23) and 12% of NF-1 (2/17). Repeated OCT in non-NF1 showed thinning of RNFL in 18/20 eyes, associated with higher logMAR scores ($P < 0.001$), disc pallor, reduced color and visual field defects.

Conclusions:

The majority of NF-1 children with OPG are asymptomatic and stable, while all non-NF-1 were symptomatic. Deterioration of optic nerve function were in tight correlation with repeated OCT measurements but not with neuroimaging. OCT may serve as a better follow-up tool than MRI for children with OPG especially when considering initiating, continuing or stopping chemotherapy.

References: None.

Keywords: Optic Pathway Glioma, Optical Coherent Tomography, Neurofibromatosis, Pediatric Neuro-Ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: This study was supported in part by the Zanvyl and Isabelle Krieger Fund, Baltimore, MD

Poster 139

Update on Treatment of Radiation Necrosis with Bevacizumab

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Introduction:

Radiation Necrosis of the CNS at times involves the visual pathways, causing irreversible blindness. Standard treatment in the Ophthalmological literature includes treatment with IV Corticosteroids, Hyperbaric Oxygen treatment, and sometimes anticoagulation. Even with these treatments, the visual outcome is generally poor. The Oncologic Literature continues to support the consideration of treatment with Bevacizumab to reverse the effect of the radiation damage

Methods:

An International literature review from 2000 to 2015 was performed, and data collected, that supports the early use of IV Bevacizumab in a patient with CNS Radiation induced Necrosis. Analysis of case reports, small case studies, as well as a Double Blind Placebo Controlled Phase II trial were reviewed and then tabulated. The beneficial effect of this treatment was then compared to reports in the literature of patients treated only with Corticosteroids, versus patients treated with Corticosteroids as well as Hyperbaric Oxygen treatment.

Results:

There is a well-documented benefit of treating patients with IV Bevacizumab who suffer from Radiation Necrosis of the CNS. The improvement was both Radiologic as well as Clinical. The Oncology literature finds radiographic improvement on post treatment MRI imaging including on the post contrast T1-weighted MRI (reduction in abnormality by 48%), fluid-attenuated inversion-recovery sequences (by >50 decrease), and FLAIR images (by 50-64% reduction in volume and abnormality. The safety profile is also acceptable.

Conclusions:

Radiation optic neuropathy is a devastating form of vision loss that is usually treated with steroids and hyperbaric oxygen. Generally the visual outcome remains very poor. The Oncologic literature continues to support the treatment of this condition with IV Bevacizumab. Ophthalmologists and Neurologists, unaware of this literature, may miss an early treatment window for this condition with this alternative treatment. We believe it is the delay in treatment with this medication that limits its usefulness.

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Keywords: Radiation Necrosis, Blindness, Bevacizumab, Hyperbaric Oxygen Treatment, Optic Neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 140**A Photothrombotic Model of Optic Neuropathy Using Mesoporphyrin IX: Our Experience with Rats vs. Mice**

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Introduction:

We recently developed a photothrombotic model of optic neuropathy in rodents using mesoporphyrin IX as the photosensitizer. While originally considering similar laser parameters for both rats and mice, our experiments showed that the optic nerve (ON) response to the photodynamic treatment applied was very different between the two species. We present here some of the challenges faced, especially when trying to set up this model in mice.

Methods:

Laser (532nm) was applied to the ON of Brown Norway rats and C57BL/6 mice before or after an intraperitoneal injection of mesoporphyrin IX. Various laser parameters were tested. Funduscopy, fluorescein angiography (FA) and spectral domain optical coherence tomography (SD-OCT) were performed at different time points to evaluate the result of the laser applied.

Results:

The laser power output and duration of laser treatment were found to be the most significant factors in determining the type and extent of ON lesion induced. Laser parameters previously used to induce ON ischemia in rats - ie. 50mW, 12sec, 500um - successfully led to ischemic injury after mesoporphyrin IX injection, as determined by the fluorescein leakage and retinal edema shown on the FA and OCT, respectively. On the contrary, in mice, application of 50mW laser for 3 seconds using a 300um spot proved to be too powerful, leading to occlusion of major retinal vessels even without having administered any mesoporphyrin IX.

Conclusions:

Photodynamic therapy with Mesoporphyrin IX can lead to ischemic ON injury in rats without much difficulty. On the other hand, standardizing the laser parameters to be used in order to induce the desired ON lesion in mice proved to be quite challenging. Given that laser treatment alone can have extensive vasoocclusive effects in mice, it is advisable to thoroughly examine laser parameters prior to commencing projects using with photothrombotic models.

References: None.

Keywords: Ischemic Optic Neuropathy, Photodynamic Treatment, Mesoporphyrin IX, Animal Model

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 141**The Photopic Negative Response as an Objective Measurement of Visual Function in Patients with Leber's Hereditary Optic Neuropathy**

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Introduction:

The photopic negative response (PhNR) is a slow negative component of a flash photopic full field ERG which has been shown to be specific for retinal ganglion cell (RGC) activity. Direct evaluation of RGC function is important in patients with Leber's Hereditary Optic Neuropathy (LHON) in which functional improvement with Idebenone and EPI-743 can take years to be clinically measurable, presumably due to the time required for CNS remodeling. Thus there is a need for objective non-invasive clinical metric in patients with LHON which does not rely on fixation and has the promise of directly measuring RGC activity. The purpose of this study was to evaluate the use of PhNR as a potential clinical metric for patients with LHON.

Methods:

Full field ERG recordings using a sequence of 50 brief red flash stimulus on blue background were collected in eight subjects with LHON using standard ERG recording techniques. The PhNR was identified using a computer based automated detection system and data was manually examined to remove movement artifacts. The Humphrey Visual Field mean deviation and visual acuity was correlated to PhNR amplitudes in patients with LHON.

Results:

The PhNR was recordable in most patients with LHON. The PhNR amplitude decreased with decreasing HVF mean deviation. The PhNR amplitude and HVF were best fit by an exponential decay function ($r^2=0.71$). There was no meaningful correlation between decimal visual acuity and PhNR amplitude ($r^2=0.21$).

Conclusions:

PhNR may be a useful objective clinical metric in patient with decreased visual function and central scotomas from LHON. The strong correlation between HVF mean deviation and PhNR amplitude suggest that this may be a useful objective outcome measure for future clinical trials.

References: None.

Keywords: Optic Neuropahty, Visual Fields, Diagnostic Tests

Financial Disclosures: The authors had no disclosures.

Grant Support: This study was supported by an unrestricted research grant from Stealth Biotechnology.

Poster 142

Neuro-Ophthalmic Manifestations of Costeff Syndrome

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Introduction:

Type III 3-methylglutaconic aciduria (OPA III) is a neuro-ophthalmologic syndrome consisting of early-onset bilateral optic atrophy caused by mutation c.143-1G>C variant. Since Costeff described phenotype of 19 patients in 1989 several reports described approximately 40 patients, but most of them lack details about neuro-ophthalmic phenotype. Our aim was to characterize the clinical course of the neuro-ophthalmic manifestations of this syndrome.

Methods:

Consecutive patients seen at the neuro-ophthalmology unit were included. All patients underwent comprehensive neuro-ophthalmic evaluation including meticulous visual function history and medical documents review. Best corrected visual acuity, color vision evaluation, visual field testing, and motility, pupillary, slit lamp and dilated fundus examinations were recorded. Optical coherence tomography (OCT) performed whenever possible due to poor fixation.

Results:

Nine patients were evaluated (6 females). Poor vision was the presenting symptom in 4 patients. Average visual acuity (VA) was 1.5 logMAR. Humphrey visual field performed by 5 patients revealed generalized depression with temporal loss. All demonstrated dysmetric saccades. Four had strabismus, 3 exotropia, 1 esotropia. Seven patients demonstrated nystagmus. OCT testing was possible in 6 patients that revealed nerve fiber and retinal thinning. VA correlated with age possibly implying some progression over time.

Conclusions:

This study compiled information regarding neuro-ophthalmic manifestation of OPA III patients. Contrary to established literature poor vision was the presenting symptom in only 50% of our patients. All had decreased VA and variable degree of optic atrophy as previously reported. Nystagmus found as reported previously. Dysmetric saccades found might be the result of the cerebellar atrophy found on MRI of our patients. The thinning of RNFL was expected but the retinal thinning, even in the young patients, might be the result of ganglion loss found also in OPAI. The results may help informing the young patients about visual prognosis. Similarly, OCT may help monitoring experimental therapies when available.

References: None.

Keywords: Optic Neuropathy, Genetic Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 143**Pediatric Optic Neuritis Prospective Outcomes Study**

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Introduction:

The Optic Neuritis Treatment Trial (ONTT) provided a vast amount of knowledge with regard to ON in adults. Despite this, there are little prospective data related to pediatric ON(PON). There are differences between adult and PON that may impact visual recovery and the diagnosis of MS. Furthermore, no studies have prospectively evaluated other metrics such as low contrast visual acuity (LCVA), retinal nerve fiber layer thickness (rNFL), or quality of life (QOL) in PON.

Methods:

This study will be conducted by the Pediatric Eye Disease Investigator Group (PEDIG) with cooperation of the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC), funded through PEDIG. The pilot study includes two years of enrollment and two additional years of follow-up of up to 100 subjects (3 to <16 years) for prospective data collection to assess the ability to enroll sufficient patients for a future randomized controlled trial, and to evaluate clinical outcomes in this population. The primary clinical outcome measure is visual acuity. LCVA and, if performed, optical coherence tomography of the rNFL and ganglion cell thickness will be collected. In addition, NMO antibody and QOL measures will be analyzed. Treatment decisions will be at investigator discretion.

Results:

The primary outcomes are to (1) assess feasibility for enrollment into a PON protocol, and (2) assess the cohort's visual acuity at 6 months from enrollment. Secondary aims will include the characterization of PON in a multicenter cohort of children, visual acuity at 1 and 2 years, rNFL measurements, and satisfying the diagnosis MS at 2 years.

Conclusions:

This study represents an opportunity for our neuro-ophthalmic and the pediatric-ophthalmic communities to work together to collect data on a rare disease. We are excited at the prospect that this collaboration brings not only for PON but potentially for other rare pediatric neuro-ophthalmic diseases. We welcome participation from all interested members of both NORDIC and PEDIG.

References: None.

Keywords: Pediatric Optic Neuritis

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 144**Visual Outcomes of Diabetics and Prognostic Factors in Non-Arteritic Ischaemic Optic Neuropathy**

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Introduction:

Diabetics have a greater risk of non arteritic ischemic optic neuropathy (NAION) but visual outcomes compared with non-diabetics are unknown. Aims: To compare visual outcomes, prevalence of bilateral /sequential ION and risk factors for NAION in diabetics and non diabetics. To identify prognostic factors for poor visual outcomes in NAION

Methods:

This was a retrospective cohort study of diabetics and non-diabetics with a clinical diagnosis of NAION, presenting within 4 weeks of symptom onset with follow up for >3 months. Using population average logistic regression models, we assessed risk factors for visual prognosis.

Results:

The median follow-up duration was 24.6 weeks in diabetics and 34.5 weeks in non diabetics. 87.5% presented within 2 weeks of symptom onset. In non-diabetics, the most prevalent risk factor was a small disc:cup ratio (70%); for diabetics, they were hypertension (87%), hyperlipidaemia (84%), "disk-at-risk" (51%). 31% diabetics and 21% non-diabetics had sequential NAION. 50% of non-diabetics present/complete follow up with >20/40 VA. 33% of diabetics, present/complete follow-up with >20/40. Similar proportions of diabetics and non-diabetics (17%, 21%) present with or have a final vision of <20/100 (35%, 30%) Final VA in those with >6 months demonstrates no difference between diabetics and non diabetics (p=0.7). Ischemic heart disease (IHD) (OR 5.4 p=0.002) and age (OR 1.5 p=0.05) prognosticate for final VA <20/100. Presence of diabetes does not impact visual outcome. Patients with sleep apnea are less likely to have worse VA (OR=0.22, p=0.04).

Conclusions:

Only 50% of diabetics have a disk-at-risk configuration while this is present in 70% of non-diabetics. The natural history of vision in diabetics with NAION is not significantly different from non-diabetics although they have a higher prevalence of cardiovascular risk factors and higher prevalence of sequential NAION. Of all risk factors, including diabetes, only ischemic heart disease and age independently prognosticate for poor visual outcome.

References: None.

Keywords: Optic Neuropathy, Vascular Disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 145

Categorization and Staging of Retinal Degeneration Using Pathway-Specific Alterations in Retinal Ganglion Cell Stimulus-Response Relationships

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Introduction:

To improve categorization and staging of retinal degenerations, we sought to identify disease-specific alterations in retinal signal processing pathways. We adapted a method to distinguish specific subclasses of ON and OFF responses in retinal ganglion cells (RGCs) using stimulus-response (S-R) relationships (Volgyi et al, J Neurosci 2004) and identifying specific shifts in sensitivity, gain, and dynamic range.

Methods:

We used *in vitro* multielectrode recording to sample ON and OFF responses of individual RGCs to full field flash stimuli of 17 intensities (0-34 $\mu\text{W}/\text{cm}^2\cdot\text{s}$, 1 sec) presented in randomized order, in the retina of 14 day old wild-type (*wt*) and *rd1* mice. For each RGC the number of spikes during the 1 sec following flash on- or offset was plotted vs. stimulus intensity and fit to a Michaelis-Menten relationship, and responses were classified into several types according to parameters extracted from the best fit curves for all cells in each strain.

Results:

In both *wt* and *rd1* mice, ON cells segregate into three and OFF cells into four groups, comparable to mature RGCs (Volgyi et al). For most response groups, *rd1* curves were right-shifted parallel to *wt* curves, but high-sensitivity ON and OFF *rd1* cells had decreased slope (gain) relative to *wt*, whereas low-sensitivity OFF *rd1* cells had a more markedly elevated threshold and steeper slope (gain). This pattern suggests differential changes in photoreceptor input to ON and OFF pathways, or in bipolar and amacrine cell circuits that modify them.

Conclusions:

Shifts in the parameters of RGC S-R curves occur as degeneration progresses in the *rd1* mouse. The nature and degree of these changes differ among subgroups of RGCs, suggesting distinctive signatures for particular forms of retinal degeneration. We are investigating characteristic shifts in S-R curves in other models of retinal degeneration. Ultimately, this method may help diagnose and stage patients with blinding diseases.

References:

Volgyi B, Deans MR, Paul DL, Bloomfield SA. Convergence and segregation of the multiple rod pathways in mammalian retina. J. Neurosci. 24:11182-11192, 2004.

Keywords: Retina, Retinal Degeneration, Ganglion Cells, Electrophysiology, Pediatric Neuro-Ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: March of Dimes Research Award # 12-FY11-200.

Meningiomas of the Optic Nerve. Lessons Learned Over Three Decades

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Introduction:

Optic nerve sheath meningiomas, considered rare in the past, represent one-third of tumors affecting the optic nerve. The advent of imaging studies has dramatically increased our ability to make this diagnosis usually (without resorting to tissue biopsy). Published case series are small and it can be difficult to draw conclusions based on duration of follow up (especially as slow growing). The role of OCT is evolving.

Methods:

A retrospective review of 31 patients seen with optic nerve meningiomas with long-term (up to 34 year) follow-up. Attention was particularly directed to the results of natural history, radiation therapy, and the use of OCT.

Results:

Most patients were referred for progressive visual loss (several were picked up fortuitously by imaging). Visual acuity at the time of referral ranged from 20/20 to NLP. OCT often showed swelling and “green disease” with either normal or only minimally reduced nerve fiber layer thickness in spite of clear evidence of optic neuropathy (afferent pupillary defect, visual field changes, and decreased central acuity).

Conclusions:

Although the good news about meningiomas is they grow SLOWLY, the bad news about meningiomas is they GROW slowly. Although obviously variable in natural history, most of these patients over time (if untreated) will have worsening visual function. Fractionated radiation therapy (both conventional radiation therapy and proton beam) can result in dramatic improvement in function, reduction of disc edema, and resolution of opticociliary shunt vessels. While progression in spite of treatment is possible, the vast majority of cases do very well. In view of the immediate effect of radiation therapy on disc swelling, it is probably not necessary to wait for clear progression before instituting radiation therapy. Rare cases of involvement of the optic canal, if ectopic, may be treated with surgery, but this is unlikely to be of benefit in the majority.

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Keywords: Optic Nerve Sheath Meningioma, Stereotactic Radiation Therapy, Proton Beam Therapy, OCT

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 147**Autologous Bone Marrow Derived Stem Cells for Treatment of Neuro-Ophthalmic Disorders: Report of 25 Patients**

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Introduction:

The new field of reparative and regenerative medicine has exploded with genetic therapy methods, stem cell therapy options (foreign or autologous fat, skin, bone marrow), and new drug therapies. We report the effect on the vision of 25 neuro-ophthalmology patients with bilateral visual loss using autologous bone marrow derived stem cell (BMSC) therapy, which requires no immunosuppression.

Methods:

Twenty-five patients from the Midwest with bilaterally blinding disorders entered the Stem Cell Ophthalmology Treatment Study (SCOTS), approved by the University of South Florida's IRB, registered with the NIH (NCT01920867 on www.clinicaltrials.gov) to recruit 300 patients (2013-2016). It is funded by the patients. These authors, not a part of that study, agreed to do pre-op and 3,6,9,12 month post-op exams, reducing families' expense and travel time. Data collected included: visual acuity by Snellen and ETDRS, anterior and posterior segment exams, visual fields (Humphrey, Goldmann or both), and OCT measurement of macular and peripapillary RNFL thickness. Each eye was assigned to: Arm 1: periocular (PO) injections BMSC, with intravenous (IV) injections; Arm 2: intravitreal intraocular (IO) injection, plus PO and IV; or Arm 3: vitrectomy plus intra-retinal or intra-nerve injections of stem cells plus PO, IV and IO as above.

Results:

25 patients (47 eyes) were treated: 20 patients with optic nerve disorders, 5 with retinal disorders. 27/47 eyes (58%) gained visual acuity, 13 (28%) neutral (+ or -3 letters), 3 eyes (6%) lost acuity, 4 eyes (8%) too soon to report. Visual fields improved in most eyes. OCT macular thickness peaked at 1 week to 7 months. 13 of 19 genetic disorder eyes improved (68%) with autologous DNA stem cells. 14 of 28 acquired disorder eyes improved (50%). Only 1 of 6 NLP eyes regained bare LP.

Conclusions:

SCOTS benefits: >60% improved vision, 22/25 patients more independent, active, happy.

References:

Weiss, Levy, Benes, Stem Cell ophthalmology treatment study (SCOTS) for retinal and optic nerve diseases: a case report of improvement in relapsing auto-immune optic neuropathy, Neural Regeneration Research, vol 10, pp 1507-1515, 2015.

Keywords: Optic Neuropathy, Retina, Genetic Disorders, Therapy, Autologous Stem Cells

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 148**Clinical Features of Optic Neuritis in Patients over 45 years-old.**

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Introduction:

Optic neuritis typically occurs in younger patients with a peak incidence in the third and fourth decade of life. Clinical and radiographic features of patients with optic neuritis older than age 45 have not been previously published.

Methods:

Retrospective review of cases of optic neuritis in patients older than 45 years-old treated at a tertiary care center from 2003 to 2014. Clinical features, MRI results, Humphrey visual field results were recorded and analyzed. Inclusion criteria are age > 45 years-old, first episode of optic neuritis in a given eye, and recovery defined as improvement of 2 lines of visual acuity or 3 dB on Humphrey automated perimetry. Exclusion criteria included bilateral optic neuritis, steroid dependence, and severe vision loss or mild vision loss without the previously defined recovery.

Results:

We project having 50 patients. To date, 11 patients met the criteria above, of which 7 were female. Average age was 56.7 years-old. 9 of 11 had eye pain. 1 had optic disc swelling. Initial visual acuity was $\leq 20/40$ in 4, 20/50 to 20/190 in 4, and $\geq 20/200$ in 3. Subsequent acuity was $\leq 20/40$ in 10, 20/50-20/190 in 1, and $\geq 20/200$ in 0. Initial automated perimetry in 8 patients showed an average mean deviation of -11.0 dB. Improvement on subsequent automated perimetry in 7 patients was 7.1 dB. MRI was done in 10 cases. The optic nerve showed abnormalities in 7 and the brain showed abnormal T2 lesions in the white matter in 7. Average follow up was 2.0 years with no diagnoses of multiple sclerosis.

Conclusions:

Compared to the Optic Neuritis Treatment Trial, the clinical characteristics were similar. Imaging showed a similar rate of optic nerve abnormalities. Although there were a higher percentage of patients with abnormal brain MRI, no patients progressed to develop multiple sclerosis.

References: None.

Keywords: Demyelinating Disease, Neuroimaging, Visual Fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 149

Transcorneal Electrical Stimulation in Optic Neuropathies

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Introduction:

Aim was to achieve improvement in vision and visual fields in optic neuropathies by transcorneal electrical stimulation (TES) .

Methods:

20 patients with non-arteritic anterior ischemic optic neuropathy and 10 patients with traumatic optic neuropathy were stimulated 40 minutes per day for 10 consecutive days by TES. Patients with optic neuropathy were treated 2 months after the acute event.

Results:

In both groups, improvement in vision and visual fields was achieved. The average visual acuity improvement in the two groups was 2 Snellen lines. Visual field improvements after 10 days of TES were documented. Expansion of fields reached approximately 25 percent. This was found to be highly significant. (p: 007)

Conclusions:

TES may be considered as a safe and effective treatment in certain optic neuropathies.

References: None.

Keywords: TES, AION, TON

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 150

Aquaporin 4 Antibody in the Korean Patient with Newly Onset Optic Neuritis

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Introduction:

To evaluate the prevalence of aquaporin 4 antibody (AQP4-Ab) in the newly onset optic neuritis patients and investigate the characteristics of seropositive patients.

Methods:

36 women and six men with newly onset isolated optic neuritis were included in this study between January 2013 and December 2014. AQP4-Ab was detected and all blood samples was obtained prior to treatment and within one week from attack. The patients were sub-grouped into either a seropositive group or a seronegative group according to AQP4-Ab. Differences in age, gender, initial visual acuity, and final visual acuity between groups were analyzed.

Results:

Six (14.3%) of these patients (five women and one man) exhibited AQP4-Ab. There was no significant difference in mean age between study groups (positive group: 38.7 ± 11.5 years, negative group: 42.3 ± 14.7 years, $P=0.548$). Bilateral simultaneous involvement was more common in seropositive patients than in seronegative patients (occurred in two out of six seropositive patients and in one out of 36 seronegative patients, $P = 0.007$). With regards to poor visual outcome (worse than 1.0 LogMAR), seropositive patients exhibited more severe visual loss than seronegative patients. None of the seropositive patients exhibited myelitis symptoms during the follow-up period (mean follow-up period: 8–32 months).

Conclusions:

The prevalence of AQP4 antibody was often detected in the newly onset optic neuritis patients. In the patients with bilateral involvement or poor initial visual acuity, the AQP4 antibody test should be considered.

References: None.

Keywords: Optic Neuropathy, Demyelinating Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 151**Change of Th17 lymphocytes and Treg/Th17 in Typical and Atypical Optic Neuritis**

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Introduction:

Typical and atypical optic neuritis (ON) are two types of autoimmune inflammatory diseases of the optic nerve that causes acute vision loss, and which are difficult to distinguish in their early stages. The disturbance in the balance of Th17 and Treg lymphocytes is thought to play an essential role in these autoimmune inflammatory diseases. To detect the clinical relevance of Th17 and Treg in peripheral blood and the ratio of Treg/Th17 in patients with typical and atypical ON. To explore potential methods with which to distinguish typical and atypical ON based on their distinct pathogenesis.

Methods:

We studied consecutive patients aged 14-70 years with typical ON (n=30) or atypical ON (n=33) within 4 weeks of their acute attack. Routine clinical tests and ophthalmological examination were performed in all patients. Blood samples were collected from untreated patients and from gender- and age-matched healthy controls (n=30). The proportion of peripheral blood Th17 cells and Treg cells was determined by flow cytometry.

Results:

Patients with atypical ON had a higher proportion of Th17 cells than patients with typical ON (3.61 ± 1.56 vs 2.55 ± 1.74 , $p < 0.01$) or controls (1.45 ± 0.86 , $p < 0.01$). The proportion of Th17 cells in patients with typical ON was also markedly higher than in controls ($p < 0.01$). The mean percentage of Treg cells in atypical ON (6.31 ± 2.11) and typical ON (6.80 ± 2.00) were significantly lower when compared to controls (8.29 ± 2.32 , both $p < 0.01$). No significant difference in Treg frequency was observed between typical ON and atypical ON ($p > 0.05$).

Conclusions:

The frequency of Th17 cells is higher in atypical ON than typical ON, and patients with atypical ON have a greater imbalance of proinflammatory and regulatory cells than patients with typical ON when compared with controls. These changes are indicative of distinct pathological mechanisms and may provide useful information to distinguish typical and atypical ON.

References: None.

Keywords: Demyelinating Disease, Optic Neuropathy, Th17 Cell, Treg Cell, Treg/Th17 Ratio

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 152**Vitamin A deficiency presenting as unexplained visual loss to neuro-ophthalmology clinic**

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Introduction:

Vitamin A is fat soluble nutrient, essential for conjunctival and corneal epithelial cells, retinal photo-transduction, and RPE cell viability. Vitamin A deficiency can cause night blindness, retinopathy and xerophthalmia. More common in developing countries due to malnutrition than in developed countries, where it is usually secondary to malabsorption. We present here a case series of vitamin A deficiency patients, presenting as unexplained visual loss to our neuro-ophthalmology clinic. We characterize the precipitating factors, demographics and workup leading to diagnosis and treatment.

Methods:

10 adult patients were seen over a 15 year period in a single neuro-ophthalmology practice presenting with visual loss. All patients had low vitamin A levels and vision improved after replacement treatment.

Results:

Of the 10 patients, 3 were male 3, 7 female. The average age was 58 years (range 42-72). The median number of encounters before neuro-ophthalmic exam was 2 (range 0-6). The average duration of symptoms was 6 months (range 1-12). 3 patient had an MRI, and 1 patient had a CT prior to the referral. Most common referral diagnosis was optic neuropathy. No patients had any other signs of vitamin A deficiency. All patients had recovery after treatment. The precipitating factors were: abdominal/bariatric surgeries (5 patients), pancreatitis (2 patients), cholecystectomies (2 patients), and in one patient the cause was believed to be caused by medication (Deferasirox-oral iron chelator).

Conclusions:

Vitamin A deficiency is an underdiagnosed cause of vision loss that can be seen in patients with no clear cause for vitamin deficiency and with no other signs of hypovitaminosis. Patients may not complain of night vision difficulties, which can delay the diagnosis. With normal exam, a long, time consuming and costly work up to the patient and the health system. Instead, a simple blood test and a trial of supplement vitamin A can improve or even resolve the symptoms quickly.

References: None.

Keywords: Vitamin A, Deficiency, Vision loss

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 153**Hemiatrophy of Macular Ganglion Cells in Patients with Retrochiasmal Lesions**

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Introduction:

Lesions in the optic tract or along the thalamocortical pathway cause a homonymous hemianopia. Irreversible retrochiasmal damage may lead to optic atrophy. As the macular area is overrepresented in the afferent visual system, a retrochiasmal lesion may be best detected at the level of the macula. We sought to determine the anatomic changes of the macular ganglion cell layer in patients with retrochiasmal lesions.

Methods:

In a consecutive retrospective case series we included 85 eyes from patients with homonymous hemianopia and macular optical coherence tomography (OCT). We used automatic layer segmentation to determine thickness of individual retinal layers.

Results:

We found that a significant portion of patients with lesions at the level of the optic tract, the optic radiation or the visual cortex displayed ganglion cell loss in the macula. The ganglion cell loss respected the vertical meridian leading to a characteristic macular ganglion cell 'hemiatrophy'. In contrast to the disc fovea angle, the vertical meridian separating the temporal and nasal hemiretina was not tilted.

Conclusions:

Macular ganglion cell layer analysis in patients with retrochiasmal lesions allows a better topical diagnosis with a higher sensitivity than can be achieved with assessment of the optic disc. The vertical respect that is important in the visual field analysis has an anatomic pendant in the macula.

References: None.

Keywords: Optical Coherence Tomography, Ganglion Cell, Optic Tract, Atrophy, Retrograde Degeneration

Financial Disclosures: The authors had no disclosures.

Grant Support: This study was supported by the Swiss National Science Foundation

Poster 154

Disorders of Higher Visual Processing in Patients after Stroke

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Introduction:

Damage to specific areas outside the primary visual cortex can cause selective deficits of higher visual processing. Patients with stroke may have undetected abnormalities of higher visual processing because these are not routinely assessed. If present, these could impact significantly on recovery and residual function. This pilot study aimed to determine the extent of these abnormalities in patients who had recovered from stroke.

Methods:

26 patients (65.5 ± 13.9 years; 12 female) who had recovered from stroke were compared with 29 age-matched controls (67.6 ± 13.1 years; 17 female). Ophthalmological causes of visual loss were excluded. Higher visual function was assessed using Ishihara charts and Farnsworth-Munsell D15 (FMD15), kinematography, random dot testing (depth), stereofly, line bisection, and the Cambridge facial memory test (CFMT).

Results:

Looking at the entire group, stepwise regression showed that random dot and CFMT were the most significant predictors of stroke ($F_{1,77} = 5.08$, $p = 0.027$). At a false positive rate of 10%, random dot classified 38.4% (± 17.6% SE) of patients and CFMT classified 28.0% (± 9.1% SE). Principal component analysis revealed two independent factors which accounted for 29.9% and 21.3% of the variance, respectively. Variables which contributed significantly to the first factor were random dot, FMD15, CFMT and kinematography. Line bisection, Ishihara and CFMT contributed to the second factor. The receiver operator characteristic yielded an area under the curve of 0.75 ± 0.071 (mean ± SE).

Conclusions:

Many patients with stroke had undetected abnormalities of higher visual processing. As a group, this was most obvious in terms of random dot testing for depth perception. These findings have potential relevance to the process of rehabilitation and to residual post-stroke function. Further investigation in the form of a larger trial is warranted.

References: None.

Keywords: Higher Visual Cortical Functions, Stroke

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 155**Measuring Axonal Loss with Serial OCT Testing in Multiple Sclerosis Patients: Methods and Yield**

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Introduction:

In patients with multiple sclerosis (MS), OCT demonstrates evidence of acute axonal loss after attacks of optic neuritis and chronic progressive axonal loss even without optic neuritis. We evaluated three methods of measuring retinal ganglion cell (RGC) axonal loss in the eyes of individual MS patients, using serial tests of optical coherence tomography (OCT).

Methods:

We performed a retrospective study of serial spectral-domain OCT tests in a cohort of 50 MS patients (92 eyes) from a single clinical center and laboratory. Tests were conducted at least six months apart to assess change over time (mean interval, 2.3 years). Standard assessments included peripapillary retinal nerve fiber layer (RNFL) thickness and macular segment volumes. We also quantified optic nerve head (ONH) volumes, as previously described.

Results:

Of 92 eyes, 23 eyes (25%, 18 patients) met at least one criterion for significant reduction between tests: mean or temporal RNFL thickness (≥ 7 microns), ganglion cell + inner plexiform layer (GC+IP) volume (≥ 0.09 mm³) or ONH volume (≥ 0.09 mm³). Of these 23 eyes, seven exceeded thresholds for significant loss for all three measures. Seven other eyes did so for two measures. RNFL thickness, GC+IP volume and ONH volume were equally sensitive in detecting change. Only 1/23 eyes had a clear interval history of optic neuritis, while 5/23 had vaguer histories of visual blurring or eye pain between tests.

Conclusions:

Serial OCT testing has a reasonably high yield for identifying evidence of RGC axonal loss over time in individual MS patients, even when there is no interval history suggesting optic neuritis. Studying ocular anatomy in more than one area may increase detection and certainty of change. North American Neuro-Ophthalmology Society | 315

Keywords: Diagnostic Tests, Demyelinating Disease, Optic Neuropathy Retina, Neuro-Ophth & Systemic Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 156

Perceptual Learning Treatment of Amblyopia in Adults

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Introduction:

Recently a perceptual learning-based video game (ULTIMEYES) has been developed for treatment of various low vision conditions. The game task involves the detection of low contrast sine gratings of varying spatial frequency, where contrast is controlled adaptively to maintain performance at threshold levels. This program has previously not been utilized for amblyopia.

Methods:

This pilot study enrolled 9 adults (mean age 32 years; range 16-49) diagnosed with strabismic or anisometropic amblyopia, who had previously undergone patching treatment, and whose visual acuity in the amblyopic eye ranged from 20/40 to 20/200. Subjects underwent pre- and post-treatment testing using high and low contrast visual acuity optotypes and sensory measures including Worth-4-dot and stereoacuity at distance and near. Prescribed treatment consisted of four sessions of 20 minutes each per week for 8 weeks. The therapy was performed binocularly with the use of a polarizing filter over the dominant eye to minimize contribution ability of that eye.

Results:

Following treatment there was a statistically significant improvement in amblyopic eye ETDRS visual acuity averaging 5 letters ($p < 0.01$). Suppression on the Worth-4-dot tests at distance was reduced from 6/9 subjects pre-treatment to 3/9 subjects post-treatment.

Conclusions:

ULTIMEYES is a perceptual-learning based therapy. Pilot data shows that 8 weeks of therapy in adults leads to significantly improved visual acuity and reduced suppression. Further study is needed in order to determine long-term effects, and compare to placebo and established amblyopia treatments. ULTIMEYES shows promise as a perceptual-learning technique to improve visual acuity and binocularity in amblyopic adults.

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Deveau and Seitz (2014). Applying Perceptual Learning to achieve practical changes in vision. *Frontiers in Psychology*, doi: 10.3389/fpsyg.2014.01166

Keywords: Adult Amblyopia, Perceptual Learning

Financial Disclosures: The authors had no disclosures.

Grant Support: NIH/NEI, Research to Prevent Blindness.

Poster 157

Imaging Features of Idiopathic Intracranial Hypertension (IIH) in Children

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Introduction:

MRI signs of intracranial hypertension are very common in adults with IIH in whom they are well characterized.¹ Our goal was to determine whether these findings are also present in children.

Methods:

50 children (<18yo) with definite IIH and an MRI performed at our institution (2007-2015) were included. Two expert neuroradiologists assessed MRIs for optic nerve head protrusion, scleral flattening, increased perioptic CSF, optic nerve tortuosity, sellar changes, enlargement of Meckel's cave, cerebellar tonsillar position, and transverse venous sinus stenosis. Findings were compared with those of 46 previously collected adult IIH patients meeting the same inclusion criteria.²

Results:

50 IIH children included 42 girls (26 black, 20 white, 4 other; mean age, 12.8yo [range 2-17]). Patients were analyzed in groups of prepubescent children (<11 years; n=10) and adolescents (11-17 years, n=40), and were compared to adults with IIH (>17yo, n=46). Compared to adolescents and adults, prepubescent children had a lower mean BMI (20.8 vs. 35.3 and 37.9, p<0.001), frequency of scleral flattening (50% vs. 89% and 85%, p=0.02), sellar changes (56% vs. 78% and 93%, p=0.007), perioptic increased CSF (60% vs. 84% and 89%, p=0.08), optic nerve tortuosity (20% vs. 46 % and 59%, p=0.07), and transverse sinus stenosis (67% vs. 93% and 96%, p=0.04). Adolescents had higher mean CSF-OP than prepubescent children and adults (47.8 vs. 37.0 and 36.7 cm, p<0.001). Median duration of symptoms prior to MRI was 5 weeks (range 4-12 weeks) in prepubescent children, 2 weeks (range 1-16 weeks) in adolescents, and 5 weeks (range 0-196 weeks) in adults (p=0.001).

Conclusions:

MRI findings of adolescents with IIH were similar to those described in adults. Prepubescent children (<11yo) with IIH have similar MRI findings as previously described in adults, although at a lower prevalence. This may suggest a different response of the brain and associated tissues in prepubescent children to elevated ICP.

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Keywords: Pediatric Neuro-Ophthalmology, Idiopathic Intracranial Hypertension, Neuroimaging, High Intracranial Pressure/Headache

Financial Disclosures: The authors had no disclosures.

Grant Support: Research to Prevent Blindness NIH/NEI:P30-EY006360.

Poster 158

Women with Idiopathic Intracranial Hypertension (IIH) Have a Distinct Andro-Metabolic Signature Compared to Polycystic Ovary Syndrome (PCOS) and Simple Obesity

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Introduction:

Idiopathic intracranial hypertension (IIH) is characterised by elevated intracranial pressure and occurs predominantly in obese premenopausal women. Polycystic ovary syndrome (PCOS) can coexist in IIH and patients have similar phenotypes. Here we compared the androgenic and metabolic phenotypes in IIH, PCOS and simple obesity.

Methods:

We studied 25 patients with IIH (mean age 34.4±9.2 years; mean BMI 37.8±5.2kg/m²), in comparison to 31 women with PCOS and 15 with simple obesity; all three groups were matched for age and BMI. Women with IIH were studied before and after a weight loss intervention (mean BMI change -5.8±3.0kg/m²). In all participants we performed comprehensive metabolic phenotyping and steroid profiling. Serum androgens were measured by liquid chromatography-tandem mass spectrometry; 24-hour urinary steroid excretion was analysed by gas chromatography/mass spectrometry. Urinary steroid profiles were correlated with clinical parameters of IIH severity.

Results:

Serum testosterone (T) in IIH was comparable to PCOS and significantly higher than controls (p=0.01). Serum androstenedione (A) was significantly increased in PCOS (p=0.008) but IIH did not differ from controls. Insulin resistance as assessed by HOMA-IR did not differ between IIH and controls. Total glucocorticoid excretion was significantly higher in IIH compared to controls (p=0.01) and decreased after weight loss (p=0.02). Similarly, the urinary ratio of 5α-THF/THF, a marker of systemic 5α-reductase activity, was significantly increased in IIH compared to controls (p=0.04). The An/Et ratio correlated significantly with baseline markers of papilloedema (Optical Coherence Tomography) in IIH (R=0.47, p=0.02).

Conclusions:

These results indicate a distinct andro-metabolic signature in IIH, characterised by increased testosterone but not androstenedione. In IIH, Testosterone and 5α-reductase activity falls following therapeutic weight loss alongside a significant reduction in disease activity (intracranial pressure and papilloedema). These findings may be driven by increased activity of the enzyme aldoketoreductase type 1C3 (AKR1C3) which activates androstenedione to testosterone in adipocytes.

References: None.

Keywords: Idiopathic Intracranial Hypertension, Pathogenesis, Androgen Profile, Poly Cystic Ovary Syndrome

Financial Disclosures: The authors had no disclosures.

Grant Support: Dr Alexandra Sinclair is funded by an NIHR Clinician Scientist Fellowship (NIHR-CS-011-028) and by the Medical Research Council, UK (MR/K015184/1). This work was supported by the West Midlands Neuroscience Teaching and Research Fund.

Poster 159

Headache Characteristics in Pediatric Patients with Definite Pseudotumor Cerebri Syndrome and Intracranial Hypertension

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Introduction:

Revised diagnostic criteria for Pseudotumor Cerebri Syndrome (PTCS) were published in 2013[1]. This manuscript did not suggest a specific diagnosis for patients in whom there was clinical suspicion for PTCS where data did not support the diagnosis. Clinically it is unclear whether patients without papilledema who have headache features suggestive of increased intracranial pressure benefit from lumbar puncture and/or medications used to lower cerebrospinal fluid(CSF) pressure.

Methods:

In this study we performed a retrospective review to characterize the headache features of 59 subjects with Definite PTCS (47 primary, 12 secondary) and 30 with Intracranial Hypertension (IH) who did not meet criteria for PTCS.

Results:

Headaches were present in all subjects with Definite PTCS and 29/30 with IH. There was insufficient information in the chart to classify the headaches of 28 subjects with Definite PTCS & 6 with IH. This was related to primary symptom – there was less information about headache characteristics for subjects who presented with significant vision loss or papilledema. Headaches were consistent with migraine or probable migraine in 29/31 subjects with Definite PTCS and 21/23 with IH. The headaches were consistent with tension-type (TTH) in 2/31 subjects with Definite PTCS and 1/23 with IH. 1 subject with IH had headaches which did not fit criteria for either migraine or TTH.

Conclusions:

Consistent with prior studies, headache characteristics are similar across these groups. However, data analysis is ongoing. The final sample size will be 161. This will include subjects with Normal OP, and will characterize other features of headache, effect of LP, and response to treatments which could lower CSF pressure in all groups. The long-term goal of this research is to inform a prospective study which could clarify whether patients without papilledema who have headaches with features suggestive of increased ICP derive benefit from LP and/or treatments designed to lower CSF pressure.

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Friedman DI, Liu GT, Digre KB. "Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children." *Neurology*, 81(13): 1159-65, 2013

Keywords: Pseudotumor Cerebri, High Intracranial Pressure/Headache, Pediatric Neuro-Ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: -CHOP Research Institute Summer Scholars Program -CHOP Pediatric Headache Research Fund.

Poster 160

Radiographic Features of Pediatric Idiopathic Intracranial Hypertension

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Introduction:

Adult patients with idiopathic intracranial hypertension (IIH) may harbor characteristic radiographic signs on magnetic resonance imaging (MRI). These signs have not been extensively evaluated in children. The purpose of this study is to examine the radiographic findings of pediatric IIH to characterize salient features and gain a deeper understanding of disease pathophysiology.

Methods:

Retrospective, case-control study of pediatric patients with and without IIH from the ophthalmology department at single tertiary care center was performed. Clinical data including demographics, lumbar puncture results, and ophthalmic findings were obtained. Patient MRI/MRV was evaluated for presence of an enlarged perioptic subarachnoid space, posterior globe flattening, protrusion of the optic nerve head, empty sella turcica, prominent arachnoid granulations, skull base crowding, Chiari malformation, ventriculomegaly, and transverse sinus stenosis.

Results:

Neuroimaging and clinical findings of 49 patients with IIH and 30 control patients were evaluated. Compared to controls, IIH patients had significantly larger perioptic subarachnoid space ($p < 0.001$), and higher incidences of posterior globe flattening ($p < 0.001$), protrusion of the optic nerve head ($p < 0.001$), and empty sella turcica ($p < 0.001$). The presence of prominent arachnoid granulations, skull base crowding, Chiari malformation, ventriculomegaly, and transverse sinus stenosis did not reach significance. Multivariate models were developed for predicting IIH in children.

Conclusions:

Several highly sensitive key radiographic findings in pediatric IIH were identified and models were developed for predicting pediatric IIH. In the evaluation of pediatric patients, there are characteristic radiographic findings on MRI that should raise concern for IIH.

References: None.

Keywords: High Intracranial Pressure/Headache, Neuroimaging, Pediatric Neuro-Ophthalmology, Pseudotumor Cerebri

Financial Disclosures: The authors had no disclosures.

Grant Support: Fight For Sight-NANOS Research Award.

Poster 161**Idiopathic Intracranial Hypertension: A Retrospective Evaluation of the Management and Outcomes at One Large Tertiary Care Center**

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Introduction:

Idiopathic intracranial hypertension (IIH) is a common and potentially blinding disorder that affects most frequently young overweight women. The NORDIC IIH treatment trial defined the value of acetazolamide and weight loss in the management of IIH. The goal of this study was to reflect upon our outcomes based upon our traditional strategy for managing patients and also to explore outcomes across a greater range of visual disability than was studied in the IIH treatment trial study.

Methods:

Retrospective acquisition of data from the patients 18 years and older who were diagnosed with IIH at our center between 2010 and 2015. A total of 111 patients were identified. Data was entered into our customized database and analyzed with respect to patient demographics, history, clinical and radiological signs, results of lumbar puncture, and whether surgery was performed.

Results:

Our preliminary data on 35 patients showed headache as the major symptom in 83% and papilledema with concurrent vision changes in 85% of patients. The average mean deviation score among all patients in whom initial visual field testing could be performed (55 eyes in 35 patients) was -2.83 dB in the right and -3.71 dB in the left eye. Papilledema and headaches improved in more than 2/3 of patients after initiation of Diamox treatment (typical dose 1.0-1.5 g/d), none of these patients required surgery. The remainder of the analysis is in process.

Conclusions:

Surgery was only uncommonly required for management of our patients. Our standard treatment approach, which was usually acetazolamide (doses typically 1 – 1.5 grams), was adequate to control symptoms and visual function in the great majority of patients.

References: None.

Keywords: Pseudotumor Cerebri, High Intracranial Pressure, Headache

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 162**The Translaminar Gradient Influences Papilledema Severity**

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Introduction:

Recent studies have suggested that intracranial pressure (ICP) may play a role in the development of glaucoma. It has been specifically hypothesized that the translaminar gradient (TLG) between intraocular pressure (IOP) and the cerebrospinal fluid pressure in the optic nerve sheath may influence optic nerve conformation and axonal damage. This study aims to examine whether the TLG influences the degree of papilledema observed in patients with idiopathic intracranial hypertension (IIH).

Methods:

In this university-based retrospective study, the electronic medical record was used to identify patients being assessed for IIH from 2011-2015 who underwent lumbar puncture (LP), optical coherence tomography (OCT) scan of the peripapillary retinal nerve fiber layer (RNFL), and measurement of IOP, all within a three month period. Exclusion criteria included optic nerve gliosis, pallor, or anomalous shape, or interval surgery or change in medication that could affect ICP or IOP. Translaminar gradient (the difference between ICP and IOP) and ICP were plotted against average RNFL thickness, and the Pearson correlation coefficient was calculated.

Results:

34 patients (mean age 37 years; 15% were male) met the criteria. Among patients with LP opening pressure ≥ 25 cm H₂O (n=16), there was a significant correlation between TLG and OCT RNFL average thickness. TLG was more highly correlated with OCT RNFL thickness than absolute LP opening pressure (Pearson correlation $R^2 = 0.45$, $p = 0.004$ for TLG, compared to $R^2 = 0.38$, $p = 0.011$ for LP opening pressure).

Conclusions:

Our data suggests that the optic nerve translaminar pressure gradient correlates with the degree of papilledema more closely than ICP alone. This observation of the influence of IOP on papilledema carries significant pathophysiologic and clinical implications.

References: None.

Keywords: Pseudotumor Cerebri, Papilledema

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 163

Persistence of Transverse Sinus Stenosis After Lumbar Puncture in Idiopathic Intracranial Hypertension (IIH)

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Introduction:

Diffuse or focal distal stenosis of both transverse venous sinuses is a classic sign of raised intracranial pressure (ICP), particularly IIH.^{1,2} Although some stenoses result from intrinsic sinus anomalies and are a primary cause of intracranial hypertension, others result from external compression of the distal transverse sinus and are reversible with treatment of increased ICP or after lumbar puncture (LP).^{3,4,5} Our goal was to evaluate transverse sinus stenosis (TSS) immediately after the diagnostic LP in patients with IIH.

Methods:

Twelve treatment-naïve IIH patients (11 women, 1 man, mean age 28y [range 18-42], mean BMI 36Kg/m² [range 24-53]) seen at our institution after 12/2009 who underwent a high-quality standardized contrast-enhanced brain magnetic resonance venogram (MRV) less than 30 minutes after their diagnostic LP were included. The degree of TSS was calculated by dividing the width of the stenosis by the apparent normal width of the sinus, as previously described.²

Results:

All patients had elevated CSF-opening pressure (median 35cmH₂O [IQR 32-41]). Median CSF-closing pressure was 17cmH₂O (IQR 16-19). All patients had residual bilateral TSS on the post-LP MRV (median 61% [IQR 50%-74%]). Three of these patients had a pre- and a post-LP MRV, which demonstrated a reduction in the degree of stenosis in all 3 patients after the LP, but only by less than 25%.

Conclusions:

As previously suggested², all IIH patients have some degree of bilateral TSS, which may contribute to elevated ICP, but is not associated with clinical outcome. Substantial bilateral TSS persists immediately after acute reduction of the ICP by LP. Possible explanations include: 1) resolution of TSS is delayed after a decrease of ICP; 2) some degree of TSS persists indefinitely in some IIH patients as previously suggested.⁶ Our findings reinforce that clinical features, not the presence or degree of TSS, should be used to determine management in IIH.²

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Keywords: Pseudotumor Cerebri, Neuroimaging, Transverse Sinus Stenosis, High Intracranial Pressure/Headache, Venous Stenting

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 164

Comparative Detection of Optic Disc Abnormalities with Digital Images Obtained with an iPhone Camera attached to a PanOptic Ophthalmoscope vs. Standard Fundus Photography

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Introduction:

Neurogenic visual loss often causes optic disc abnormalities that need to be evaluated urgently by non neuro-ophthalmologists. The ability to transmit digital photographs to a specialist makes it possible for a neuro-ophthalmologist to remotely evaluate optic nerves in real time. The purpose of this study was to evaluate the relative diagnostic accuracy of detecting optic disc abnormalities in photographs taken by an iPhone4S camera attached to the PanOptic Ophthalmoscope (ICPO) vs. those obtained with standard fundus camera photography.

Methods:

New patients ≥18 years of age referred to the MEEI Neuro-ophthalmology service for acute vision loss or headache were enrolled, which was approved by the local IRB. Fundus photographs were taken of all patients before and after pupil dilation with ICPO and post-dilation with a standard fundus camera. The photographs were evaluated by two neuro-ophthalmologists who were masked to the clinical impression and the reason for referral.

Results:

Twenty-nine patients (58 eyes) were enrolled. Roughly 20% of the cases were clinically diagnosed with either optic disc edema (20.7%) or optic disc pallor (19.0%). When reviewing photographs, the mean false positive rate was 9.3% (undilated ICPO), 22.9% (dilated ICPO), and 10% for dilated standard fundus photography. The mean false negative rate was 41.3%, 33.7% and 31.5% for the three groups respectively. The mean accuracy in detecting optic disc edema in the three groups was 45.8 % (95%CI, 25.6 – 67.2), 50.0% (95%CI, 29.1 – 70.9), 58.3(95%CI, 36.6 – 77.9) respectively. The mean accuracy in detecting optic disc pallor was 27.3% (95%CI, 10.7 – 50.2), 45.5% (95%CI, 24.4 – 67.8), 63.6% (95%CI, 40.7 – 82.8) respectively.

Conclusions:

Blinded reviewers of ICPO photography allows for limited accuracy in detecting optic disc edema that was not statistically different from the standard fundus camera photography. There was a trend to higher accuracy with Frisén grade 2-4 versus Frisén grade 1 edema.

References: None.

Keywords: Optic Disc Abnormalities, Diagnostic Tests, Digital Images

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 165

Quantitative Analyses of Retinal Microvascular Network in Alzheimer's Disease

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Introduction:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with cognitive symptoms appearing long after neural degeneration has begun. Accumulating evidence implicates vascular dysfunction in AD pathogenesis, but assessing the cerebral microvasculature is difficult. The microvasculature in retina and brain are similar anatomically and physiologically. In this project, optic coherence tomography angiography (OCTA) was used to quantitatively analyze the retinal microvascular network density in patients with AD or mild cognitive impairment (MCI).

Methods:

The macula ($3 \times 3 \text{ mm}^2$ centered on the fovea) was imaged by Cirrus OCTA prototype (Carl Zeiss Meditec, Dublin, CA). Five AD, 5 MCI and 10 age-matched normal controls (NC) were recruited. Image processing was performed to separate microvessels (width $<25 \mu\text{m}$) from the *en face* angiograms. Fractal analyses using box counting (D_{box}) representing vessel density were performed. The relationships between the microvascular density and macular ganglion cell layer (GCL) thickness were also analyzed.

Results:

The retinal microvessel networks of all subjects (mean age, 50 – 85 yrs; men: women = 10:10) were clearly visualized. D_{box} (AD median=1.763, range=1.665 to 1.776; MCI median=1.749, range=1.737 to 1.767) was highly correlated with GCL thickness in AD ($r = 0.90$, $P < 0.05$) and MCI patients ($r = 0.71$, $P < 0.05$). The D_{box} of parafoveal microvessels of the 2.5 mm annular zone was 1.746 (SD: 0.046) in AD and did not differ significantly from MCI (1.751, SD: 0.011) ($P = 0.40$). The D_{box} in AD and MCI subjects combined did not differ from controls (1.752, SD: 0.025) ($P > 0.05$).

Conclusions:

This preliminary study demonstrated the feasibility of quantitative analysis of retinal microvascular network in patients with AD or MCI. While retinal microvascular network density did not differ across groups in this study, further research in a larger sample is needed to investigate if retinal microvascular dysfunction exists in AD.

References: None.

Keywords: Alzheimer's Disease, Mild Cognitive Impairment, Retinal Microvascular Network Density, Fractal Analysis (D_{box}), Optic Coherence Tomography Angiography

Financial Disclosures: The authors had no disclosures.

Grant Support: NANOS Pilot study, NIH Center Grant P30 EY014801, Research to Prevent Blindness (RPB), Department of Defense (DOD- Grant#W81XWH-09-1-0675).

Neuro-ophthalmology Training in Ophthalmology Residency Programs in the United States

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Introduction:

Significance: The status of neuro-ophthalmology education in ophthalmology residency training programs is unknown in the United States. **Background:** There is literature detailing resident experiences for surgical procedures, however there are no articles that detail the teaching of a non-procedural specialty within ophthalmology. There are no ACGME requirements for neuro-ophthalmology (NO) training within ophthalmology residency programs. Each program independently determines the amount of NO training and the residency level of training within ophthalmology. Recent studies of ophthalmology residents on satisfaction with their residency NO training rate ranged from 55% to 91%.

Methods:

A survey was sent to residency directors and/or neuro-ophthalmologists at all ophthalmology residency programs in the United States using the Ophthalmology Residency Matching Program to determine the amount of NO training that residents receive.

Results:

One hundred surveys were obtained from a total of 113 ophthalmology programs (88% response rate). Ninety two percent of ophthalmology residency programs had a NO rotation although every program except one had neuro-ophthalmology training during residency. Neuro-ophthalmology training consisted of a solid block of time or scattered days, with the total number of days ranging from 4 to 80. Most rotations occurred within post-graduate year 2 or 3 with an average of just over 1 resident/clinic (1.18).

Conclusions:

This is the first evaluation of the amount of NO training that occurs within ophthalmology residencies participating in the matching program in the US. Future studies could evaluate if there is any correlation between resident satisfaction in NO training and the amount of training. Determining extent of NO training within neurology residency programs is another area of interest.

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Keywords: Neuro-Ophthalmology, Residency, Education

Financial Disclosures: The authors had no disclosures.

Grant Support: This work was supported in part by an unrestricted grant from Research to Prevent Blindness, New York.

Poster 167

Relationship Between Cyclotorsion and Visual Vertical: Dependence on Sighting Dominance

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Introduction:

Eye torsion appears as a major determinant of the subjective visual vertical (SVV). Apparent paradox is that monocular vision is spontaneously used in some visuospatial skills while monocular SVV was shown to be unreliable. Based on the large interindividual variability of eye cyclotorsion, this study compares the dependence of monocular SVV on torsion in sighting and non sighting eyes.

Methods:

84 healthy volunteers, 25 M, 59 F, aged 20 to 50, Normal Acuity and Binocular vision. RE dominant :57, LE dominant : 27. Ten measures of SVV each eye and each participant. Ten eye fundus photographs with Scanning Laser Ophthalmoscope (SLO). ANOVAs were carried out separately on the measures of eye torsion and SVV, including sighting eye, preferred hand and sex as between-subject factors, and eye (left, right) as repeated factor. A Bravais-Pearson coefficient was calculated for each sighting dominance group and each eye.

Results:

Averaged on both eyes, excyclotorsion also appeared slightly greater ($F_{1,76}=4.69$; $p=0.033$) in the right sighting group (6.12°) than in the left sighting group (5.44°), but the difference between LE and RE did not change according to sighting group ($F_{1,76}=2.06$; $p=0.155$). Value of SVV was greater for RE than for LE in 70.2 % of the participants. Mean difference between monocular SVV of LE (-0.19°) and RE ($+0.34^\circ$), was significant ($F_{1,76}=5.95$; $p=0.017$). It was not significantly affected by sighting side ($F_{1,76}=0.27$; $p=0.605$). When the non sighting eye was considered, SVV correlated significantly with OT whether the non sighting was the RE ($r_{25}=0.40$; $p=0.039$) or the LE ($r_{55}=0.27$; $p=0.043$). It was not the case for the sighting eye, right ($r_{55}=0.13$; $p=0.345$) or left ($r_{25}=0.08$; $p=0.692$).

Conclusions:

The torsion of non sighting eye correlated with monocular SVV, while that of sighting eye did not

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Keywords: Cyclotorsion, Visual Vertical, Sighting Dominance

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 168**Medication Reconciliation in a Neuro-ophthalmology Clinic**

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Introduction:

The purpose of this study was to quantify and categorize the type of medication errors we may encounter in the patient record, and also to evaluate the relevance of these errors with respect to neuro-ophthalmologic care. We aimed to evaluate the accuracy of the medication list prior to the patient being examined in our clinic. Time-stamping on the electronic medical record allowed us to distinguish medication changes from medication errors (changes which should have been documented at the previous reconciliation).

Methods:

We prospectively evaluated consecutive patients meeting inclusion criteria of having a time-stamped confirmed medication reconciliation prior to evaluation, having full recall of their medications, and having pharmacy staff available. Medications were reviewed and errors recorded, categorized, and rated by expected relevance to the forthcoming neuro-ophthalmologic evaluation (1=possibly, 2= probably, 3=definitely relevant).

Results:

Seventy-seven patients were evaluated. Sixty-two had at least one medication error. There were 296 medication errors total. The type of error included: Not on list: 112 (38%); No longer taking: n=93 (31%); Dosage error: n=76 (26%); and Duplicate: n=15 (5%). The errors were classified as having: Possible: n=248 (84%), Probable n=42 (14%), and Definite (n=6, 2%) relevance to forthcoming neuro-ophthalmologic care.

Conclusions:

Despite documentation that a medication list is updated and accurate, there remains a significant chance that an error is present. Six percent (4/77) of our patient charts contained a highly relevant medication error.

References: None.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 169

Visual Quality of Life in Migraine

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Introduction:

Previous research has shown that patient-reported quality of life (QOL) data can be useful in determining the severity of disease burden in migraine, but previous studies have not assessed how migraine affects visual QOL. In this study, we are assessing vision-specific QOL in migraine patients.

Methods:

We assessed individuals with chronic and episodic migraine using the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25), the 10-item NEI-VFQ-25 Neuro-Ophthalmic (NO) Supplement, and the Headache Impact Test (HIT-6). We compared these results to those from previously published disease-free controls, and to results from other neuro-ophthalmic disease QOL studies. We intend to enroll at least 120 participants.

Results:

Our preliminary results reveal that among 21 participants with chronic migraine (17 women and 4 men; mean age \pm SD of 50.8 \pm 13.2 years), vision-specific QOL scores were significantly decreased compared to previously published disease-free controls ($p=.0001$). Among 19 participants with episodic migraine, with or without aura (13 women and 6 men; mean age \pm SD of 51.7 \pm 18 years), vision-specific QOL scores were also decreased compared to disease-free controls. Results for the NO supplement were statistically significant ($p=0.0013$), but these results may not be statistically significant for the NEI-VFQ-25 ($p=.0867$). Chronic migraineurs had decreased visual QOL scores compared to those with episodic migraine. Scores for the NEI-VFQ-25 and the NO supplement for chronic migraine were similar to previously published results for patients with other neuro-ophthalmic disorders such as MS, myasthenia gravis, and ischemic optic neuropathy. Subjects with episodic migraine had QOL scores that were better than patients with other neuro-ophthalmic disorders.

Conclusions:

Migraine affects visual QOL. Patients with chronic migraine may have visual QOL similar to patients with other neuro-ophthalmic disorders. These findings suggest closer attention to, and study of, vision in migraine is indicated, and could have important implications in the treatment of migraine.

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Keywords: Headache, Quality of Life, Photophobia, Aura

Financial Disclosures: The authors had no disclosures.

Grant Support: Supported in part by an Unrestricted Grant from Research to Prevent Blindness, Inc., New York, NY, to the Department of Ophthalmology & Visual Sciences, University of Utah.

Poster 170

Cognitive Enhancement For Visual Field Testing

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Introduction:

Abnormal Humphrey Visual Field (HVF) testing in healthy adults can be the result of decreased mental alertness and vigilance, even with normal reliability indices. Methylphenidate is a stimulant intended for the treatment of Attention deficit and Hyperactivity Disorder (ADHD) which is also used for cognitive enhancement. Our aim was to evaluate the effect of methylphenidate on HVF testing in normal adults without ADHD.

Methods:

This was a prospective randomized controlled study. Sixteen patients with an unexplained visual field defect were randomly assigned into an interventional and control groups. Both groups repeated the same HVF test (8 subjects in each group). The interventional group was given 10mg methylphenidate one hour before the test. Patients completed the Adult ADHD Self-Report Scale (ASRS-v1.1) and Montreal Cognitive Assessment (MoCA) questionnaires. One eye was randomly selected for statistical analysis. The Mean deviation (MD), Pattern Standard Deviation (PSD) and reliability indices were compared. Three experienced ophthalmologists that were masked to the subjects' identity, group assignment and the order of the tests reviewed both tests for a clinically significant difference between the first and second HVFs. Wilcoxon Rank Sums test and Fisher Exact test were used for statistical comparisons.

Results:

Median age was 65.5 for the methylphenidate group (interquartile range [IQR]: 51-77) and 53.5 for controls (IQR: 47-67, $p=0.24$). MD improved in the methylphenidate group (median +3.96 dB, IQR: 2.43-5.39) compared to no change in controls [median -0.15 dB, IQR: (-1.0) – (+2.22), 1-sided Wilcoxon, $p=0.046$]. PSD decreased in the methylphenidate group [median -3.32 dB, IQR: (-4.43) – (-0.82)] compared to no change in controls [median +0.16 dB, IQR: (-0.48) – (+2.13), $p=0.006$]. Clinical assessment of the visual fields yielded improvement in 7 (87.5%) of the methylphenidate group compared to 2 (25%) of the controls ($p=0.04$).

Conclusions:

This preliminary (ongoing) study may suggest that methylphenidate improves HVF testing in non-ADHD adults.

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Keywords: Diagnostic Tests, Perimetry, Visual Fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 171**Assessing the Cost Inefficiency Attributable to Surgical Instrument Trays Used in Adult Strabismus Surgery**

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Introduction:

This study aims to quantify the cost to the healthcare system attributable to inefficient use of instrument trays during adult strabismus surgeries performed at our institution. We plan on predicting the potential savings involved in developing a standardized adult strabismus instrument tray that excludes unnecessary instruments.

Methods:

This is a single-site observational study. Data on frequency of instrument use will be obtained through a survey distributed to the three ophthalmologists who routinely perform strabismus surgery at our institution. The survey includes a list of all instruments present on the three most commonly used instrument trays for this type of surgery at this site. The surgeons are asked to place each instrument into one of the following three categories: (a) always used, (b) occasionally used (once every 4 OR days), or (c) never used. To evaluate the costs associated with tray usage, the following data will be obtained from the central sterile processing (CSP) unit of the hospital: tray decontamination and reassembly time, costs associated with missing or damaged instruments, and the CSP operative cost. Potential cost savings associated with eliminating from the trays those instruments that are deemed never used and developing a standardized adult strabismus tray that excludes these instruments will be calculated.

Results:

Data collection is currently under way.

Conclusions:

Pending collection and analysis of data.

References: None.**Keywords:** Strabismus, Cost Analysis**Financial Disclosures:** The authors had no disclosures.**Grant Support:** None.

Poster 172

Comparison of the Surgical Treatment of Superior Oblique Palsy: Inferior Oblique Myectomy Versus Combined Contralateral Inferior Rectus Recession

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Introduction:

To compare inferior oblique (IO) myectomy with combined contralateral inferior rectus (IR) recession for the treatment of superior oblique (SO) palsy.

Methods:

A retrospective review of the medical records of patients with SO palsy who underwent surgical treatment with either IO myectomy or IO myectomy and contralateral IR recession between 2006 and 2015. Group 1 (n=21) underwent IO myectomy alone to correct hypertropia, while group 2 (n=22) underwent IO myectomy plus contralateral IR recession. Analysis of the magnitude of corrected hypertropia in primary position and contralateral gaze, magnitude of postoperative drift and, success rate (defined as residual hypertropia less than 4 PD) was performed.

Results:

Preoperatively, there was no statistical difference in mean vertical deviation in primary position between the two groups (11.0 PD and 13.7 PD, respectively (p=0.17)). However, there was a significant difference in mean vertical deviation in contralateral gaze between group 1 and 2 (13.7 PD and 17.9 PD, respectively, p<.000). Mean vertical deviation measurements at postoperative months 3 were 1.3 PD and -1.5 PD (p=0.02) in primary position and 2.0 PD and 1.2 PD in contralateral gaze (p=0.034). Mean corrected hypertropia in primary position was 9.3 PD and 15.2 PD in group 1 and 2 (p=0.006), and in contralateral gaze was 11.8 PD (group 1) and 16.7 PD (group 2) (p<.000). Success rate of group 1 was 90.5% and that of group 2 was 72.7% (p=0.058).

Conclusions:

Both IO myectomy and IO myectomy combined with contralateral IR recession were effective in the treatment of SO palsy. IO myectomy alone lead to a slight undercorrection whereas a combined procedure lead to a slight overcorrection in primary position. Both procedures often result in a slight undercorrection in contralateral gaze and have a similar surgical success rate.

References: None.

Keywords: Ocular Motility Disorders And Nystagmus, Neuro-Ophthalmic Disorders Of Neurologic And Systemic Diseases, Superior Oblique Palsy, Inferior Oblique Myectomy, Contralateral Inferior Rectus Recession

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 173

MRI Findings in Children with Pseudotumor Cerebri Syndrome (PTCS), Intracranial Hypertension, and Normal Opening Pressure Without Papilledema.

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Introduction:

Revised diagnostic criteria for pseudotumor cerebri syndrome (PTCS) include findings on neuroimaging, which can be used if papilledema is not present. We compared neuroimaging in children suspected to have PTCS, in order to facilitate the identification and treatment.

Methods:

We reviewed 237 pediatric subjects from our PTCS database and from recent lumbar punctures (LPs) performed for clinical suspicion of PTCS. We retrospectively classified 123 subjects with MRIs in the following comparison groups: 61 with Definite PTCS, 13 with Probable PTCS, 24 with Intracranial Hypertension (IH) and 25 with normal opening pressure (OP). A neuroradiologist, who was blinded to the diagnostic group, assessed MRIs for empty sella, posterior globe flattening, distention of perioptic subarachnoid space (>5.5mm) and tortuosity of the optic nerve and transverse sinus stenosis.

Results:

Empty sella was found almost exclusively in Definite PTCS (88%). Posterior globe flattening and transverse sinus stenosis were found most commonly in the Definite PTCS group at 36% and 38%, respectively. Distention of the perioptic subarachnoid space and optic nerve tortuosity were found in 25% of those with Definite and Probable PTCS and in 1% of those with IH. In those with normal OP, no more than 6% had any one of the criteria examined. Three of 4 criteria were present in 72% with Definite PTCS, 16.7% with Probable PTCS, 4.8% with IH, and 6.7% with normal OP. Between-group comparisons with Fisher's exact test for each of the 4 criteria, and for the combined score, were significant with p-value <0.001. The positive predictive value of 3 or more MRI criteria for definite or probable PTCS is 95%. The negative predictive value is 58.6%.

Conclusions:

In children, three of four neuroimaging criteria have a robust positive predictive value for PTCS. Of these, empty sella was found the most often in definite PTCS.

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Keywords: Pseudotumor Cerebri, Neuroimaging, Pediatric Neuro-Ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 174

Hyperintense Optic Nerve Heads on Diffusion Weighted Imaging: Is this Sign Specific to Papilledema?

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Introduction:

Hyperintensity of optic nerve heads on Diffusion Weighted Imaging (DWI) has been described for papilledema. The purpose of this study was to evaluate if similar changes are associated with other causes of disc edema specifically optic neuritis and anterior ischemic optic neuropathy.

Methods:

In this retrospective study, 18 controls, 16 patients with optic neuritis, 18 patients with papilledema, and 4 patients with anterior ischemic optic neuropathy who had undergone magnetic resonance imaging of brain within 4 weeks of presentation were included. Two neuro-radiologists blinded to the diagnosis independently reviewed the DWI for the presence of hyperintense signal at each optic nerve head as well as the retrobulbar optic nerve. These groups were compared for the prevalence of optic nerve head or retrobulbar nerve hyperintensity.

Results:

For both readers independently, presence of likely or definite hyperintensity of optic nerve head on DWI had sensitivity of 5.9% for detection of papilledema and 35.3% for detection of optic neuritis. This finding was not specific for papilledema or optic neuritis based on the first reader who reported likely hyperintensity in 2/36 (5.5%) control eyes; the second reader did not report this in any control eyes. Also, none of the six eyes with anterior ischemic optic neuropathy showed this finding. Sensitivity of presence of hyperintensity of retrobulbar optic nerve on DWI in detection of optic neuritis was 0% for the first reader and 17.6% for the second. This finding of hyperintensity of retrobulbar optic nerve was specific for optic neuritis, with none of control eyes, eyes with papilledema, or those with anterior ischemic optic neuropathy demonstrating this finding.

Conclusions:

Hyperintensity of the optic nerve head on DWI can be seen with both papilledema and optic neuritis. In optic neuritis, hyperintensity of optic nerve head may be seen in absence of corresponding hyperintensity in retrobulbar optic nerve. In our study, we found hyperintense signal on DWI in retrobulbar optic nerve to be specific for optic neuritis.

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Keywords: Neuroimaging, Optic Neuropathy, Pseudotumor, Demyelinating Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 175**Cerebral Correlates of Melanopsin-Mediated Retinal Photoreception**

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Introduction:

Intrinsically-photosensitive retinal ganglion cells (ipRGCs) expressing melanopsin, mediate non-visual photic responses, subserving circadian functions and pupillary reactions to light. The cerebral correlates of the retinal ipRGCs reception are not known, in healthy individuals.

Methods:

In order to specifically select the responses of the ipRGCs, we have performed a fMRI study, and scanned 17 healthy subjects, who were exposed to perceptually similar white lights (metamer-like lights) with high and low levels of melanopic excitation (High_Mel versus Low_Mel), allowing minimal excitation differences for cones and rods.

Results:

The contrasts between High_Mel and Low_Mel revealed significant bilateral activation of the frontal eye fields, suggesting that ipRGCs stimulation might enhance cortical signaling in areas of the brain that are known to be involved in attention and oculomotor responses. Other activated regions included areas in the inferior temporal gyri, caudate nuclei and the pineal gland.

Conclusions:

Our study suggests that ipRGCs stimulation activates not only the expected cerebral areas involved in circadian rhythms, but also cerebral regions classically involved in attentional and ocular motor responses.

References: None.

Keywords: Melanopsin, fMRI

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 176

Optic Nerve Magnetic Resonance Imaging Characteristics in Inherited Optic Neuropathies

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Introduction:

Inherited optic neuropathies include dominant optic atrophy (DOA), Leber's hereditary optic neuropathy (LHON), and Wolfram syndrome (DIDMOAD). DOA is the most common of these, and mutations in *OPA1* account for 40-60% of DOA cases. Few studies have examined or compared findings on neuroimaging of the optic nerves in inherited optic neuropathies.

Methods:

Using an updated retrospective database of 111 patients with bilateral optic atrophy referred for genetic testing, magnetic resonance (MR) images were analyzed and compared across genotype groups. Patients were screened using next generation sequencing of 243 genes (including *OPA1*, *WFS1*) and the mitochondrial genome (includes all LHON mutations). T2 signal was quantified in MR images (3T) of the orbits and/or brain and normalized to internal standards within each slice. A sample of patients without ocular, central nervous system or visual diagnoses was used to validate the T2 quantification methods.

Results:

Eight patient with and 19 without *OPA1* mutations had MR images available for analysis. There were 2 patients with DIDMOAD and 1 patient with LHON in our sample who also had MR images available. The optic nerves of optic atrophy patients appeared smaller with increased normalized T2 signal compared to controls. There was a wide range of variability in the intensities of optic nerve T2 signals among optic atrophy patients.

Conclusions:

Increased T2 signal intensity is not a typical feature of neurodegenerative disease and may reflect nuances in optic atrophy specific to this group of conditions. Differences in T2 signal could represent differences inherent to distinct hereditary optic neuropathies and/or the degree of atrophy or gliosis. Further characterization of these differences on MR imaging can help guide diagnostic genetic testing and provide insight into differences in the pathophysiology of hereditary optic neuropathies.

References: None.

Keywords: Optic Neuropathy, Genetic Disease, Neuroimaging

Financial Disclosures: Eric D. Gaier, Katherine Boudreault, Isao Nakata, Dean M. Cestari and Janey Wiggs declare that they have no conflict of interest. Joseph F. Rizzo III owns equity in Bionic Eye Technologies and Visus Technologies, which are working on an implanted and portable device for the blind, respectively. Dr. Rizzo also serves as Medical Director for Neurology and Ophthalmology for Magic Leap, Inc., which is developing a head-mounted "gaming" device.

Grant Support: None.

Poster 177**Sarcopenia and Radiographic Changes in the Aging Orbit**

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Introduction:

Sarcopenia is defined as age related muscle wasting and is in part characterized by fat infiltration of skeletal muscle. This study investigated age related magnetic resonance imaging (MRI) changes to assess for fatty infiltration of the extraocular muscles as evidence of sarcopenia.

Methods:

In this retrospective study, the electronic medical records were used to identify 108 patients (216 orbits) who underwent orbital MRI. Patients with pathology involving orbit muscle or fat were excluded. For coronal, non-contrast enhanced, T1 weighted images, the region of interest (ROI) tool was used to measure signal intensities within the medial rectus muscles and intraconal fat. The muscle-fat proportion was calculated by dividing fat by muscle signal strength. Patients were divided into four groups: age 18 to 30 years (G1), 31-49 (G2), 50-69 (G3) and ≥ 70 (G4) and mean muscle-fat proportion was calculated for each. Analysis of variance (ANOVA) was used to compare the means between groups.

Results:

Mean proportion of muscle-fat signal increased significantly with advancing age: 0.27 ± 0.02 (G1), 0.29 ± 0.02 (G2), 0.32 ± 0.03 (G3), 0.40 ± 0.06 (G4). Group four was significantly different than all other groups ($P < 0.01$), indicating the medial rectus muscle signal in older individuals more closely matched that of surrounding fat.

Conclusions:

This preliminary data suggests that sarcopenia related fat infiltration of the extraocular muscles may occur and is detectable with MRI. This has implications regarding age related changes in extraocular motility, such as reduced supraduction and blepharoptosis.

References: None.

Keywords: Sarcopenia, MRI, Fatty Infiltration

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 178

A Comparison of Patients with Isolated Diplopia and Giant Cell Arteritis Versus Those from Other Causes

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Introduction:

Diplopia as a presenting feature of GCA is uncommon and reported to occur in 3-6% of all cases [1-3]. Clinicians often face an older patient presenting with acute or sub-acute onset of diplopia. Although GCA is an uncommon cause for double vision [3,5], many individuals obtain a GCA work up including laboratory evaluation to rule out GCA due to its potential for vision loss. This study will evaluate the differences in patients presenting diplopia, subsequently diagnosed with biopsy-proven giant cell arteritis with patients presenting diplopia from other causes.

Methods:

This is a retrospective multi-center study that will enroll patients presenting with diplopia with biopsy proven GCA. For each study group patient, 5 age-matched (+/- 5 years) controls presenting with diplopia without a diagnoses of GCA will be collected. Data on the demographics, presence of other ocular signs and symptoms, other systemic and laboratory markers will be compared between subjects and controls.

Results:

Preliminary data includes 12 patients and 33 controls that were matched with respect to age and race. Of the patients with GCA, third nerve palsies (n=6) and sixth nerve palsies (n=5) were most common. Patients with GCA were more likely to present with headache (100%), jaw claudication (75%), malaise (42%), myalgia (58%), scalp tenderness (58%), neck pain (42%), and PMR (33%) as well as elevated markers (ESR 75%,; CRP 83%). Ocular ischemic lesions were common in patient with GCA (n=4) presenting as AION, PION, cotton wool spots, and choroidal ischemia. Risk factors such as hyperlipidemia, hypertension, type 2 diabetes and smoking history were not significant among the two groups.

Conclusions:

Patients with diplopia from GCA are more likely to present with systemic symptoms, ocular ischemia, and elevated markers of inflammation and should be promptly evaluated and treated when GCA is suspected.

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Keywords: Giant Cell Arteritis, Diplopia, 6th Nerve Palsy, 3rd Nerve Palsy, Skew

Financial Disclosures: The authors had no disclosures.

Grant Support: Research to Prevent Blindness.

Poster 179

Prevalence of Thymoma in Ocular Myasthenia Gravis

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Introduction:

The prevalence of thymoma in ocular myasthenia gravis has not been explicitly investigated in the medical literature. Published data vary and chiefly consist of smaller case series. The purpose of this study is to determine the prevalence of thymoma in a large cohort of patients with ocular myasthenia gravis.

Methods:

A retrospective multicenter analysis was conducted. We reviewed charts of 158 patients who met diagnostic criteria for ocular myasthenia gravis without generalized disease at initial presentation. The main outcome measure was the percentage of patients with thymoma as diagnosed by chest imaging. Conversion to generalized disease and duration of follow-up also were evaluated. These data will be added by review of additional charts. The medical literature was searched for articles or abstracts in the English language containing data regarding the prevalence of thymoma among other cohorts of patients with ocular myasthenia gravis.

Results:

Of the 158 patients in our cohort, 8 (5.1%) were found to have thymoma. Of these, 3 (37.5%) had disease progression to generalized myasthenia gravis. Nine case series of patients presenting with ocular myasthenia gravis were analyzed. Cohort size varied from 15 to 147, with prevalence of thymoma ranging from 0% to 20%.

Conclusions:

Among our patients presenting with ocular myasthenia gravis, approximately 5% were found to have thymoma. This was distinct from the next largest case series published but not inconsistent with the body of literature. Previous studies have suggested that thymoma may have prognostic implications indicating increased likelihood of generalization of disease and early identification may allow resection prior to the onset of invasive thymoma.

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Keywords: Myasthenia, Neuro-Ophth and Systemic Disease, Paraneoplastic Syndromes

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 180**Absence of Bacteria in the Temporal Arteries of Patients with Giant Cell Arteritis**

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Introduction:

An infectious trigger for giant cell arteritis (GCA) has been considered but no organism has conclusively been linked to GCA. We have previously presented data at NANOS linking GCA to a strain of bacteria. We performed confirmatory experiments to determine if GCA is caused by a bacterial infection. We cultured superficial temporal artery biopsies (STABs) and analyzed the cultures for bacterial growth. We also used 16S rRNA sequencing technology to identify bacterial genomic sequences in STABs.

Methods:

STABs were collected from 3 groups: Subjects with histopathologic features of GCA ("positive"), subjects with normal STABs and without clinical features of GCA ("negative"), and subjects with normal STABs and with clinical features of GCA ("indeterminate"). A portion of the specimen was sent for histopathologic analysis. Homogenized arteries were plated onto 3 different growth media. DNA samples were used as a template in PCR reactions using bacterial 16S rRNA primers. Investigators performing experiments were masked to the affected status of the samples.

Results:

Eighteen arteries were analyzed: 10 positive; 5 negative; and 3 indeterminate. The only bacteria that could be cultured was *S. epidermidis*. 16S rRNA sequencing failed to identify bacterial DNA sequences in any of the specimens.

Conclusions:

It is unlikely that *S. epidermidis* has a pathogenic role in GCA. PCR sequencing did not identify any bacterial DNA sequences in any of the arteries. These results suggest one of two possibilities, either bacteria do not reside in the temporal arteries of subjects with GCA or 16S rRNA sequencing is not sensitive enough to detect bacterial genomic material from temporal arteries. Although this study does not rule out the possibility that a bacterium causes GCA, it does suggest that it is unlikely that GCA is caused by a live bacterial strain residing in the artery walls of these patients.

References: None.

Keywords: Giant Cell Arteritis, Bacteria, 16S rRNA

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 181

Incidence and Evaluation of Third Nerve Palsy Using a Population-Based Method

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Introduction:

Among cases of diplopia caused by cranial nerve palsies, oculomotor paresis is the most worrisome because some are the result of life-threatening aneurysms. Although there exists a number of studies on third nerve palsy from academic centers, all are subject to referral bias. The purpose of this study was to determine the population-based incidence and causes of third nerve palsies using a well-established medical records linkage system designed to capture data on patient-physician encounters.^{1,2}

Methods:

The medical records of all patients who were newly diagnosed with third nerve palsy from January 1, 1978, through December 31, 2014, were retrospectively reviewed. Incidence rates were adjusted to the age and gender distribution of the 2010 US white population.

Results:

We identified 150 new cases of third nerve palsy over the 37-year period, yielding an age- and gender-adjusted annual incidence of 4.2/100 000 (95% confidence interval, 3.5-4.9/100 000). The incidence was low among children and young adults. There was a significant increase among patients over the age of 60 ($P < 0.001$), predominantly due to presumed microvascular third nerve palsies. The causes of third nerve palsy in order of frequency were presumed microvascular (40%), trauma (12%), compression from neoplasm (11%), post-neurosurgery (9%), compression from aneurysm (6%), idiopathic (5%), stroke (4%), congenital (3%), pituitary apoplexy (2%), Tolosa-Hunt syndrome (2%), giant cell arteritis (1%) and other (1%). Ten (17%) patients with presumed microvascular third nerve palsies had pupil involvement, while pupil involvement was seen in 16 (64%) patients with compressive third nerve palsies.

Conclusions:

This population-based cohort demonstrates a higher incidence of presumed microvascular third nerve palsies and a lower incidence of aneurysmal compression than previously reported. While compressive lesions had a significantly higher likelihood of pupil involvement, pupil involvement did not exclude microvascular third nerve palsy and lack of pupil involvement did not rule out compressive third nerve palsy.

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Keywords: Third Nerve Palsy, Epidemiologic Study

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 182**The CHOP Sign: Saccadic Correction With Horizontal Prism. A Novel Method to Identify Functional Monocular Vision Loss**

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Introduction:

This case series describes a novel exam tool and its utility in distinguishing functional monocular vision loss (FMVL) from organic monocular vision loss (OMVL).

Methods:

Patients with monocular vision loss were evaluated. The patient was directed to view a distant target and asked if they could see it with each eye independently. Those who denied seeing the target with the lower acuity eye were included. Alternate cover testing was performed, initially without prism and then a 12-diopter base out prism was introduced over the normal eye. Patients who demonstrated no corrective saccades (- CHOP sign) were presumed to not see the target with the lower acuity eye. Those that demonstrated corrective saccades (+ CHOP sign) were presumed to see the target with both eyes.

Results:

Five patients who demonstrated corrective saccades and five who did not were identified. Pertinent history, exam (acuity, colors, RAPD, fundus, vertical prism dissociation, OKN) and testing results (VFT, OCT, ERG, imaging) are described and led to a diagnosis of FMVL or OMVL for each case. Corrective saccades (+ CHOP sign) reliably identified patients with FMVL and absence of corrective saccades (- CHOP sign) identified patients with OMVL.

Conclusions:

In this case series, the CHOP sign provided an objective method that reliably distinguished FMVL from OMVL.

References: None.

Keywords: Non-Organic Visual Disorders

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 183**Risk Factors of Ischemic Optic Neuropathy in Korean population**

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Introduction:

To analyze the clinical features and risk factors of Korean patients with ischemic optic neuropathy (ION).

Methods:

Medical records of 39 Korean patients (study group) who were diagnosed as having ION and 54 patient (control group) who underwent healthy inspection were retrospectively reviewed and the risk factors of ION including age, sex, associated systemic disease, past medical history, social history, hematologic findings were investigated using statistical analysis.

Results:

The mean age of the 39 patients was 62.44 ± 14.69 years (range, 28-91 years). There were 31 patients (79.4%) with associated systemic diseases such as hypertension (56.4%), hyperlipidemia (41.1%), diabetes mellitus (33.3%), cerebrovascular disease, migraine, and heart disease with a decreasing order. 14 patients (35.8%) with a mean age of 63.41 years were smoker. Risk factor for ischemic optic neuropathy were diabetes mellitus (odds ratio; OR = 4.000, $p = 0.009$) and hyperlipidemia (OR = 6.817, $p < 0.001$) smoking history (OR = 3.220, $p < 0.018$). None of risk factors differed significantly between the two groups (hypertension $p = 0.064$, IHD $p = 0.396$, LVH = $p = 0.307$)

Conclusions:

Ischemic optic neuropathy is closely related to diabetes mellitus, hyperlipidemia and smoking in Korean patients, as compared to the control group

References: None.

Keywords: Ischemic Optic Neuropathy, Diabetes Mellitus, Hyperlipidemia, Smoking, Korean Patients

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 184

Neuromyelitis Optica Spectrum Disorder: Disease Course and Long-Term Visual Outcome

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Introduction:

NMO spectrum disorder (NMOSD) is an autoimmune disease that classically manifests as attacks of optic neuritis (ON) and transverse myelitis (TM). The prevalence, course, and severity of NMOSD varies considerably. Few studies report the neuro-ophthalmological disease course and visual outcome. We describe the course and long-term visual outcome in a cohort of NMOSD patients treated in a single tertiary referral center

Methods:

The database was searched for all patients with NMOSD who were treated in our center from 2005 through 2014. Data collected included detailed visual outcome, grade of final visual disability, neuroimaging and optical coherence tomography results. Details on relapses, acute episodes and maintenance therapies were recorded

Results:

Of the 18 patients with NMOSD who were followed for a mean duration of 7.5 years, 14 (78%) were female. Mean age at presentation was 37.6±17.7 years. Patients with acute attacks were treated with high-dose intravenous methylprednisolone and offered immunosuppressive maintenance. Optic neuritis (ON) occurred in 12 patients, with a cumulative total of 37 ON episodes. At the end of the follow-up period, no patient had become legally blind and only one patient had lost her driver's license. Pain associated with acute ON was common (83%) whereas optic disc edema was a rare finding in our cohort (6%).

Conclusions:

In this retrospective series of 18 patients with NMOSD, followed for a mean of 7.5 years, acute-phase treatment was given within 8 days of relapse, followed by maintenance therapy. Good functional vision and driver's license were preserved in 17/18 patients

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Keywords: Neuromyelitis Optica Spectrum Disorder, Optic Neuritis, Visual Outcome

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 185**Repeatability and Validity of the Ice Test in the Evaluation of Ptosis in Myasthenia Gravis**

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Introduction:

The ice test has been reported to show a sensitivity of 90% and a specificity of 100% in the diagnosis of ocular myasthenia gravis (MG). However, there is lack of consensus on the criteria of positive response and little is known of the repeatability of the ice test in myasthenic ptosis and controls. This study was conducted to determine the repeatability and validity of the ice test in diagnosing MG according to different criterias.

Methods:

Thirty-one patients with ptosis related to MG and 38 controls with non-myasthenic ptosis were included. All patients were tested with the ice test twice on separate days in the afternoon. The margin reflex distance (MRD) was measured before and immediately after 5-minute application of ice on the eyelids. The ice test was judged 'positive' if improvement of MRD was ≥ 1 mm (criteria 1) or ≥ 2 mm (criteria 2) after the ice test.

Results:

Repeated ice tests showed consistent results in 68% of MG, and 97% of controls with ptosis. Repeated ice tests increased the sensitivity of diagnosing MG by 18% (criteria 1) and 21% (criteria 2) compared to a single test. The sensitivity and specificity of repeated ice tests were 97% and 87% by criteria 1, and 65% and 97% by criteria 2. There was no significant difference in the results between ocular MG and generalized MG ($p = 0.558$).

Conclusions:

The results of the ice test was variable in one third of myasthenic ptosis. Repeated ice tests may enhance the sensitivity of the test. MRD improvement of 1 mm or more after repeated ice tests is very sensitive for screening MG, and further evaluation is necessary in these patients.

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Keywords: Myasthenia Gravis, Ice Test

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 186

Case Series of Posterior Cortical Atrophy

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Introduction:

Posterior cortical atrophy (PCA), a visual variant of Alzheimer's disease, is an increasingly prevalent disease with today's aging population. Distinguishing between PCA and other causes of visual impairment is essential in the early diagnosis and treatment. Clinical presentation is heralded by subjective vision loss, yet a normal ophthalmic examination - there is not yet definitive diagnostic criteria and it may be underdiagnosed. Through the advances in understanding the early signs and symptoms of this disease, the prospect of early diagnosis, and thus eventually, prevention and treatment is optimistically hopeful.

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 to evaluate for commonalities. We have identified 30 patients from 3 academic institutions with the disease thus far and have begun preliminary data analysis.

Results:

Preliminary data analysis demonstrates that patients reported trouble reading (78%) and difficulty with depth perception (44%) as the most common concerns. Recurrent signs included abnormal color plates (100%), simultanagnosia (75%), hemianopsia (44%), decreased stereopsis (100%), and abnormal Amsler's grid (44%). We will presents at a table describing the most common findings in our cohort of patients.

Conclusions:

Earlier diagnosis is key to developing new treatments, hopefully aimed at impacting PCA in a disease modifying state. Additionally, patients can better understand their diagnosis at an earlier stage and make the necessary life style adjustments. 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 as we continue to collect cases, we hope this will lead to firm diagnostic criteria and increased awareness.

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Keywords: Posterior Cortical Atrophy, Alzheimer's Disease, Simultanagnosia, Benson's Disease, Visual Impairment

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 187**Evaluating the Incidence of Arteritic Ischemic Optic Neuropathy and Other Causes of Vision Loss From Giant Cell Arteritis**

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Introduction:

Giant cell arteritis (GCA) is a potentially blinding condition, so determining the incidence of permanent vision loss, especially arteritic ischemic optic neuropathy (AION), is important and may help guide the screening and treatment of this disease. The goal of this study is to evaluate the population-based incidence of AION and other causes of permanent vision loss from GCA using a well-established medical records linkage system designed to capture data on patient-physician encounters.^{1,2}

Methods:

The medical records of all patients who were newly diagnosed with GCA from January 1, 1950, through December 31, 2009, were retrospectively reviewed to identify and determine the incidence and causes of permanent vision loss. Systemic symptoms of GCA and visual outcomes were also determined.

Results:

Among the 245 new cases of GCA over the 60-year period, 20 (8.2%) patients suffered permanent vision loss due to GCA. The occurrence rate of AION was 6.9% (95% CI: 4.0% – 11.1%) accounting for 85% of cases of permanent vision loss. The occurrence rate of central retinal artery occlusion (CRAO) was 1.6% (95% CI: 0.4% – 4.2%) and cilioretinal artery occlusion was 0.4% (95% CI: 0.01% – 2.3%). The population-based age- and sex-adjusted annual incidence of AION among persons age ≥ 50 years was 1.3 (95% CI: 0.7 – 2.0) per 100,000 population. 20% of patients with permanent vision loss from GCA had an occult presentation without constitutional symptoms. Overall, there was no significant difference between presenting and final visual acuities.

Conclusions:

Using population-based data, we provide the most accurate incidence of permanent vision loss from GCA. This study confirms that visual outcomes from GCA-related vision loss are poor and that 20% of patients with permanent visual loss from GCA can present without systemic symptoms of GCA.

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Keywords: Arteritic Ischemic Optic Neuropathy, Giant Cell Arteritis, Occult

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 188**Yield of the Clinical Neuro-Ophthalmologic Examination in Patients with Concussion**

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Introduction:

Due to the widespread nature of ocular motor anatomic pathways, traumatic brain injury and its mildest form, concussion, affect eye movements in many ways. However, the extent to which concussion results in ocular motor deficits detectable on clinical examination is unclear. Existing literature suggests a high incidence of convergence insufficiency, saccadic deficits, and smooth pursuit impairment. We sought to identify the incidence of ocular motor dysfunction in a multidisciplinary concussion center-based neuro-ophthalmologic practice.

Methods:

We performed a retrospective chart review of all patients with a concussion-related diagnostic code seen in the practice of four neuro-ophthalmologists between 8/1/2014 and 8/1/2015. Those with pre-existing ocular motor deficits or significant positive neuroimaging findings (i.e. subdural or intracranial hemorrhage, orbital fractures) were excluded from the analysis.

Results:

Seventy patients with a concussion-related diagnosis were identified. Fifty-eight subjects (mean age 30.8 ± 14.7 , age range 11-65, 30 males, 28 females) met inclusion criteria. Loss of consciousness was documented in 13 (22.4%). Twenty-four (41.4%) reported a history of multiple concussions. The most common symptom was headache (n=36, 62.1%), followed by photosensitivity (n=19, 32.8%). Difficulty reading or using screens were reported in 11 (19%) and 9 (15%), respectively. Ocular motor dysfunction was seen on neuro-ophthalmologic examination in 16 (27.6%) patients; findings predominantly included convergence insufficiency (n=13, 22.4%). Reduced stereopsis, ocular flutter, impaired VOR cancellation, and gaze-evoked nystagmus were each found in single patients. One patient had square wave jerks, but it was unclear if these were pathologic. Deficits of saccades were not identified by clinical examination.

Conclusions:

Results of this neuro-ophthalmic concussion study are concordant with existing literature showing a fairly high incidence of convergence insufficiency. Interestingly, other eye movement abnormalities were rare and saccadic deficits were not detected, emphasizing the need for additional performance measures or eye movement recordings to capture concussion-related efferent visual deficits.

References: None.

Keywords: Trauma, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 189

Visual Performance of Non-Native versus Native English Speakers on a Sideline Concussion Screen: An Objective Look at Eye Movement Recordings

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Introduction:

The King-Devick (KD) test of rapid number-naming, a sensitive and rapid performance measure, adds a visual dimension to sideline testing for concussion. We performed a laboratory-based eye movement study during performance of the KD test. We sought to determine if having English as a second language results in slower KD reading times or changes in eye movements.

Methods:

We tested 27 native English speakers (NES) (mean age 32) and 27 subjects for whom English was a second language (ESL) (mean age 34). Participants had no history of concussion. Participants performed a computerized version of the KD. Simultaneous infrared-based videooculographic (VOG) recordings were performed using the Eyelink1000+. A Bilingual Dominance Scale survey, which quantifies primary versus secondary language dominance, was completed by all ESL subjects.

Results:

Digitized KD reading times were significantly prolonged for ESL participants, compared to NES (54.4 ± 15.4 sec vs. 42.8 ± 8.6 sec, $p=0.001$, t -test). Average intersaccadic intervals (ISI), a combined measure of saccade latency and fixation duration), were significantly longer for ESL participants (402 ± 116.9 msec vs. 317.7 ± 53.9 msec, $p=0.002$, t -test). The total number of saccades for ESL participants was significantly higher (149 ± 28 vs. 135 ± 18 , $p=0.03$, t -test).

Conclusions:

This study highlights performance disparities that linguistics may impose on rapid number-naming tasks. Concussion screening is best implemented by establishment of pre-season baselines to allow for intra-subject comparisons after impact in sport. If pre-season baseline data are unavailable, caution should be taken in comparing non-native English speaker reading times to a NES normative control KD time database.

References: None.

Keywords: Trauma, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 190

Historical Trends in the Diagnosis of Peduncular Hallucinosi

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Introduction:

Peduncular Hallucinosi (PH) refers to dream-like visual hallucinations during wakefulness that are typically caused by a focal lesion in the rostral brainstem. The conventional understanding of PH is that associated eye movement abnormalities are frequently, if not always, present. However, in the era of modern neuroimaging, PH has been increasingly diagnosed in patients without any objective deficits on physical examination. We sought to determine how modern neuroimaging has impacted the diagnosis of PH.

Methods:

We reviewed all available cases of PH, beginning with Lhermitte's original description in 1922. Papers reported in languages aside from English were translated. Patients with afferent visual loss, toxic exposure, and pre-existing psychiatric disease were excluded from the analysis. We grouped the patients according to whether or not a neuroimaging study had been performed. We then determined the frequency of objective clinical abnormalities among patients in each group.

Results:

A total of 95 cases were collected, of which 84 cases met criteria for inclusion in the study. Twenty-eight reports were translated from 7 different languages. Among cases diagnosed without a neuroimaging study, 16/21 (76%) had associated eye movement abnormalities. However, among modern cases that included CT or MRI imaging, associated eye movement abnormalities were significantly less frequent, occurring in only 22/63 (34%; $p=0.001$).

Conclusions:

Although eye movement abnormalities have historically been considered a key clinical feature supporting the diagnosis of PH, we found that in the era of modern neuroimaging, co-occurring eye movement abnormalities are far less frequent and are not a requisite feature of the diagnosis.

References: None.

Keywords: Peduncular Hallucinosi, Hallucinations, Magnetic Resonance Imaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 191

Opening Pressure Assessment Following Venous Stenting for Idiopathic Intracranial Hypertension

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Introduction:

Increasing evidence supports a role of venous sinus stenosis in the pathogenesis of idiopathic intracranial hypertension (IIH). Numerous retrospective studies have demonstrated improvement in symptoms and papilledema after stenting, but few have diligently compared pre and post opening pressure (OP). We measured the pre and post OP in 19 patients who underwent stenting for IIH, 10 of whom were enrolled in a prospective trial evaluating the effect of stenting on visual fields and optic nerve morphology

Methods:

All patients fulfilled the modified Dandy criteria for IIH and were either refractory or intolerant to medical therapy or presented with fulminant vision loss. Lumbar puncture (LP) was performed prior to venous stenting, and again at approximately 3 months.

Results:

Mean age at presentation was 27.5 and all patients were female. Mean BMI increased from 36.0 to 36.8. Stenosis was bilateral in 10 (52.6%) and unilateral on the dominant side in 9. Mean OP reduced from 40.4 (SD 11.3) to 20.9 (SD 5.72) with a mean change of -19.47 cm H₂O. Median OP reduced 45% from 39 to 21 cm H₂O (P<0.0001, Wilcoxon signed rank-sum test). Bivariate analysis found a lower pre-stent BMI in those patients who demonstrated a post-stent absolute change in OP > 25. (38.6 vs. 28.9, P<0.03). Pre-stent BMI correlated with %change in OP (Pearson Correlation coefficient: -0.63, P = 0.004). 2/19 (10.5%) patients developed a new stenosis during follow up.

Conclusions:

The clinical improvement observed with venous stenting in IIH patients is accompanied by an objective reduction in OP. The % improvement in OP weakly correlates with pre-stent BMI (but not pre-stent OP), suggesting that the degree to which the stenosis contributes to the elevation in OP may be smaller in more severely obese patients. A prospective trial comparing venous stenting to shunting is needed to confirm its efficacy in OP reduction.

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Keywords: Idiopathic Intracranial Hypertension, Venous Stenting, Lumbar Puncture, Opening Pressure

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 192**Multiple Sclerosis Patients with Depression are More Likely to Subjectively Rate Their Vision Poorly**

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Introduction:

Depression is a common condition in patients with multiple sclerosis (MS), and is routinely assessed in our MS center using the Patient Health Questionnaire-9 (PHQ-9). Patient-reported outcomes (PRO) are increasingly utilized in clinics and in clinical trials to assess the impact of neurological symptoms on patients' function. The aim of this study was to determine if depression negatively affects a patient's rating of their visual function.

Methods:

This was a retrospective, observational study of patients diagnosed with MS or clinically isolated syndrome (CIS). A clinic database and electronic medical record were used to identify patients with a PHQ-9, multiple sclerosis performance scales (MSPS) vision subscore, and visual acuity performed within 3 months. MSPS vision subscore was dichotomized into two categories (0 or 1 indicating better vision vs 2, 3 or 4 indicating poorer vision) and PHQ-9 was dichotomized into two categories (≥ 10 indicating depression vs < 10 , no or mild depression). Visual acuity was measured using near card assessment of best corrected visual acuity. Logistic regression models were used to assess the relationship between dichotomized MSPS vision subscore, visual acuity, and PHQ-9.

Results:

363 patients met the inclusion criteria. In the univariate analysis, patients with a dichotomized PHQ-9 score ≥ 10 were 4.1 times more likely to have a MSPS vision in the higher categories ($p < 0.001$). In the multivariate analysis, visual acuity (worst eye) and PHQ-9 score (continuous) were both predictive of a worse vision rating. For every 1 point increase in PHQ-9 score, the odds of being in the poor MSPS vision subscore category was 1.122 times that of the better category ($p < 0.0001$).

Conclusions:

This study shows that patients with depression may overestimate their visual disability on patient-reported outcomes. Future studies should evaluate for this effect in more comprehensive patient-reported measures of visual function.

References: None.

Keywords: Demyelinating Disease, Depression, Visual Acuity

Financial Disclosures: Robert Bermel has served as a consultant for Biogen, Novartis, Genzyme, Genentech. Other authors have no disclosures.

Grant Support: None.

Poster 193

Causes of Eye Pain: A Multicenter Center Experience

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Introduction:

Eye pain is a common presenting complaint caused by eye disorders such as keratitis and dry eye as well as neurological disorders such as tumors and headache. Although a common symptom, no previous study has reviewed the causes of eye pain in ophthalmology and neurology clinics from large referral institutions. We aimed to determine the causes of eye pain presenting to two tertiary eye and neurologic centers.

Methods:

This cross-sectional study analyzed patient records from the Departments of Ophthalmology and Neurology at two major universities. Entry criteria included all patients seen in those departments between January 2012 to December 2013 with the main complaint of eye pain. We had IRB approval.

Results:

We screened 16,482 patient files at U2 and 62,532 files at the U1. We analyzed the causes of eye pain in 1488 patients from U2 and 814 patients from U1. 1385/1488 (93%) of the U2 patients and 584/814 (72%) U1 were from ophthalmology; 103/1488 (7%) U2 patients and 230/814 (28%) U1 patients were from neurology. The three most common ophthalmologic diagnoses at U2 were conjunctivitis (27%), keratitis (11%), and blepharitis (8%), and the three most common neurologic diagnoses were optic neuritis (2.5%), zoster ophthalmicus (1.1%) and migraine (0.6%). The three most common ophthalmologic diagnoses at U1 were dry eye (13%), migraine (9%), and blepharitis/keratitis (6%), and the two the most common neurologic diagnoses were migraine/headache (61%) and optic neuritis (5%).

Conclusions:

Eye pain was caused by ocular inflammation in the ophthalmology clinic in both institutions; however, more migraine was identified at U1. In the neurology clinics, optic neuritis and migraine were the most frequent causes in both institutions. These findings may help neurologists and ophthalmologists look for the most frequent causes of eye pain in their populations. Different referral bias and patients may account for some of the differences between institutions.

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Evans RW, Foroozan R. Eye pain without visual symptoms. Headache. 2007 Sep;47(8):1206-9.

Keywords: Eye Pain, Dry Eye, Migraine, Optic Neuritis, Conjunctivitis, Keratitis

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 194

Retinal Nerve Fiber Layer Thickness in HTLV-1 Patients

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Introduction:

The Human T-cell leukemia virus type 1 (HTLV-1) is the first discovered human retrovirus. Although the vast majority of infected individuals are asymptomatic carriers (a.c.HTLV-1), HTLV-1 can induce Tropical Spastic Paraparesis/HTLV-1 Associated Myelopathy (TSP/HAM), a progressive, inflammatory, and demyelinating myelopathy. HTLV-1 intermediate uveitis is the most frequent ophthalmic manifestation, in the setting of which optic disc edema can be observed. An actual acute optic neuropathy (ON) can also occur during the course of TSP/HAM, the whole clinical presentation mimicking a progressive form of multiple sclerosis. Previous reports have suggested subclinical involvement of the optic nerve in HTLV-1 patients using visual evoked potential. The goal of our study was to determine whether there is subclinical ON in a.c.HTLV-1 and TSP/HAM patients using retinal nerve fiber layer (RNFL) thickness.

Methods:

We prospectively included a.c.HTLV-1 and TSP/HAM patients between January 1st,2014 and March 31st,2015. All patients had a complete eye examination. Visual acuity (VA) and RNFL thickness were measured and compared to age- and sex-matched control groups including patients seen in our refraction clinic with no previous medical or surgical history.

Results:

Twenty-nine a.c.HTLV-1 (group1) and 29 TSP/HAM patients (group2) were included. Average RNFL thickness was 99.9+/-14.3 µm in group1 and 87.8+/-19.2 µm in group2. Average RNFL thicknesses were lower in both groups, when compared to controls. The difference was significant in patients with TSP/HAM (87.8+/-19.2 vs. 97+/-7.8 µm;p=0.003) who also had significantly decreased VA.

Conclusions:

We report here the first study about RNFL thickness in patients with TSP/HAM. In these patients, there is decrease of the RNFL thickness with subtle but definite decrease of VA. This suggests that subclinical ON occurs in the natural history of the disease. The diagnosis of TSP/HAM must be evoked as a differential of primary progressive multiple sclerosis in a population at risk. Moreover, RNFL thinning with no evidence of glaucoma should raise suspicion for HTLV infection and TSP/HAM in a population at risk.

References: None.

Keywords: Optic Neuropathy, HTLV-1, TSP/HAM

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 195

Sabril Vision Study: Retinal Structure and Function in Adult Patients with Refractory Complex Partial Seizures (rCPS) Treated with Vigabatrin

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Introduction:

Visual deficits have been reported in retrospective, cross-sectional studies in vigabatrin-treated patients. This study evaluated visual-field (VF) and retinal-structure changes following adjunctive vigabatrin treatment in vigabatrin-naïve adults with rCPS.

Methods:

Prospective, longitudinal, single-arm, open-label study (NCT01278173). Eligible patients (≥ 2 seizures/month who failed ≥ 3 therapies) performed reliable perimetry (Humphrey automated static) and retinal-structure assessment (spectral-domain optical coherence tomography) pre-vigabatrin exposure. Following vigabatrin initiation, testing occurred within 1 month (reference) and at 3, 6, 9, and 12 months. Endpoints included: mean change from reference in mean deviation (dB) and average retinal nerve fiber layer (RNFL) thickness, visual acuity (VA) changes from baseline, and number of patients who met pre-defined vision-parameter changes at 2 (confirmed) or 3 (persistent) consecutive visits.

Results:

Sixty-five of 91 screened patients received ≥ 1 vigabatrin dose (all-patients-treated set [APTS]); 55 had ≥ 1 valid reference and post-reference assessment (full-analysis set [FAS]). Thirty-six APTS patients with valid pre-/post-reference values completed all planned visits (per-protocol set [PPS]). Thirty-eight (59%) APTS patients completed the study; 27 (42%) withdrew (none for VF changes); 32% and 15% had abnormal RNFL thinning and VA at baseline, respectively; 20% had abnormal near VFs vs reference. No significant mean near-VFs changes were observed (PPS); mean change in average RNFL thickness *increased* significantly (1-year data: Left-eye: 6.37 μ m, CI:[4.66,8.09]; Right-eye: 7.24 μ m CI:[5.47,9.01]; PPS). No confirmed 3-line decreases in VA (FAS) were observed; 3 patients had pre-defined confirmed/persistent near-VF changes (FAS). All vision-related AEs were non-serious; the most common was vision blurred (9%).

Conclusions:

Prior to vigabatrin initiation, rCPS patients may already exhibit vision deficits. Adjunctive vigabatrin treatment (up to 1-year) did not significantly change population near VFs (despite 3 patients meeting pre-defined near-VF-change criteria). RNFL thickening (unknown clinical significance) was observed. Limitations include: single-arm, open-label design; patients' inability to perform ophthalmic/VF examinations; and short-term vigabatrin-exposure duration. Funding: Lundbeck, LLC

References: None.

Keywords: Vigabatrin, Refractory Epilepsy, Vision Study, Perimetry, Visual Field

Financial Disclosures: Sergott: Consultant and speakers' bureau: LundbeckWechsler: Ad boards and consulting: Cyberonics, Eisai, Gerson Lehrman, Lundbeck, Sunovion, UCB, Upsher-SmithDribinsky:Salary, LundbeckWhittle: Salary, LundbeckFeng: Salary, LundbeckLee: Salary, LundbeckIsojarvi: Salary, Lundbeck.

Grant Support: None.

Poster 196

Patterns of Change in Macular Thickness on OCT in Normal Pregnancy and Pregnancy Complicated by Hypertension: A Tool for Assessing Dynamic Function of the Microcirculation

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Introduction:

The macula is a capillary bed with a microcirculation homologous to that of CNS tissues. Unlike arterioles of most organs, the eye and brain autoregulate (AR) capillary transudation such that it remains within physiologic limits despite large variations in pressure and flow within the systemic circulation. Pregnancy is accompanied by 40-60% greater blood volume and cardiac output and increased capillary permeability. These test the integrity of the AR reflex. Our study assesses whether SD-OCT measurements of retinal macular thickness can profile dynamic changes in AR response in pregnancy.

Methods:

Sequential SD-OCT measurements of macular thickness were obtained in over 100 pregnant women; 32 have complete data at gestational ages < 20 wks, 20-40 wks, at delivery and ≥ 2 wks post delivery. Women with normal pregnancies, pre-existing hypertension and pregnant, and hypertensive disorders of pregnancy were included. Differences in retinal thickness from the internal limiting membrane to the retinal pigment epithelium in each ETDRS segment were compared. Clinically meaningful change was defined as $\geq \pm 4\mu\text{m}$ (Test-Re-test Coefficient of Repeatability) in 3 or more contiguous segments.

Results:

The retina thins 5-15 μm in early normal pregnancy (14 patients). Two patients with pre-existing, poorly controlled hypertension had delayed thinning, but only with progressive elevations in blood pressure (BP). Retinae thickened in 10 patients with preeclampsia/severe hypertension with capillary leak occurring into macular tissues even before BP started rising. As retinal edema worsened near term, BPs rose precipitously.

Conclusions:

Preliminary data show SD-OCT is able to characterize changes in retinal thickness in response to hemodynamic events accompanying normal pregnancy. Arteriolar constriction due to capillary permeability left-shifts the AR curve in early normal pregnancy. This differs from renal AR. AR fails in most preeclampsia. Insights gained from this work may enhance understanding of a broad spectrum of disorders involving the microcirculation, including preeclampsia, hypertension, diabetes and dementia.

References: None.

Keywords: Pregnancy, Hypertension, Preeclampsia, Autoregulation, Microcirculation

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 197**The Association Between Multiple Sclerosis and Uveitis**

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Introduction:

Uveitis and multiple sclerosis (MS) are considered to be somewhat associated. What is the prevalence of MS-associated uveitis? We set out to study this question through a systematic search of contemporary literature.

Methods:

A systematic search of the database Pubmed.com using the following MeSH-terms '[Multiple Sclerosis]' AND '[Uveitis]' was undertaken. All studies with a prevalence of MS-associated uveitis were included. Of the 215 original hits 26 studies were included. Additional 6 studies from the related citations were included.

Results:

The prevalence of MS in patients with uveitis differs from 0,7% to 30,4%, while the prevalence of uveitis in patients with MS differs from 0,65% to 36,7%. All types of uveitis are seen among the patients with multiple sclerosis.

Conclusions:

The 32 studies are difficult to compare due to differences in the size of the cohort, differences in study design as well as different diagnostic criteria for MS and especially uveitis. Based on the biggest retrospective studies the prevalence of MS-associated uveitis seems to be approximately 1% - both for patients with uveitis as well as for patients with MS. To further investigate the association between MS and uveitis bigger prospective studies are needed.

References: None.

Keywords: Multiple Sclerosis, Uveitis

Financial Disclosures: The authors had no disclosures.

Grant Support: Travel grant to participate in theECTRIMS congress 2015 with Genzyme.

Poster 198**Asymmetric Fundus Autofluorescence Findings in Parkinson's Disease**

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Introduction:

Motor asymmetry is one of the criteria for the diagnosis of Parkinsons disease (PD). Interocular asymmetry in spectral domain optical coherence tomography (SD-OCT) of the retina and possibly nerve fiber layer has also been documented.

Methods:

The files of 20 PD patients diagnosed at other neurology clinics were examined. Fundus autofluorescence (FAF) images of these patients were observed by two ophthalmologists in a masked fashion. Hyper or hypofluorescent lesions which suggested neurodegeneration were taken into consideration. The mean age of the patients was 69.

Results:

In 15 patients hypo and hyperfluorescent lesions were on the nasal side of the retina. In patients who had early PD, degenerative lesions were on the nasal side. Diffuse degeneration on FAF was detected in the middle stages of the disease. 5 patients had this kind of distribution. This asymmetric appearance was in parallel with the asymmetric findings in motor functions.

Conclusions:

Since FAF detects lipofuscin in the retina, the images were consistent with retinal damage. Lipofuscin gives damage to the tissues by mechanically obstructing the flow into and out of the cells and slowing down the elimination of waste materials. The predilection of neurodegeneration for the nasal retina and the asymmetric appearance on FAF was not reported before, to the best of our knowledge. Studies with larger series may give important information about the early detection of PD by ophthalmologic examination. Our study suggests that imaging of the nasal retina early in the disease may reveal findings consistent with the asymmetric nature of PD.

References: None.

Keywords: FAF, Parkinson's, Asymmetry, Retina

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 199

Visual Symptoms and Movement Disorders: Establishing a Neuro-ophthalmology Clinic Designed for Patients with Movement Disorders

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Introduction:

We aim to share knowledge gained with the development of a subspecialty clinic within neuro-ophthalmology for patients with visual complaints in the setting of a movement disorder, including: Idiopathic Parkinson's Disease (IPD), Progressive Supranuclear Palsy, dementia with Lewy Bodies, Parkinsonism, ataxia, and others. Barriers to the delivery of high-quality, neuro-ophthalmic care that is patient-centered include the multifactorial, fluctuating, and progressive nature of the visual symptoms and the need for extended appointments to accommodate fatigue and cognitive impairment. To address these barriers, we established a monthly neuro-ophthalmology clinic dedicated to patients with movement disorders.

Methods:

Based on input from ophthalmic technicians, movement disorder specialists, optometry, and patients, we began a monthly, neuro-ophthalmology clinic with specialized facets of care for patients with movement disorders. The clinic is staffed by a neuro-ophthalmologist, an optometrist, a movement disorders fellow, and an ophthalmic technician. Standardized procedures were introduced and are being refined and developed, including the use of the Self-Administered Gerocognitive Exam (or SAGE) and disease-specific rating scales.

Results:

Ease of scheduling, defined goals for visits, and patients' perception of care were subjectively improved. Standardized data collection is ongoing. Most patients referred have IPD or Parkinsonism and complain of problems driving, reading and/or double vision, while others are referred specifically to aid in the diagnosis of the primary movement disorder. Cognitive impairment is common.

Conclusions:

We believe the establishment of a neuro-ophthalmology clinic to address the unique needs of patients with movement disorders will ease the inherent burdens associated with evaluating, diagnosing, and treating visual complaints in this population. Cognitive impairment may be more common than expected and/or contributing to visual complaints in this unique population. Standardized data collection will aid in the delivery of high-quality, patient-centered, neuro-ophthalmic care and increase our understanding of the causes and management of visual complaints in this population.

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Keywords: Quality of Care, Visual Complaints and Movement Disorders, Multispecialty Neuro-Ophthalmology Clinic, Patient-Oriented Care, Cognitive Impairment

Financial Disclosures: The authors had no disclosures.

Grant Support: Movement Disorders fellows receive funding provided by University Hospital

Poster 200

Pseudotumor Cerebri Secondary to Venous Sinus Occlusion

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Introduction:

Pseudotumor cerebri (PTC) is characterized by increased intracranial pressure (ICP) without any focal neurological sign and symptom with normal cerebrospinal fluid constituents. We are presenting cases of pseudotumor who had cerebral venous sinus occlusion as a cause of raised ICP.

Methods:

40 cases of PTC were followed up for a period of one to two years. In all patients a detailed neuro-ophthalmic examination and lab investigations were performed. Contrast enhanced MRI & MRV, MRA were carried out in all cases. In cases of venous sinus stenosis the pressure gradient across the stenosis was recorded. Finally all cases of venous sinus occlusion were subjected to digital subtraction angiography (DSA).

Results:

Out of 40 cases of PTC there were 16 cases where cause of raised ICP was venous sinus occlusion. Out these 16 cases, 3 had right transverse sinus stenosis with significant pressure gradient >10cm water while 13 cases had superior sagittal sinus and / or transverse sinus thrombosis. Out of these 13 cases of venous sinus thrombosis, 4 cases underwent venous sinus stenting with glued occlusion of secondary dural AVM (Arterio venous malformation) as they had rapidly falling vision which could not be controlled on maximal medical treatment. In 9 cases of venous sinus thrombosis PTC resolved over a period of 6 months on medical treatment.

Conclusions:

After stenting of venous sinus occlusion if signs and symptoms of increased ICP reappear then one should suspect secondary dural AVM formation. When the medical treatment fails and visual loss is rapid then lumboperitoneal shunt or optic nerve fenestration may be considered prior to stenting of venous sinus. As some of our cases could not undergo stenting on time due to financial constraint, had irreversible visual loss.

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Keywords: Pseudotumor Cerebri, Cerebral Venous Sinus Thrombosis, Cerebral Venous Sinus Stenosis, Venous Sinus Stenting

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 201

Comparison of the Surgical Treatment of Superior Oblique Palsy: Surgery Versus Combined Preoperative OnabotulinumtoxinA Injection

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Introduction:

To compare extraocular muscle (EOM) surgery with combined preoperative OnabotulinumA injection to the ipsilateral inferior oblique (IO) muscle for the treatment of superior oblique (SO) palsy

Methods:

A retrospective review of medical records of patients with SO palsy who underwent surgical treatment between 2006 and 2015. Group 1 (n=12) underwent preoperative OnabotulinumtoxinA injection to the ipsilateral IO and then EOM surgery to correct hypertropia, while group 2 (n=12) underwent EOM surgery only. Comparisons were made of preoperative and postoperative vertical deviation angles in primary position and the amount of corrected hypertropia, postoperative drift and success rate (defined as less than 4 PD).

Results:

Preoperatively, there was no statistically meaningful difference in mean vertical deviation in primary position between the two groups (13.0 PD and 13.5 PD, respectively ($p>0.05$)). Mean vertical deviations in primary position at postoperative 1 week measurements were -0.2 PD and 1.8 PD in group 1 and 2 respectively, and -0.7 PD and 0.3 PD in group 1 and 2, respectively, at postoperative 3 months. Mean amount of postoperative drift toward hypertropia in primary position was 0.5 PD and 1.6 PD in group 1 and 2, respectively. Success rate of group 1 was 85% and that of group 2 was 77% ($p>0.05$).

Conclusions:

Both EOM surgery and EOM surgery combined with preoperative OnabotulinumtoxinA injection to the ipsilateral IO muscle were effective in the treatment of SO palsy. Our findings support the condition that there is no reason to avoid preoperative OnabotulinumtoxinA injection while waiting for the EOM surgery in patients with SO palsy.

References: None.

Keywords: Superior Oblique Palsy, OnabotulinumtoxinA, Inferior Oblique Muscle, Extraocular Muscle Surgery, Hypertropia

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 202

Ocular Alignment After Bilateral Medial Rectus Recession in Esotropic Patients with Spinocerebellar Atrophy

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Introduction:

To compare the surgical results of esotropic patients with spinocerebellar atrophy (SCA) and controls without neurologic disorders.

Methods:

Five patients with esotropia and SCA (group 1) and 10 age matched controls without neurologic disorder (group 2) who underwent bilateral medial rectus (BMR) recession were retrospectively included. All patients underwent BMR recession by one surgeon. Surgical success was defined as esotropia less than 6 PD and exotropia less than 9 PD. Preoperative and postoperative deviation angle measurement and success rate were analyzed.

Results:

Preoperatively, there was no statistical difference in mean horizontal deviation in primary position between the two groups (18 PD and 16.4 PD, respectively ($p > 0.05$)). Mean esodeviation angles in primary position at postoperative 1 week measurements were 4.8 PD and 1.1 PD in group 1 and 2 respectively, and 6.4 PD and 3.2 PD in group 1 and 2, respectively, in postoperative 3 months. Success rate of group 1 was 40% and that of group 2 was 60% ($p < 0.05$).

Conclusions:

: SCA patients with esotropia demonstrated slight undercorrection of their esodeviation when compared with that of controls after BMR recession. Our findings support the condition that surgeon should consider increasing the amount of BMR recession when planning the surgery for esotropic patients with SCA.

References: None.

Keywords: Spinocerebellar Atrophy, Esotropia, Bilateral Medial Rectus Recession, Postoperative Undercorrection, Success Rate

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 203

Capturing the Efferent Side of Vision in Multiple Sclerosis: New Data from a Digitized Rapid Number Naming Task

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Introduction:

Visual function in multiple sclerosis (MS) has been well characterized from an afferent standpoint using low-contrast acuity, optical coherence tomography (OCT) and quality of life (QOL). Compared to controls, patients with MS also demonstrate slowed reading times on the King-Devick (K-D) test, a rapid number naming task that captures widely distributed aspects of efferent function, particularly saccades. Slowed times in MS are associated with neurologic dysfunction and reduced vision-specific (QOL). However, the ocular motor underpinnings of such slowing have not been determined. We sought to determine ocular motor performance and characterize deficits leading to slowed KD reading times using recorded eye movements during a digitized King-Devick (K-D) test.

Methods:

We tested 13 patients with MS (mean age 37) and compared their results to those of our normative database of control participants without MS (n=38, mean age 31). Participants completed the digitized K-D task with simultaneous video-oculographic eye movement recording (EyeLink 1000+). Data were analyzed off-line in Matlab and Stata 14.0.

Results:

Digitized K-D completion times in the MS cohort were longer (worse) relative to controls (52.6 ± 14.1 sec vs. 43.7 ± 8.5 sec, $p=0.02$, t -test). Intersaccadic intervals (ISI), which represent a combination of saccadic latency and fixation duration between saccades, were prolonged in MS patients (397 ± 137 msec vs. 312 ± 53 msec, $p=0.02$, t -test). Within the MS cohort, test times were longer for the digitized vs. spiral-bound hand-held K-D test (52.0 ± 9.2 sec vs. 43.7 ± 9.7 sec, $p=0.01$, linear regression).

Conclusions:

In this ongoing study of ocular motor performance in MS, we have demonstrated that K-D reading times are slower secondary to prolonged ISI. The K-D test captures efferent visual dysfunction in MS, and is likely to be a sensitive performance-based outcome measure for future research, practice and clinical trials.

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Moster S, Wilson JA, Galetta SL, Balcer LJ. The King-Devick (K-D) test of rapid eye movements: a bedside correlate of disability and quality of life in MS. J Neurol Sci, 15, 1-2, 2014.

Keywords: Ocular motility, Multiple Sclerosis, King-Devick, Saccades

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 204

Exploring the Oculomotor Effects of Sustained-Release Fampridine in Multiple Sclerosis Patients with Gait Impairment.

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Introduction:

Fampridine is a potassium channel blocker that has been shown to suppress downbeat nystagmus effectively. Its effect upon other eye movement abnormalities is largely unknown. We sought to evaluate the immediate and late effects of sustained-release fampridine 10 mg twice a day upon eye movement abnormalities in MS patients with gait impairment and to ascertain the utility of fampridine's oculomotor response in predicting gait response.

Methods:

A total of ten MS patients undergoing treatment with sustained-release fampridine to improve gait disability were submitted to binocular video-oculography and video-head impulse test (vHIT) prior to (visit 1), after 2 hours (visit 2), and after 2 weeks (visit 3) of fampridine treatment.

Results:

Among 10 enrollees, median age was 51 (41–63) years and 9 were females. The number of patients evidencing mild spontaneous nystagmus in darkness in the upright position markedly increased from visit 1 (2, 20%) to visits 2 (6, 60%) and 3 (4, 40%). Similarly, the mean number of patients showing positional nystagmus in darkness in 5 different positions was significantly higher at visit 2 (7.6) than visit 1 (5.1) ($p=0.02$). Six patients evidenced internuclear ophthalmoplegia (INO) (left, 6; right, 4) at visit 1. Importantly, the velocity versional dysconjugacy index (ratio of abducting to adducting eye mean velocity) significantly improved from visit 1 (1.62) to visit 2 (1.23) and 3 (1.23) ($p=0.03$), albeit only for left INO patients. In patients evidencing low horizontal canal (HC) gain (<0.8) at visit 1, vHIT responses significantly improved at visit 3 for the left HC ($p=0.04$) only. None of the ocular parameters and/or their change between visits was able to predict gait response to fampridine.

Conclusions:

Sustained-release fampridine seems to improve eye velocity dysconjugacy and high-frequency vestibular loss in MS patients. The development of spontaneous and positional nystagmus in darkness after treatment with fampridine deserves further investigation.

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Keywords: Aminopyridines, Downbeat Nystagmus, Multiple Sclerosis, Internuclear Ophthalmoplegia, Video-Head Impulse Test

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 205**Diagnostic Ability of the Three-step Test According to the Presence of the Trochlear Nerve in Superior Oblique Palsy**

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Introduction:

To compare the diagnostic ability of the three-step test in unilateral superior oblique palsy (SOP) according to the presence of the trochlear nerve on high-resolution MRI.

Methods:

Diagnosis of unilateral SOP was made by the following 3 absolute criteria, (1) hyperdeviation in the primary position on alternating prism cover test, (2) unilateral underaction of the ipsilateral SO muscle with or without inferior oblique overaction, and (3) lack of evidence of other ocular motility disorders causing vertical deviation, plus 1 of 2 supportive criteria (4) a positive Bielschowsky head-tilt test, (5) unilateral atrophy of the SO muscle on MRI. Eighty-seven patients with a trochlear nerve (present group) and 79 patients without a trochlear nerve (absent group) were included. The sensitivities of each components of the three-step test were evaluated as well as factors related to sensitivities.

Results:

All three steps were positive in 78% of the present group and 72% of the absent group ($P = 0.471$). Step 1 plus 2 was positive in 83% of the present group versus 73% of the absent group ($P = 0.187$). Step 1 plus 3 was satisfied in 95% of the present group versus 99% of the absent group ($P = 0.370$). Patients who were positive in all three steps (complete group) had a larger amount of hyperdeviation during contralateral gaze ($P < 0.001$), ipsilateral tilt ($P = 0.038$) and adduction ($P < 0.001$) compared to those who were negative in at least one step (incomplete group). Superior rectus muscle contracture was more frequent in the incomplete group (24%) compared to the complete group (9%) ($P = 0.014$).

Conclusions:

The diagnostic ability of the three-step test in SOP was equivocal irrespective of the presence of the trochlear nerve. The sensitivity of the three-step test increased when only two steps were applied.

References: None.

Keywords: Superior Oblique Palsy, Three-Step Test, Bielschowsky Head-Tilt Test

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 206

A Detailed Analysis of Oculomotor Function in 16 Patients with Spinocerebellar Ataxia Type 3 (SCA 3).

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Introduction:

Oculomotor abnormalities in SCA 3 patients include the presence of square wave jerks (SWJ), saccade dysmetria, gaze-evoked nystagmus (GEN), positional nystagmus (pN), and caloric hyporreflexia. However, eye movement static and dynamic disconjugacy and high acceleration vestibular responses have been scarcely studied.

Methods:

Sixteen patients with genetically confirmed SCA 3 underwent neurological assessment applying the scale for the assessment and rating of ataxia (SARA), neuro-ophthalmological examination, binocular video-oculography and video-head impulse test (vHIT).

Results:

Patients' median age was 53.5 (26-77) years, median disease duration was 9 (2-25) years and 11 patients were female. The majority of patients (81%) showed esotropia at far. SWJ (mean number, 40/min) were present in all patients except one with concomitant horizontal saccade slowing. Dynamic overshoots within SWJ were asymmetric between eyes, giving the appearance of monocular disconjugate adducting "nystagmus" in two patients. Mean ocular pursuit gain (0.8) and saccade velocity ($>300^\circ/\text{sec}$ in 81% of patients) were relatively preserved. However, horizontal saccades were markedly disconjugate between eyes, being shorter and slower in the abducting eye (amplitude and velocity disconjugacy ratio, 0.95). Phase-plane analysis further showed that saccade velocity disconjugacy persisted during the entire eye excursion in 2/3 of patients. Spontaneous nystagmus in dark was an unusual finding (18%) while GEN and pN were both present in 75% of patients. vHIT evidenced right and/or left horizontal canal (HC) low gain (<0.8) in 75% of patients, which was negatively correlated with SARA score (right HC, $r=-0.7$, $p=0.001$; left HC, $r=-0.6$, $p=0.005$).

Conclusions:

A vergence abnormality possibly induced by cerebellar pathology is hypothesized to be an additional cause of disconjugate saccade velocity between eyes that remains throughout the whole eye displacement. Convergent strabismus may equally help to explain fixation instability disconjugacy in patients with SCA 3. Horizontal canal gain may be a potential biomarker of SCA 3.

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Keywords: Eye Movements, Strabismus, Spinocerebellar Ataxia Type 3, Video-Oculography, Video-Head Impulse Test

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 207**Measurement of Ocular Torsion with Digital Image Analysis in Face Turn and Head Tilt for Assessment of a Superior Oblique Palsy**

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Introduction:

The superior oblique intorts the globe, and its paresis results in pathologic excyclotorsion. Abnormal torsion can be clinically detected by fundus assessment. Typically fundus torsion is assessed in primary position. We hypothesized that additional assessment of fundus torsion in face turn and head tilt would improve diagnostic accuracy.

Methods:

Study participants underwent a full neuro-ophthalmic and sensorimotor examination. Fundus images of each eye were taken for primary position, 45 degrees face turn (right and left), and 15 degrees of head tilt (right and left). Torsion was assessed by an experienced strabismus specialist and by digital analysis software, measuring the angle between the fovea and the center of the optic nerve.

Results:

Fifteen normal subjects and twenty-five patients with clinical features of a unilateral superior oblique palsy were recruited. In primary position the mean torsion for normal subjects was 6.4 degrees of excyclotorsion (SD 3.6). Only 9 of the 21 superior oblique cases demonstrated abnormal torsion in primary position, and an additional 4 cases had abnormal torsion only in the contralateral eye. There was significant correlation with double-maddox readings ($p < 0.01$) and high correlation with the subjective fundus assessment of the expert ($p < 0.0001$). The degree of torsion in side gaze was not significantly different from primary position in either population. Relative to the sagittal axis of the skull, ipsilateral and contralateral head tilt produced a significant but slight change in torsion for both normal subjects and superior oblique palsy cases but there was no significant variation between the two populations.

Conclusions:

A significant amount of patients with clinical findings of a superior oblique palsy have normal fundus torsion. An experienced strabismus surgeon is able to accurately assess fundus torsion. Additionally evaluating torsion in side gaze or head tilt does not add diagnostic value.

References: None.

Keywords: Superior Oblique Palsy, Fundus Torsion, Double Maddox

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 208**Dental Malposition in Patients with Congenital Superior Oblique Muscle Palsy**

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¹Center of Dental Medicine, Dept. of Orthodontics, University of Zurich, Zurich, Switzerland, ²Dept. of Ophthalmology, University Hospital Zurich, Zurich, Switzerland, ³Dept. of Ophthalmology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

Introduction:

Patients with congenital superior oblique palsy tend to adopt a head tilt to the contralateral side to maintain binocular single vision. Facial asymmetries as a consequence of a long-standing head tilt have been reported previously. The aim of this study was to analyze the effect of habitual head tilt due to congenital superior oblique palsy on dental occlusion.

Methods:

The study was designed as a descriptive cohort study. Ten patients with congenital superior oblique palsy (3 female, 7 male; mean age 51.7 [y] \pm 15.8 SD, ranging from 19 to 69 [y]) underwent an orthodontic examination. Preoperative amounts of vertical, torsional and horizontal deviation were measured using Harms tangent screen and the results were correlated with orthodontic findings.

Results:

Three orthodontic parameters were found to correlate significantly or at least as trend with orthoptic parameters. Midline deviation of the upper jaw to the face (Mili UJ/F; ρ =0.623; p =0.054) as well as anterior positioning of upper first molar in the sagittal plane (6+6 ant; ρ =0.594; p =0.07) correlate with vertical deviation in primary position. Vertical distance between tips of upper and lower incisors, so called overbite, correlates with horizontal deviation measured in primary position (ρ =0.768; p =0.016).

Conclusions:

Based on our results we propose that in some patients with congenital superior oblique palsy the upper jaw rotates slightly towards the non-paretic side, inducing an anteriorization of the upper molar teeth on the paretic side. In our preliminary study three orthodontic parameters could be found to correlate with orthoptic measurements. Further studies should investigate whether in patients showing these orthodontic parameters a congenital superior oblique palsy can be found more frequently than in subjects without such characteristics.

References: None.

Keywords: Adult Strabismus, Ocular Motility, Head Tilt, Consequences Of, Dental Occlusion, Orthodontics

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 209

Rapid Number Naming and Quantitative Eye Movements May Reflect Contact Sport Exposure in a Collegiate Ice Hockey Cohort

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Introduction:

The King-Devick (K-D) test of rapid number naming is a reliable visual performance measure that is a sensitive sideline indicator of concussion when time scores worsen (lengthen) from pre-season baseline. We determined the relation of rapid number naming time scores on the K-D test to video-oculographic eye movement performance during pre-season baseline assessments in a collegiate ice hockey team cohort.

Methods:

Athletes from collegiate ice hockey team received pre-season baseline testing as part of an ongoing study of rapid sideline/ rinkside performance measures for concussion. These included the K-D test (spiral bound cards and tablet computer versions). Participants also performed a laboratory-based version of the K-D test with simultaneous infrared-based video-oculographic recordings using EyeLink 1000⁺. This allowed measurement of temporal and spatial characteristics of eye movements, including saccade velocity, duration and inter-saccadic intervals.

Results:

Among 13 male athletes, aged 18 to 23 years (mean 20.5±1.6 years), prolongation of the inter-saccadic interval (ISI, a combined measure of saccade latency and fixation duration) was the eye movement measure most associated with slower baseline KD scores (mean 38.2±6.2 seconds, $r=0.88$, $p=0.0001$). Older age was a predictor of longer (worse) K-D baseline time performance ($r=0.57-0.70$, $p=0.008-0.04$) as well as prolonged ISI ($r=0.62$, $p=0.02$) in this collegiate cohort. Slower baseline K-D times were not associated with greater numbers of reported prior concussions.

Conclusions:

Rapid number naming performance at pre-season baseline is best correlated with ISI when eye movements are recorded. Baseline K-D scores notably worsened with increasing age but not with number of prior concussions in this small cohort. These findings suggest that duration of contact sport exposure, rather than concussion history, may influence pre-season baseline rapid number naming performance.

References: None.

Keywords: Rapid Number Naming, Concussion, Eye Movements, Saccades, King-Devick Test

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 210**Adaptation to New Onset Incomitance**

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Introduction:

Incomitance is characterized by gaze dependent deviations of ocular alignment. The physiological mechanisms that maintain equal horizontal ocular alignment in all gaze directions (concomitance) in healthy individuals are poorly explored. We investigate adaptive processes in the vergence system that are induced by horizontal incomitant vergence stimuli (stimuli that require a gaze dependent vergence response in order to re-establish binocular single vision).

Methods:

We measured horizontal vergence responses elicited after healthy subjects shifted their gaze from a position that required no vergence to a field of view that required convergent eye movement.

Results:

Repetitive saccades into a field of view with a convergence stimulus rapidly decreased phoria (defined as the deviation of ocular alignment in absence of binocular stimulus). This change of phoria was present in all viewing directions, but was more pronounced in the gaze direction with a convergence stimulus. We also found that vergence velocity rapidly increased and vergence latency promptly decreased. We found gaze dependent modulation of phoria in combined saccade-vergence eye movements, and also in pursuit-vergence eye movements.

Conclusions:

Acute horizontal, gaze-dependent change of vergence, such as may be encountered in new onset paretic strabismus, will rapidly increase vergence velocity, and decrease latency. Gaze specific (concomitant) and gaze independent (incomitant) phoria levels will adapt and thus reduce induced phoria and promote concomitance.

References: None.

Keywords: Vergence, Saccade, Pursuit, Adaptation, Incomitance

Financial Disclosures: The authors had no disclosures.

Grant Support: M.A. was supported by the Swiss National Science Foundation

Poster 211

Decreased Binocular Summation in Strabismic Amblyopes and Effect of Strabismus Surgery

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Introduction:

Binocular summation (BiS) is the improvement in visual function using binocular vision surpassing the better eye alone. Previous studies have demonstrated diminished BiS in non-amblyopic strabismic patients. We examined effects of strabismic amblyopia and strabismus surgery on BiS.

Methods:

We prospectively enrolled 13 strabismic patients with amblyopia, 26 age-matched normal controls, and 26 strabismic patients without amblyopia. Strabismic patients were tested before and after realignment surgery. Visual acuity was tested binocularly and monocularly using high-contrast ETDRS charts and Sloan low-contrast charts at 2.5% and 1.25% contrast. BiS was calculated as the difference between the binocular and better eye scores.

Results:

Patients with strabismic amblyopia had subnormal BiS at both 2.5% (1.7 letters in strabismic amblyopes vs. 6.2 letters in normal controls, $p=0.001$) and 1.25% contrast (-0.46 vs. 5.9 letters, $p = 0.0075$). There was no difference in BiS between strabismic amblyopes and non-amblyopic strabismic patients. After strabismus surgery, BiS improved in amblyopic patients who had measurable stereoacuity preoperatively, from -2.6 to 6.0 letters on 2.5% contrast charts ($p = 0.03$), but did not improve after surgery in patients without stereo. Among patients with different strabismus subtypes, there was no significant difference in postoperative improvement in BiS.

Conclusions:

Both strabismic amblyopes and non-amblyopic strabismic patients have decreased BiS, but amblyopia may not further degrade BiS in the setting of strabismus. BiS may improve after strabismus surgery in amblyopic patients with measurable stereoacuity.

References:

Pineles SL, Demer JL, Isenberg SJ, Birch EE, Velez FG. Improvement in binocular summation after strabismus surgery. *JAMA Ophthalmol*, 133, 326-32, 2015.

Pineles SL, Velez FG, Isenberg SJ, Fenoglio Z, Birch E, Nusinowitz S, Demer JL. Functional burden of strabismus: decreased binocular summation and binocular inhibition. *JAMA Ophthalmol*, 131,1413-9, 2013.

Keywords: Strabismus, Amblyopia, Binocular Summation, Strabismus Surgery

Financial Disclosures: Stacy Pineles grants:NIH/NEI K23EY021762Research to Prevent Blindness Walt and Lily Disney Award for Amblyopia ResearchKnights Templar Eye FoundationOppenheimer Family Foundation.

Grant Support: Stacy Pineles Grant Support: NIH/NEI K23EY021762 Research to Prevent Blindness Walt and Lily Disney Award for Amblyopia Research Knights Templar Eye Foundation Oppenheimer Family Foundation.

Poster 212**Stability of Human Binocular Alignment: A Video-Oculographic Luminance Study**

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Introduction:

To evaluate the stability of human binocular alignment under conditions of altered fixation and luminance.

Methods:

We measured horizontal binocular alignment in examined 8 healthy orthotropic subjects using infrared video-oculography (VOG) under conditions of binocular fixation and luminance change. Each testing condition was preceded by a binocular fixation period in room light (475 lux) to define the baseline binocular alignment. We then measured binocular alignment in darkness without fixation, in darkness with a distant fixational target, and in room light through a semi-translucent filter that precluded fixation. We determined whether these experimental conditions induced significant binocular alignment change from each baseline binocular alignment statistically using the signed rank test.

Results:

The mean horizontal binocular alignment in the dark was similar to baseline binocular alignment ($0.2^\circ \pm 2.8^\circ$; $p=0.4$). The mean horizontal binocular alignment when fixing in a room light was similar to baseline binocular alignment ($-1.4^\circ \pm 1.6^\circ$; $p=0.08$). The mean horizontal binocular alignment in the dark when a fixational target was provided showed an exo-drift compared to baseline alignment ($2.3^\circ \pm 1.0^\circ$; $p=0.0004$).

Conclusions:

The human brain does not require visual input to maintain binocular alignment on a short-term basis. The resilience of binocular alignment reflects the presence a subcortical memory system or tonus mechanism which is probably calibrated by phoria adaptation, a sensorimotor process that resets the baseline phoria toward zero to eliminate binocular disparity. Ocular proprioception may play a secondary role.

References: None.

Keywords: Ocular Motility, Higher Visual Cortical Functions, Higher Visual Functions

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 213**Pitfalls and Rewards for Implementing Emergent Bedside Oculomotor Testing in Patients with Acute Vestibular Syndrome**

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Introduction:

Patients with Acute Vestibular Syndrome (AVS) commonly presents to the Emergency Department and pose management challenges given concerns for posterior fossa strokes. A three-step bedside oculomotor examination called HINTS Plus (Head-Impulse, Nystagmus, Test-of-Skew Plus acute hearing loss) was shown to accurately identify small infarcts as a cause of AVS. We studied the feasibility of implementing HINTS testing in the ED, aiming to reduce unnecessary neuroimaging and improve posterior circulation stroke detection.

Methods:

A Quality Improvement project was launched in April 2015 after education about HINTS testing significance, performance and documentation. ED physicians were encouraged to obtain immediate neurological or stroke consultation in patients with acute vertigo. Brain imaging was not performed if HINTS suggested peripheral vestibular etiology. If central process was suspected, thin brainstem cuts MRI and vascular imaging were performed. Head CT was performed if presentation was within the time-window for thrombolysis. All patients were assessed for follow-up at 7 days.

Results:

Encountered and defeated pitfalls in the QI process were the performance of oculomotor examination, findings' documentation and interpretation and protocol applicability in patients with vertigo characteristics different than AVS. 37% of AVS patients had peripheral HINTS examinations and definitive peripheral vestibulopathies. 40% of patients had central HINTS exams with various underlying pathologies. tPA was administered in 2 cases, with excellent outcomes. 44% of patients underwent acute brain imaging. Direction-changing nystagmus and skew deviation were sensitive markers for central pathology. 57% of patients that became asymptomatic after vestibular suppressant's administration before HINTS testing or had episodic vertigo, demonstrated lack of corrective saccade.

Conclusions:

HINTS ED evaluation is feasible and valuable, by identifying patients in need of further CNS imaging or acute stroke therapy and safely avoiding neuroimaging for patients with peripheral HINTS exams. The impact on the cost of care and repeat consultation rates is pending determination.

References:

1. Kattah, Talkad, Wang, Hsieh, Newman-Toker. Three-Step Bedside Oculomotor Examination More Sensitive Than Early MRI Diffusion-Weighted Imaging. *Stroke*. 2009;40:3504-351
2. Newman-Toker, Kerber, Hsieh, Pula, Omron et al. HINTS Outperforms ABCD2 to Screen for Stroke in Acute Continuous Vertigo and Dizziness. *ACADEMIC EMERGENCY MEDICINE* 2013; 20:987–996
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5. Kerber. Vertigo and Dizziness in the Emergency Department. *Emerg Med Clin North Am*. 2009 February ; 27(1): 39

Keywords: Vertigo, Nystagmus, Skew Deviation, Head Thrust, Stroke

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 214

Head Tilt Observation Study

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Introduction:

Vertical ocular misalignments can produce significant symptoms even when the degree of strabismus is small. Those can be difficult to detect and are frequently missed. We observed that most patients who have vertical misalignment often have a resting head tilt. Thus, we performed a study to assess the sensitivity and specificity of the presence of a resting head tilt correlating to a vertical strabismus.

Methods:

Patients were included if they presented to our Neuro-ophthalmology clinic and were observed to have a resting head tilt. In such cases, data was recorded regarding a vertical/oblique diplopia, an awareness of the head tilt, history of head trauma, whether the referring provider noted the head tilt, and the results of a sensorimotor exam including a Maddox rod evaluation. Thirty-five patients were identified with a head tilt.

Results:

Our preliminary results showed that 94% of those patients (33/35) had a vertical ocular misalignment, 76% (25/33) of whom described diplopia. The misalignment was detected by alternate cover test in 25% of cases. When this test was negative, Maddox rod identified 75% of the remainder. Of those, 18% were aware of the head tilt, which was recognized by 17% of the referring healthcare providers.

Conclusions:

This preliminary study revealed a very high sensitivity and specificity for the predictive value of a resting head tilt to be associated with a vertical ocular misalignment. An important outcome was the value of using a Maddox rod test. Its use, however, induces phorias, and the next phase of our study will include an assessment of a false positive yield with the Maddox rod test (i.e. how often is it positive in patients without a head tilt). Attention to the presence of a resting head tilt should prompt clinicians to search for even subtle vertical misalignment, as correction with prism often provides symptomatic improvement.

References:

1. Wade NJ. The effect of monocular and binocular observation on visual orientation during head tilt. *Am J Psychol.* 1969 Sep;82(3):384-8.
2. Muthusamy B, Irsch K, Peggy Chang HY, Guyton DL. The sensitivity of the bielschowsky head-tilt test in diagnosing acquired bilateral superior oblique paresis. *Am J Ophthalmol.* 2014 Apr;157(4):901-907

Keywords: Head Tilt, Ocular Vertical Misalignment

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 215**Factors Influencing Success of Prisms In The Management of Diplopia From Various Causes**

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Introduction:

Prospective studies evaluating prism satisfaction amongst patients with various kinds of ocular deviations are lacking. Our objective was to evaluate systematically various factors such as type and amount of ocular deviation, fusional ability, amount of prism given, type of glasses, that can influence the success of prisms in patients with diplopia. By means of a questionnaire patients were queried about their overall satisfaction with prism use as well as the side effects they experienced.

Methods:

Prospective, consecutive, single center study of adult patients with binocular diplopia. Details of ocular misalignment and prisms prescribed were collected. A survey questionnaire was administered specifically inquiring into advantages and disadvantages of prism glasses.

Results:

Of the 110 patients enrolled in the study, there were 69 females and 41 males with a mean follow up of 7 months. Prisms were prescribed for esodeviation (41), exodeviation (12), hyperdeviation (35) and combined deviations (22) from various etiologies. The mean horizontal alignment was 7.6PD and mean vertical alignment was 6.3 PD. The average horizontal prism prescribed was 6.4PD and mean vertical prism prescribed was 5PD. The overall satisfaction with prism was 88 % with improvement noted in diplopia (90%), enhanced depth perception (44%), improved driving (57%) and reading (51%). The side effects of prisms reported that were bothersome to the patients were increased weight (5%), altered depth perception (16%), distortion of vision (10%) and seeing halos (7%).

Conclusions:

Overall the satisfaction of prisms in our prospective cohort of patients was high across all ocular misalignments and for wide range of deviations. Improvements were reported by patients with regards to driving, reading and other day today tasks. Noticeable side effects in this cohort included altered depth perception and visual distortion.

References: None.

Keywords: Diplopia, Prisms, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 216

Screening for Thymoma in Suspected Ocular Myasthenia Gravis: A Retrospective Study

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Introduction:

Thymoma can be associated with ocular myasthenia gravis (OMG). The yield of thymic imaging to screen for thymoma in suspected OMG patients is not known.

Methods:

A retrospective study of consecutive patients with suspected OMG seen in a neuro-ophthalmology clinic from Jan 2013-Sept 2015

Results:

42 patients (57% men) with a median age of 50 years (range 20-86) were included. 43% were seropositive for anti acetylcholine receptor (anti-AChR), one seropositive for muscle specific kinase antibody. 36 patients had thymic imaging by magnetic resonance (MR) or computed tomography (CT). 2/36 (6%) had thymoma confirmed on imaging and histology. Both were seropositive to anti-AChR. Anti-striated muscle antibody, tested in one, was negative.

Conclusions:

Thymic imaging to exclude thymoma is recommended in all patients with ocular myasthenia gravis.

References: None.

Keywords: Ocular Myasthenia Gravis, Thymoma

Financial Disclosures: The author had no disclosures.

Grant Support: None.

Poster 217**The Ocular Motor Underpinnings of Rapid Number-Naming as a Sideline Performance Measure for Concussion**

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Introduction:

The King-Devick (KD) test of rapid number-naming, a sensitive and rapid performance measure, adds a visual and eye movement outcome to sideline testing for concussion. We performed a laboratory-based study to characterize ocular motor behavior during the KD test in a cohort of patients with concussion to identify the features leading to KD reading time prolongation in concussion.

Methods:

We tested 12 subjects with a history of concussion (mean age 31) and compared their results to those of our normative database of non-concussed control participants (n=38, mean age 31). Participants performed a computerized version of the KD rapid number-naming task. Simultaneous infrared-based video-oculographic recordings were performed using Eyelink 1000*, allowing measurement of temporal and spatial characteristics of eye movements (saccade velocity and duration, inter-saccadic interval, etc.).

Results:

Average inter-saccadic intervals (a combined measure of saccade latency and fixation duration) were significantly greater among concussed subjects compared to non-concussed controls (394.43 ± 140.64 msec vs. 312.45 ± 52.54 msec, $p=0.036$, t -test). Digitized KD reading times were prolonged in concussed participants versus non-concussed controls (52.43 ± 14.20 sec vs. 43.68 ± 8.54 sec, $p=0.032$, t -test). In addition to temporal differences, concussion was also associated with larger average deviations of horizontal saccade endpoints from the centers of to-be-read numbers (0.37 ± 0.35 deg vs. 0.13 ± 0.31 deg, $p=0.02$, t -test). There were no differences in saccade velocity, duration, amplitude, or in vertical deviation from number centers.

Conclusions:

Results of this study demonstrate that prolonged intersaccadic intervals and larger deviations of saccade endpoints likely underlie the increased reading times for the KD test in the setting of concussion. A sensitive and rapid sideline performance measure, the KD test of rapid number-naming relies upon a diffuse network responsible for saccade target selection and planning and captures deficits in efferent visual function characteristic of concussion.

References: None.

Keywords: Trauma, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: JRR supported by NICHD 5K12 HD001097 (RMSTP program).

Poster 218

Clinical Manifestations of Extraocular Muscle Paresis in Patients with Miller Fisher Syndrome

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Introduction:

To determine the clinical manifestations of extraocular muscles (EOM) paresis in patients with Miller Fisher syndrome.

Methods:

We retrospectively reviewed the medical records of patients with Miller Fisher syndrome who have been presented with ophthalmoplegia between 2010 and 2015. Antecedent infections, involved EOMs, strabismus pattern in primary position, involved cranial nerves, and laboratory findings were analyzed. We compared patients with complete ophthalmoplegia (CO) and patients with incomplete ophthalmoplegia (IO).

Results:

A total of 28 patients, including 15 males and 13 females, were included in the study. The mean age was 39.3 ± 19.95 years. Twenty-five had symptoms of antecedent infection. The mean time of complete recovery was 13.1 ± 7.60 weeks. Twenty-three had positivity to the serum anti-GQ1b antibody. The most involved EOM and the latest recovered EOM were lateral rectus muscle. CO was observed in 10 patients and IO was observed in 18 patients. The mean age was 59.8 ± 16.98 years in CO, and 27.9 ± 10.52 years in IO. The proportion of female was 80.0% in CO, and 27.8% in IO. The occurrence of facial palsy was 70.0% in CO, and 22.2% in IO. Patients with an elevated CSF protein were 55.6% in CO, and 17.6 % in IO (the mean checked time from initial symptoms; 3.7 days).

Conclusions:

Lateral rectus muscle was the most involved and the latest recovered EOM. Patients with complete ophthalmoplegia were much older, higher ratio of female, higher incidence of facial palsy, and more elevated CSF protein than patients with incomplete ophthalmoplegia.

References: None.

Keywords: Miller Fisher Syndrome, Extraocular Muscle Paresis, Guillain–Barré Syndrome, Complete Ophthalmoplegia, Anti-GQ1b Antibody

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 219**Differentiating Decompensated Superior Oblique Muscle Dysfunction from Ischemic Fourth Cranial Nerve Palsies**

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Introduction:

Isolated fourth cranial nerve palsies are commonly caused by decompensation of a dysfunctional superior oblique muscle ("decompensated palsies"). The differentiation of this cause from palsy caused by presumed microvascular ischemia ("ischemic palsy") at the time of initial diagnosis has value. The diagnosis a decompensated palsy is traditionally suggested by finding abnormally high vertical fusional vergences. This study was undertaken to discover if abnormally high fusional vergences are reliable in this task and whether there are other clinical characteristics that could fortify the differentiation between these two causes.

Methods:

Retrospective review of case records of adult patients diagnosed with isolated fourth cranial nerve palsies examined and followed at our clinics over the past 15 years. The gold standard of diagnosis for an ischemic palsy was full recovery within 6 months of onset. The gold standard for diagnosis of a decompensated palsy was persistence of the palsy beyond that time period and reasonable exclusion of alternative diagnoses.

Results:

Vertical fusional vergences were not always definitely increased in decompensated palsies. Nor was the presence of torsional misalignment on double Maddox rod testing. However, vertical misalignment greater in contralateral upgaze than downgaze was more common in decompensated palsies and served as a powerful discriminator.

Conclusions:

Vertical misalignment greater in contralateral upgaze than downgaze is characteristic of decompensated fourth cranial nerve palsy and is useful in differentiating this cause from an ischemic palsy. Adding this sign to increased vertical fusional vergences improves differential diagnosis.

References: None.

Keywords: 4th Cranial Nerve, Palsy, Ischemic, Decompensating

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 220

Retinal Thinning and Neurodegeneration in Xeroderma Pigmentosum: Evidence from Optical Coherence Tomography

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Introduction:

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease with cutaneous, ophthalmic and neurological manifestations. Although the etiology for XP neurodegeneration is poorly understood, it is known that complementation groups C, E and XP variants (V) are spared the severe, progressive neurological deficits that occur in more than 25% of patients from groups A, B, D, F and G. The aim of this study was to explore the association between retinal thickness measurements and neurodegeneration in patients with XP from different complementation groups.

Methods:

This was a cross-sectional study. Forty patients with XP and normal retinal examinations were divided into two groups based on their complementation group and associated likelihood of developing neurodegeneration. Group 1 contained 23 patients, with no or minimal neurological deficits, from complementation groups A, B, D, F and G. Group 2 contained 17 neurologically intact patients, from complementation groups C, E, and the variant type. A third control group was obtained from a normative database. Using spectral-domain optical coherence tomography (SD-OCT), we compared peripapillary retinal nerve fiber layer (pRNFL) and macular thickness between the groups.

Results:

We found a statistically significant reduction in both pRNFL ($p < 0.01$) and macular thickness ($p < 0.001$) for Group 1 compared with healthy controls. In contrast, there was no statistically significant difference between pRNFL and macular thickness in patients from Group 2 compared to the control group. When Group 1 and Group 2 were compared, a statistically significant reduction in total pRNFL ($p = 0.024$) and macular thickness ($p = 0.002$) was found in Group 1.

Conclusions:

Our results suggest that retinal SD-OCT scans provide a quantifiable method for assessing early neurological abnormalities in patients with XP. These findings demonstrate the potential role of retinal thickness as an anatomic biomarker and diagnostic indicator for XP neurodegeneration.

References: None.

Keywords: Xeroderma Pigmentosum, Neurodegeneration, Optical Coherence Tomography, Retinal Nerve Fiber Layer, Macular Thickness

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 221

FOTO-ED Phase III: What Happens When You Try to Teach Emergency Providers to Read Fundus Photographs?

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Introduction:

During FOTO-ED Phase II (n=355), emergency providers (EPs) reviewed 68% of patients' non-mydratic fundus photographs, identifying 46% of the relevant abnormalities during their routine evaluations without additional ophthalmology training.¹ We undertook a quality improvement project to determine whether a web-based educational module would improve how often and how well they reviewed fundus photographs.

Methods:

Patients presenting to our Emergency Department (ED) from March-December 2014 with headache, focal neurologic defect, visual change, or diastolic blood pressure ≥ 120 had non-mydratic fundus photography. Photographs were provided through the electronic medical record. In May 2014, a web-based educational module was released (9 training pages + pre/posttest [35 questions each]). Core EPs who worked frequently in the ED were required to complete the module by Oct 2014.

Results:

587 patients were included, 74 with abnormalities (12.6%): 24 disc pallor, 20 disc edema, 16 isolated retinal hemorrhage, 9 grade III/IV hypertensive retinopathy, and 5 retinal vascular occlusion. 61% (359/587) were evaluated by the 14/16 (88%) core EPs who completed training. EPs spent a median of 31 minutes (IQR:24-42) on training; post-test scores improved by a median of 4% (IQR:2-14%;p=0.06). Pre- vs. post-training, they reviewed 45% (80/177) vs. 43% (78/182;p=0.73) of photographs, correctly identified abnormal images in 67% (10/15) vs. 57% of cases (8/14;p=0.88), and correctly identified as normal 80% (52/65) vs. 84% (54/64;p=0.67). Untrained EPs reviewed 35% (79/228), correctly identified 50% of abnormalities (6/12), and 79% of normals (53/67). Only their review frequency significantly differed from those who completed training (p=0.03).

Conclusions:

FOTO-ED demonstrated that EPs perform substantially better with fundus photography than with direct ophthalmoscopy. However, our web-based, in-service training did not result in further improvements at our institution. Developing new tools to provide relevance to fundus findings in patient management scenarios and to better integrate them into EP clinical decision-making may prove more valuable.

References:

1. Bruce BB, Thulasi P, Fraser CL, Keadey MT, Ward A, et al. Diagnostic accuracy and use of nonmydratic ocular fundus photography by emergency physicians: phase II of the FOTO-ED study. *Ann Emerg Med.* 2013;62:28-33.

Keywords: Optic Neuropathy, High Intracranial Pressure/Headache, Retina, Stroke

Financial Disclosures: The authors had no disclosures.

Grant Support: Research to Prevent Blindness, K23-EY019341, R01-NS089694, P30-EY006360.

Visual Structure Biomarkers of Traumatic Brain Injury (TBI) in Contact Sport Athletes using Optical Coherence Tomography (OCT)

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Introduction:

It is estimated sports-related concussion afflicts 3.8 million American athletes each year. Recent research suggests that repeated head trauma may be associated with the development of neurodegenerative changes in the brain. These changes in the brain can begin months, years, or even decades after the last brain trauma and are not visible on standard brain scans. As the eye is an extension of the brain, this study investigates the retinal structure in active and retired professional contact sport athletes with a high risk of concussion (football, boxing, hockey, soccer and rugby) compared to age-matched controls to determine if visual structure measures may be an in vivo clinical biomarker to detect nerve damage related to repeated head trauma.

Methods:

Patients with history of elite-level, high TBI risk contact sport exposure (Boxing, n=13), moderate TBI risk contact sport exposure (Football, n=20) and elite-level, non-contact sport athletes or non-athlete controls (n=25) underwent Spectral-Domain OCT optic nerve and macula scans.

Results:

Boxing athletes demonstrated significant thinning in average Retinal Nerve Fiber Layer (RNFL) compared to Controls (Boxers: $84.31 \pm 9.81 \mu\text{m}$ vs. Controls: 94.72 ± 11.10 , $p = 0.01$, Figure 1) and Football athletes (Boxers: $84.31 \pm 9.81 \mu\text{m}$ vs. Football: 93.70 ± 9.03 , $p = 0.04$). Average Ganglion Cell Complex (GCC) thickness was thinner in Boxing athletes compared to Football athletes (Boxers: $76.85 \pm 7.85 \mu\text{m}$ vs. Football: $80.10 \pm 8.16 \mu\text{m}$), and compared to Controls (Boxers: $76.85 \pm 7.85 \mu\text{m}$ vs. Controls: $82.16 \pm 5.86 \mu\text{m}$) however these differences were not statistically significant. No significant differences in average macular thickness or volume were observed between groups.

Conclusions:

Retinal structure thinning quantified using non-invasive OCT imaging is evident in high TBI risk contact sport athletes and may serve as an important biomarker of sport-related TBI exposure. Continued investigations will examine correlations with visual function and determine changes over time.

References: None.

Keywords: Trauma, Neuroimaging, Retina, Diagnostic Tests

Financial Disclosures: The authors had no disclosures.

Grant Support: Study supported by the Illinois Society for the Prevention of Blindness Research Grant.

Poster 223

Optic Neuritis History Does Not Influence OCT Measurement in Long-Standing Secondary Progressive Multiple Sclerosis

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Introduction:

Optical coherence tomography (OCT) is a useful outcome measure of neuronal integrity in relapsing-remitting MS (RRMS) trials.^{1,2} Its role in secondary progressive MS (SPMS) is promising but less well-understood.³⁻⁵ Retinal nerve fiber layer (RNFL) and macular thinning is generally attributed to prior optic neuritis (ON);⁴ however, OCT thinning in the absence of ON has also been demonstrated.^{6,7} This study addresses the influence of ON history on OCT readings in SPMS.

Methods:

Fifty participants in a prospective interventional clinical trial underwent baseline spectral domain OCT in each eye after pharmacologic dilation. OCT was repeated annually over a 2-year period and reviewed by an experienced OCT reader. Self-reported histories of ON were confirmed as available via medical records. Mean and quadrant RNFL thicknesses, macular volume, and mean ganglion cell layer plus inner plexiform layer (GCIPL) thicknesses were compared between patients with and without a history of ON. Two-year data was compared to baseline using paired t-tests, Tukey pairwise comparisons and multiple comparison modeling where necessary.

Results:

Scans of seventy-eight eyes from 42 subjects passed quality control. Mean (standard deviation) age was 59 (6.4) years and 60 percent of subjects were female. Mean duration of MS was 30 (9.6) years and of SPMS was 10 (5.6) years. Mean expanded disability status score was 5.4 (1.5). No significant differences between mean or quadrant RNFL thicknesses or macular volumes were observed based on ON history at baseline (corrected $p < 0.05$). A non-significant trend towards effect of ON on GCIPL thickness was initially found ($p = 0.08$). History of ON was not associated with change in any OCT measure from baseline to 2 years.

Conclusions:

History of ON did not influence RNFL or GCIPL thicknesses in an advanced SPMS cohort over 2 years, suggesting that ON is not a true confounder when using OCT outcome measures for neuroprotective trials in this population.

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Keywords: Diagnostic Tests (OCT), Secondary Progressive Multiple Sclerosis, Demyelinating Disease, Neuro-Ophth and Systemic Disease (MS)

Financial Disclosures: The authors had no disclosures.

Grant Support: Dr. Spain is supported by a Career Development Award from the VA. Pilot study support from Oregon Clinical and Translational Research Institute (OCTRI), grant number UL1 RR024140.

Poster 224

Peripapillary Subretinal Hemorrhage: Clinical and Ocular Coherence Tomography Findings in 5 Cases

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Introduction:

Peripapillary subretinal hemorrhage (PSH) has been described as a benign condition occurring in patients with myopia and tilted, dysplastic discs.¹⁻² Recognizing these hemorrhages is important as they are not always associated with drusen, ischemic optic neuropathy (ION), or peripapillary subretinal neovascular membranes, and do not require further work-up as they resolve spontaneously with no visual deficit.¹ Although their etiology is unknown, it has been shown that patients with PSH have smaller optic discs and more nerve fiber crowding than age-matched controls.² Here, we examine five cases of PSH studied with ocular coherence tomography (OCT) to better understand the anatomy of the optic disc in relation to the hemorrhage.

Methods:

A patient database extending from 1981 until August, 2015 was searched for diagnoses of “hemorrhage” and “tilted” or “hypoplastic” disc. Inclusion criteria were ophthalmoscopic evidence of PSH. Exclusion criteria included any findings other than PSH. Case histories, ocular examination, OCT, and ancillary testing were reviewed. Time of follow-up was recorded.

Results:

Five patients (six eyes) were identified with PSH. All had isolated peripapillary hemorrhages, one of which was temporal, and the rest nasal and superonasal. On OCT, the optic disc tissue extended over Bruch’s membrane into the photoreceptor layers, creating a ridge adjacent to the disc and elevating retinal layers from the RPE. There was no evidence of vitreopapillary traction causing the ridge. Upon comparing OCT with fundus photos, the hemorrhage was consistently found adjacent to the optic disc ridge.

Conclusions:

Previous papers describe PSH occurring only nasally, whereas we have found one patient with a temporal PSH and a temporally tilted nerve. We hypothesize that PSH occurs where optic disc tissue extends into the photoreceptor layers, as seen on OCT, placing stress on the border tissue of Elschnig and basement membrane causing blood to escape from adjacent choriocapillaris.

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Keywords: OCT, Peripapillary, Subretinal, Hemorrhage, Retina

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 225**The Utility of a Hand-Held, Non-Mydriatic Fundus Camera for the Detection of Optic Nerve Edema**

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Introduction:

To determine the sensitivity of pictures obtained with a portable, hand-held non-mydriatic fundus camera (Pictor Plus, Volk Optical, Inc.) as an alternative to the dilated fundus examination for the detection of optic nerve edema.

Methods:

Retrospective review of non-mydriatic, fundus photographs of patients age 18 and older with normal and/or edematous optic nerves presenting to Kellogg Eye Center neuro-ophthalmology clinics. The gold standard was the treating neuro-ophthalmologist's documented optic nerve examination (dilated or undilated). The photograph reader was a fellowship trained neuro-ophthalmologist who did not examine the patient. The presence of edema was recorded as either present, absent, or uncertain. Responses of "uncertain" were grouped with "present." The mean time to evaluate the photo, overall photo quality (excellent, acceptable, ungradable), and quality of the optic nerve specifically (excellent, acceptable, ungradable) was recorded.

Results:

101 eyes were included; 52 with optic nerve edema and 49 without. None of the photographs were ungradable and it took a mean of 18.9 seconds to read each photo. Photographs interpreted by a neuro-ophthalmologist correctly identified the presence or absence of optic disc edema in 88.1% of eyes. Twelve patients were misclassified (6 false positives, 6 false negatives). In 4 of 6 false positives, the reader was uncertain about the presence of optic nerve edema.

Conclusions:

Photographs taken with a hand-held, non-mydriatic camera and interpreted by a neuro-ophthalmologist correctly identified the presence or absence of optic disc edema in 88.1% of eyes suggesting that this may be an acceptable tool for the detection and/or monitoring of optic nerve edema.

Keywords: Diagnostic Tests

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 226**Morphometric Evaluation of Asymptomatic Optic Disc Elevation and Grade I Papilledema**

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Introduction:

To demonstrate morphometric characteristics of elevation of optic disc with disc photos, orbital B scan and SD-OCT (optical coherent tomography) in asymptomatic patients and to compare them to grade I papilledema

Methods:

Among the patients who were referred to Neuro-Ophthalmology clinic regarding elevation of optic disc, asymptomatic patients were selected for group 1 and the symptomatic patients with grade I papilledema were selected for group 2. All patients underwent Humphrey visual field test, ONH (optic nerve head) OCT, orbital B scan and fundus photos and the patients in group 2 underwent lumbar puncture which showed elevated opening pressure. The data were reviewed and the average thickness of retinal nerve fiber layer (RNFL) in each quadrants on OCT was calculated. The sum of temporal and nasal quadrants was compared to inferior quadrants in each group and they were compared to the Cirrus OCT normative data.

Results:

The data were obtained from 48 cases in 24 patients including 12 asymptomatic patients (group 1) and 12 symptomatic patients of grade I papilledema (group 2). In group 1, the tests suggested optic disc drusen in 16 cases and crowded optic disc in 8 cases. The comparison of thickness of RNFL to the normative data showed no statistically significant difference in group 1 and showed statistically significant difference in group 2. (Further collection of data and final analysis of statistics are pending at the time of submission.)

Conclusions:

The comparison of the sum of RNFL in the temporal and nasal quadrants to RNFL in the inferior quadrant in OCT may be used as an adjunct method for differentiation of pseudopapilledema from grade I papilledema.

References: None.

Keywords: Diagnostic Tests, Pseudotumor Cerebri

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 227**Optical Coherence Tomography Angiography and Anterior Ischemic Optic Neuropathy**

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Introduction:

OCT angiography (OCT-A) is a new technology allowing the imaging of retinal microvascular flow without the injection of an intravenous dye. It also allows the visualization of the peripapillary vascularization. Even if the most significant contribution to the vascularization of the optic nerve comes from the choroidal blood flow, the peripapillary capillaries also contribute to the vascularization of the prelaminar portion of the optic nerve. The goal of this study is to describe the peripapillary microvasculature in nonarteritic anterior ischemic optic neuropathy (NAION) with optical coherence tomography angiography (OCT-A).

Methods:

Observational study of 6 patients at the acute phase of NAION. OCT-A was performed using a 3mm x 3mm square centered on the optic disc. A qualitative comparison was made with healthy fellow eye of each patient.

Results:

In the affected eyes, OCT-A imaging demonstrated clear modifications in the radial peripapillary network. In all these eyes, a focal disappearance of the superficial capillary radial pattern was at least demonstrated and found to be twisted and irregular. In two eyes, the alteration was more severe, with a lack of vascularization in some focal areas, appearing as dark zones.

Conclusions:

OCT-A is a safe and quick imaging tool able to demonstrate a reshaping of the peripapillary capillary network likely related to a decrease of the blood flow during the acute phase of NAION. Besides qualitative evaluation, future software upgrades will allow the quantification of the peripapillary vascular density and its blood flow.

References: None.

Keywords: Diagnostic Test, Optic Neuropathy

Financial Disclosures: Jean-F Korobelnik, Zeiss consultant

Grant Support: None.

Poster 228

Macular Thickness Measurements with Frequency Domain-OCT for Quantification of Retinal Neural Loss and its Correlation with Cognitive Impairment in Alzheimer's Disease

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Introduction:

Alzheimer's disease (AD), the most common cause of degenerative dementia, is characterized by progressive cognitive deficits, including memory disturbances, aphasia, apraxia, agnosia and visual abnormalities. The purpose of this study it to evaluate the ability of frequency domain OCT (fd-OCT) to estimate neural loss in eyes with AD. We also verified the existence of correlation between AD-related cognitive impairment and macular and peripapillary retinal nerve fiber layer (RNFL) thickness measurements.

Methods:

Macular and peripapillary fd-OCT scans were obtained from 45 eyes of 24 patients with AD and 48 control eyes. Peripapillary RNFL, macular full-thickness and inner macular thickness parameters were automatically calculated by the equipment's software. The inner macular parameters included macular retinal nerve fiber layer (mRNFL) thickness, ganglion cell layer (GCL) plus inner plexiform layer (IPL) thickness (GCL+), and RNFL plus GCL+ thickness (GCL++). The Mini-Mental State Examination (MMSE) was used to assess cognition in AD and control subjects. The two groups were compared and the existence of a correlation between MMSE scores and fd-OCT measurements was verified.

Results:

The only significantly reduced peripapillary RNFL parameters were average thickness and inferior quadrant thickness. All full-thickness macular parameters were significantly smaller in AD eyes than in controls, except for inferior outer macular segment thickness. GCL+ and GCL++ were significantly reduced in AD eyes. A significant correlation was found between most fd-OCT parameters (especially macular thickness measurements) and MMSE scores.

Conclusions:

Most fd-OCT parameters, especially those in the central macular area, were reduced in AD eyes. For the first time, the inner retinal layers of the macular area were shown to be reduced in AD as well. Moreover, neuronal loss, especially as reflected in macular parameters, correlated well with cognitive impairment in AD. Our results suggest that fd-OCT could be used as a swift and non-invasive diagnostic tool in the routine evaluation and follow-up of AD patients.

References: None.

Keywords: Alzheimer, Optical Coherence Tomography, Retinal Nerve Fiber, Macular Thickness Measurements

Financial Disclosures: The authors had no disclosures.

Grant Support: Supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brasília, Brazil (programas institucionais de bolsas de iniciação científica, XXVII BIC/UFJF - 2014/2015 and grant 307393/2014-3).

Poster 229**Optical Coherence Tomography Macular Volume Correlates with Walking Speed in Patients with Multiple Sclerosis**

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Introduction:

Optical coherence tomography (OCT) is used to measure the thickness of the layers of the retina. In multiple sclerosis (MS), it is used to quantify the effects of optic neuritis or MS, monitor disease progression, and assess for complications of disease modifying therapy. OCT is being evaluated as a potential biomarker in MS, for use in clinics and in therapeutic trials. The aim of this study was to evaluate the relationship between retinal thickness with walking speed in patients with MS/clinically isolated syndrome (CIS).

Methods:

This was a retrospective, observational study of patients diagnosed with MS or CIS. A clinic database and electronic medical record were used to identify patients with an OCT, timed 25 foot walk, and visual acuity (VA) performed within 3 months. The Spearman correlation coefficient was computed for pairs of variables, including OCT (retinal nerve fiber layer thickness, ganglion cell and inner plexiform layer thickness, and macular volume), VA, and timed 25 foot walk. Since history of optic neuritis was not available, the best eye and worst eye visual acuities were used. The OCT values were specific to the best and worst eye (referred to as correlated). A univariate analysis identified statistically significant variables. A multivariate analysis and stepwise selection were then performed.

Results:

370 patients met inclusion criteria. Univariate analysis identified a statistically significant correlation between 25 foot walk and all variables, except worst eye ganglion cell layer thickness. Correlation between best eye macular volume and walking speed was strongest ($r=0.890$, $P<0.001$). For each cubic millimeter increase in macular volume, walking speed increased by 0.876 feet/sec.

Conclusions:

OCT, a proposed biomarker for neurodegeneration, correlates with walking speed in patients with MS or CIS. Results indicate that degeneration of the retina (particularly macular volume) in MS/CIS may be a marker of global neurodegeneration outside the visual system.

References: None.

Keywords: OCT, Walking Speed, Demyelinating Disease

Financial Disclosures: Robert Bermel has served as a consultant for Biogen, Novartis, Genzyme, Genentech. Other authors have no disclosures.

Grant Support: None.

Poster 230**Effect of Upper Eyelid Surgery on Headaches**

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Introduction:

This study was undertaken to prospectively evaluate changes in headache related quality of life in patients with chronic headache and droopy eyelids, prior to and following blepharoplasty, ptosis repair, or brow ptosis repair.

Methods:

Prospective interventional study of adult patients undergoing upper eyelid or brow surgery for obscuration of superior visual field (study arm) and other oculoplastic procedures (control arm) with greater than one year of intermittent headache symptoms over an 18 month period. A validated headache quality of life survey, Headache Impact Test – 6, was administered to patients preoperatively and at a post-op visit (minimum of 7 weeks). Patients were excluded if they had known orbital, corneal, or intracranial pathology, received botulinum toxin, or had a change in headache medications.

Results:

Twenty eight patients (22 female, 6 male) met inclusion criteria for the study arm, and 19 patients (16 female, 3 male) for the control arm. Mean age was 58.7 for the study arm, and 60.7 for the control arm. There was no statistically significant difference in any of the headache locations. Mean preoperative HIT-6 score was 57.7 for the study arm and 58.1 for the control arm ($p=0.86$). Mean postoperative HIT-6 score was significantly better at 45.3 for the study arm and unchanged at 58.6 for the control arm ($p<0.05$). Mean follow up was 163 days and 157 days respectively. Subjectively, 18/28 in the study arm reported their headache symptoms were significantly better or resolved, as compared to 0/19 in the control group.

Conclusions:

Patients presenting to an oculoplastic clinic for management of visually significant upper eyelid position are more likely than patients undergoing other oculoplastic procedures to have improvement in headache related quality of life, and improvement or resolution of headache symptoms.

References: None.

Keywords: Eyelid Surgery, Headache, Quality of Life

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 231

Irrigation and Ultrasonic Drill-induced Heat Transmission.

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Introduction:

A variety of instruments are used to remove bone in orbital decompression surgery; the Sonopet™ ultrasonic bone curette has recently been described in this capacity (Sivak-Callcott 2005, Cho 2010, Vrcek 2015). Thermal injury to adjacent soft tissue (e.g. the optic nerve) remains a concern with this and other drills. Irrigation of the surgical field is used to mitigate this temperature rise. This study evaluates the influence of saline irrigation flow rate and temperature on Sonopet™ ultrasonic drill-induced heat transmission through bone.

Methods:

The Sonopet™ ultrasonic drill was used to burr unpreserved cadaveric porcine rib bone. Temperature was measured with a Thermoworks Super-Fast Thermopen™ probe. Standard recommended settings (saline at 21°C and 18ml/min) were compared to high flow (saline at 21°C and 40ml/min) and chilled saline with high flow (saline at 10°C and 40ml/min). The temperature of the emitted irrigation fluid itself was also measured under these same conditions while oscillating the tip without making contact with the bone.

Results:

The temperature of the emitted irrigation fluid after 15 seconds while allowing the Sonopet™ tip to oscillate without drilling bone was slightly lower with chilled saline with high flow rate compared to standard settings ($25.4 \pm 0.3^\circ\text{C}$ vs $24.6 \pm 0.3^\circ\text{C}$, t-test $p=0.047$). There was no significant difference between the change in bone temperature between the standard and high flow settings ($9.4 \pm 3.1^\circ\text{C}$ vs. $8.4 \pm 1.9^\circ\text{C}$, t-test $p = 0.39$). A significant decrease in the change in bone temperature at 15 seconds was noted when comparing chilled high flow saline to standard settings (mean change of $9.4 \pm 3.1^\circ\text{C}$ with standard settings vs. $6.3 \pm 1.1^\circ\text{C}$ with chilled high flow saline, t-test $p = 0.003$).

Conclusions:

Varying irrigation fluid flow rate and temperature influences drill-induced temperature rise of both the bone and the emitted irrigation fluid. Chilled irrigation fluid may reduce the risk of thermal injury to adjacent tissue.

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Keywords: Orbital Surgery

Financial Disclosures: Brad Rabinovitz works for Stryker Corporation, which makes the Sonopet drill.

Grant Support: None.

Clinical Feature of Unilateral Ptosis with Positive Result in Phenylephrine Test

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Introduction:

To investigate the etiology and clinical feature of unilateral ptosis in patients with positive result in phenylephrine test (PE).

Methods:

The medical records of 530 consecutive patients with ptosis were retrospectively reviewed. Twenty-six patients (26 eyes) had positive results among 44 patients who have received PE test. Underlying medical conditions were examined based on the previous medical history, laboratory test result and radiologic findings. The treatment method and the results were also evaluated.

Results:

In the 26 patients with positive result in PE test, 14 of 26 (53.8%) patients had associated disease. Nine (34.6%) patients were diagnosed to myasthenia gravis, 4 (15.4%) to Horner's syndrome and 1 (3.8%) to facial palsy. Among 17 patients who could be followed up more than 6 months, 12 of 17 (70.6%) patients have received lid surgery (Levator resection in 5 patients and conjunctivo-mullerectomy in 7 patients) and 5 (29.4%) patients have started medication. The palpebral fissure was 2.2mm increased after 6 months in patients with surgery and 2.0mm in patients with medication. There was no statistically significant difference in change of palpebral fissure between the patients with surgery and the patients with medication ($p=0.446$, Mann Whitney U test).

Conclusions:

It is probable the presence of comorbidities in patients who have unilateral ptosis with positive result in PE test and proper medication of associated disease and lid surgery showed comparable effectiveness. The phenylephrine test should be properly implemented and adequate examination should be taken to find underlying disease if the test showed positive result

Keywords: Ptosis, Phenylephrine Test, Unilateral

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 233**Optic Canal Temperature Change with Ultrasonic Drill Decompression of the Orbital Apex**

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Introduction:

Optic nerve injury is a feared complication of bony decompression of the optic canal and orbit apex. Thermal injury has been suggested as a mechanism. In this animal cadaveric model we assess the change in temperature within the optic canal while using the Sonopet™ ultrasonic bone drill to remove bone at the orbital apex.

Methods:

Six unpreserved porcine orbits were exenterated, with preservation of tissues within the optic canal and extreme orbital apex. Using a Sonopet™ ultrasonic drill, bony decompression was performed as follows: decompression was initiated 3cm anterior to the apex. A 2 mm deep x 10 mm (maximally) wide groove was created and advanced posteriorly to the opening of the optic canal using recommended drill settings of 18ml/min of room temperature (21°C) saline irrigation fluid and 100% power. Temperature at the optic canal was recorded at 15 second intervals using the Thermoworks Super-Fast Thermapen™ probe.

Results:

Mean increase in temperature was $4.54 \pm 3.57^{\circ}\text{C}$ (range 0-10.5°C). There was a significant correlation between distance from drill tip and change in temperature ($p = 0.0008$). When controlling for distance, we did not find a significant rise in temperature with drilling duration ($p = 0.74$), and while controlling for duration the correlation with distance remained significant ($p=0.0075$).

Conclusions:

In a porcine cadaveric model using the Sonopet™ to decompress the orbital apex, there was a variable change in temperature measured at the optic canal, rising up to 10.5°C above baseline. The variability may result in part from drill tip irrigation, with either obstruction from soft tissue or angle of drill tip influencing access or drainage of irrigation fluid. Our findings suggest thermal injury may be possible with decompression of the orbital apex. Further investigation is warranted.

Keywords: Orbital Surgery

Financial Disclosures: Brad Rabinovitz works for Stryker Corporation, which makes the Sonopet(TM)

Grant Support: None.

Poster 234

Brave New World: 3D Printing of the Orbit for Anatomy, Pathology, Surgical Simulation

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Introduction:

3-Dimensional printing (3D printing), or additive manufacturing, is a novel technique used for rapidly producing physical models of complex structures. These physical models can be used to teach anatomy, simulate procedures, or test surgical anatomical approaches. This project explores the application of 3D printing to ophthalmologic disease. 3D printing has become more affordable and applicable to the clinical setting. Complex orbital anatomy and pathology can be evaluated using a multifaceted approach. We propose a paradigm to create orbital models to teach anatomy and demonstrate pathologies: thyroid related eye disease, idiopathic orbital inflammatory disease, neoplasm, and maxillofacial trauma. Purpose: To demonstrate how 3D printing can be used to produce physical orbit models for the teaching of orbital anatomy, demonstrating pathology, and simulating surgical and interventional procedures.

Methods:

Under IRB approval, clinical cases of orbit anatomy and pathology were selected. Volumetric CT and MR images of the orbit were obtained on Siemens scanners (Erlangen Germany) as part of facial and orbit examinations. Using commercially available software (Mimics, USA), DICOM images were converted to 3D models. Anatomic data was segmented, simplified, and prepared for 3D printing. Models were printed in PLA (polylactic acid plastic) using 3D printer (Ultimaker 2, Ultimaker BV, Netherlands).

Results:

3D models allow trainees to learn anatomy, demonstrate pathology, and test surgical approaches and reconstruction techniques. With hands-on models, learners can grasp complex anatomy, manipulate physical representations of patient specific data, and plan surgical approaches.

Conclusions:

Creating tangible physical models of anatomy and patient specific pathology allows trainees and clinicians to better visualize the critical and complex anatomy of the orbit. This project demonstrates practical application of novel additive manufacturing to orbital anatomy and pathology.

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Keywords: 3-D printing, Teaching, Anatomy, Oculoplastics

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

An Incomplete Awakening: Sleep-Induced Apraxia of Eyelid Opening

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Introduction:

Apraxia of eyelid opening has primarily been described as bilateral loss of volitional ability to open the eyes at certain times and is previously known to be associated with neurodegenerative disease. Rarely it can occur in isolation and as an idiopathic phenomenon. Recently, a few cases have been reported of unilateral apraxia of eyelid opening only upon awakening from sleep, thought to be different than daytime apraxia of eyelid opening. Here we report an additional 11 patients with apraxia of eyelid opening upon awakening.

Methods:

Retrospective, observational case series of patients collected from three separate neuro-ophthalmology practices.

Results:

All 11 patients were Caucasian women with a mean age of 59 years (range 35-80). All patients experienced complete ptosis upon awakening from sleep. Nine patients had unilateral complete ptosis, and 2 had bilateral symptoms. The duration of symptoms ranged from 3 weeks to several years. Ten of the patients reported manually elevating the eyelid to open it, while 1 patient waited for the eyelid to naturally open. After initial manual elevation, all patients reported normal function and position of the eyelids for the remainder of the day. Seven patients had a history of autoimmune disease. Slit lamp and fundus exams were negative for ocular pathology to explain the patients' symptoms. Nine of the patients had brain imaging, all negative for acute pathology.

Conclusions:

Apraxia of eyelid opening occurring only upon awakening from sleep is a rare and relatively newly described entity of which neuro-ophthalmologists should be aware. Imaging and extensive laboratory testing are unlikely warranted without associated neurologic or ocular findings. While our case series suggest that there may be a Caucasian female preponderance as well as an autoimmune relationship to this phenomenon, further reports and investigation are warranted.

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Keywords: Apraxia

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 236**Dynamic Pupillary Responses in Patients with Deep Sedation from Titrating Doses of Continuous Anesthetics**

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Introduction:

Deep anesthetic sedation is the hallmark treatment of refractory status epilepticus (RSE). Use of short half-life anesthetics promotes recovery of consciousness following discontinuation. However, some patients have an unpredictable delay in recovery, adversely affecting their prognosis. Serial neurological examinations are the key measure of recovery with pupillary light reflex (PLR) as a fundamental component of the neurological examination. Automated pupillometry in intensive care units is replacing manual pupil assessment with accurate and objective assessment, which can be monitored over time. Dynamic changes in PLR can be correlated with neurological recovery in a comatose patient.

Methods:

With approval of our institution's review board, we prospectively followed 25 patients treated for RSE with anesthetics, including propofol, midazolam and ketamine. We used portable automated pupillometers to serially monitor PLR on and during titration of anesthesia. This was correlated with serial neurological assessments.

Results:

Upon completion of enrollment we will review data, including medications, treatment response of RSE, serial pupillary assessments, and neurological exam findings. Dynamic pupillary responses will be quantified as NPI™ (Neurological Pupillary Index), comparing recorded values to normative models. This index will be correlated with doses of anesthetics and recovery of level of consciousness.

Conclusions:

This data is valuable in assessing the depth of individual or combination anesthetics and their long term neurological effects. Prognostication of patients treated with anesthetics for RSE is complicated by the recovery of level of consciousness being difficult to predict. We propose that this objective measure would be valuable in quantifying progress in patients recovering from RSE and predicting their neurological recovery.

References: None.

Keywords: Pupils, Pupillary, Reflex

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 237**The Effect of Entrance Pupil Size and Iris Pigmentation on the Melanopsin Mediated Post-Illumination Pupil Response**

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Introduction:

The influence of pupil size and iris color on afferent pupillomotor input and efferent pupillomotor output to red and blue light evoked pupil contraction was studied, using brimonidine induced anisocoria.

Methods:

Pupil responses were recorded using a binocular infrared computerized pupillometer to a series of 1 second duration Ganzfeld red and blue light stimuli (1.0, 1.5, 2.0 and 2.6 log cd/m²) given to each eye. Post-illumination pupil response (PIPR) was the difference in percent pupil contraction to blue vs. red light stimulation at six seconds following stimulus offset. One eye of nine normal subjects was treated with 0.2% brimonidine tartrate ophthalmic solution to achieve pupil size reduction. The consensual pupil response from the eye not treated with brimonidine was compared before and after treatment to study the impact of a smaller pupil to the pupillomotor input. Iris color was graded by inspection.

Results:

Brimonidine treatment produced significant reduction in pupil size in normal subjects (mean reduction in pupil size: 1.72±0.35 mm, p<0.05). The consensual PIPR response was decreased when the brimonidine-treated, miotic pupil was stimulated compared to stimulation of the untreated eye with larger entrance pupil for 2.6 log cd/m² (mean±SD: 28.5±11.6 vs. 35.9±11.2, p<0.05). Brimonidine induced miosis also significantly reduced the PIPR in the treated, miotic pupil compared to the consensual pupil (mean±SD: 9.8±9.8 vs. 16.4±7.9 for 2.0 log cd/m² and 17.1±9.2 vs. 28.5±11.6 for 2.6 log cd/m², p<0.05), indicating an additional reduction in pupil response due to efferent mechanical effects of miosis. This brimonidine induced reduction in afferent pupillomotor input and efferent pupillomotor output did not differ between subjects with dark vs. light irides.

Conclusions:

Smaller entrance pupil size causes significant reduction of afferent pupillomotor inputs and efferent pupillomotor outputs of the PIPR response and was not influenced in this study by iris pigmentation.

Keywords: Post-Illumination Pupil Response, Melanopsin Retinal Ganglion Cell, Entrance Pupil Size, Iris Pigmentation

Financial Disclosures: 1. No disclosure for Dr. Chen. 2. Dr. Kardon has the following disclosure: Veterans Administration (Rehab R&D): C9251-C, 1I01RX000889-01A1, PT120517-56 Department of Defense (DOD): W81XWH-10-1-0736, W18XWH-10-1-0561 NIH: 1R01EY023279-01 Novartis: OCTiMS

Grant Support: This project was supported in part by the University of Wisconsin Institute for Clinical and Translational Research (UW ICTR), funded through an NIH Clinical and Translational Science Award (CTSA) (grant number 1 UL1 RR025011), as well as by an unrestricted research grant to the Department of Ophthalmology and Visual Sciences at the University of Wisconsin from Research to Prevent Blindness, Inc., and a Center of Excellence grant for the Iowa City Center for the Prevention and Treatment of Visual Loss from the Department of Veterans Affairs (PR&D Division).

North American Neuro-Ophthalmology Society

42nd Annual Meeting

February 27 – March 3, 2016
JW Starr Pass Marriott • Tucson, Arizona

Program Schedule

WEDNESDAY, MARCH 2, 2016

6:30 am - 5:30 pm	Registration/Help Desk	Arizona Foyer
6:30 am - 7:30 am	Breakfast	Arizona Ballroom
6:00 am - 6:45 am	Abstract Committee Meeting	San Pedro
7:00 am - 7:30 am	Annual NANOS Business Meeting (all encouraged to attend)	Tucson Ballroom
7:30 am - 11:10 am	Neuro-Imaging [3.25 CME] <i>Moderators: Melissa W. Ko, MD and Jonathan Trobe, MD</i>	Tucson Ballroom

The symposium is organized around two topics: 1) Optimizing the use of neuroimaging techniques currently available for the main clinical problems faced by Neuro-Ophthalmologists, including transient monocular and binocular vision loss, suspected optic neuropathy, papilledema, cranial nerve palsy, homonymous hemianopia, and perceptual disorders; and 2) The forefront of neuroimaging—exciting techniques on the horizon. Each topic will be introduced by a lecture given by our invited speakers, who are vetted experts in their field and known as excellent teachers. After each lecture, the co-moderators will present cases to the two speakers, who will now act as panelists, and entertain contributions from the audience. The cases will be selected carefully by the invited speakers and co-moderators to highlight the important points.

Upon completion of this course, participants should be able to: 1) Utilize special techniques that optimize the use of current neuroimaging; 2) Recognize pitfalls associated with the use of current neuroimaging; and 3) Appraise new techniques that will shortly be introduced into neuroimaging.

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7:30 am - 8:00 am	Maximizing Current Neuro-Imaging: Tricks and Traps <i>Christine M. Glastonbury, MBBS</i>	403
8:00 am - 9:30 am	Case Presentations Related to Current Neuroimaging <i>Melissa W. Ko, MD & Jonathan Trobe, MD</i>	
9:30 am - 9:50 am	Coffee Break	Arizona Ballroom
9:50 am - 10:20 am	To Infinity and Beyond: Exploring the Realm of Advanced Imaging, <i>Ashok Srinivasan, MBBS, MD</i>	409
10:20 am - 11:10 am	Case Presentation Related to Future Neuro-Imaging, <i>Melissa W. Ko, MD & Jonathan Trobe, MD</i>	
11:10 am - 11:20 am	NOVEL Update	Tucson Ballroom
11:20 am - 12:00 pm	Jacobson Lecture: Optic Nerve Gliomas: Where have we been, Where are we now, and Where are we going? [.75 CME] <i>Presenter: Neil R. Miller, MD</i>	Tucson Ballroom
12:00 pm - 12:10 pm	Announcement of a New NORDIC Study <i>Mark J. Kupersmith, MD</i>	Tucson Ballroom
12:15 pm - 1:30 pm	Research Committee Meeting Luncheon	Signature Grill

1:00 pm - 5:00 pm Practical Introduction to Basic Statistics [4 CME]**Arizona 8-10***Moderator: Beau B. Bruce, MD, PhD*

Ever wanted to run some of your own statistics, but do not know where to begin? Do you understand some statistical concepts but that blinking cursor on your computer is accompanied by a sense of dread? Do you rightfully distrust web-based calculators or Excel for statistical analysis but do not want to buy expensive software for an occasional analysis? This course is for you!

In this optional symposium, we will review the correct use of basic statistical tests while introducing the R statistical software package as means of practically performing those statistical tests. R is the most popular statistical programming language in the world and is capable of extremely advanced analyses in addition to the basic statistics we will cover in this symposium. Amazingly, it does not cost anything to download and install!

This course is directed toward practicing physicians in academic medicine and private practice, as well as trainees, with limited or no background in basic statistics and statistical software. Participants will be required to install the necessary software on their personal laptop in anticipation of the session with the support of the program faculty.

Upon completion of this course, participants should be able to: 1) Import Excel datasets into the R statistical software package; 2) Perform basic reshaping of datasets and transformation of variables to prepare for analyses; 3) Describe the differences between continuous, nominal, and ordinal variables; 4) List resources for independent study and extension of the basic concepts learned during the program; and 5) Determine which of the following statistical tests is appropriate for a given hypothesis and perform the test within the R statistical software package: *Comparing proportions*: Binomial (exact and normal approximation), Chi-square, Fischer's, and McNemar's; *Comparing means or location*: Student's t, Wilcoxon signed-ranks, and Mann-Whitney U.

1:00 pm - 2:00 pm **Introduction to the Realm of R, Beau B. Bruce, MD, PhD**

2:00 pm - 2:30 pm **Importing and Examining Excel Datasets with Hands-On Practice,**
Beau B. Bruce, MD, PhD, Deborah Friedman, MD, MPH and Heather E. Moss, MD, PhD

2:30 pm - 2:45 pm **Break**

2:45 pm - 4:30 pm **Case Studies of Variable Types and Statistical Tests with Hands-On Practice,**
Beau B. Bruce, MD, PhD, Deborah Friedman, MD, MPH and Heather E. Moss, MD, PhD

4:30 pm - 5:00 pm **Resources for Further Progress, Q&A, Beau B. Bruce, MD, PhD,**
Deborah I. Friedman, MD, MPH and Heather E. Moss, MD, PhD

1:30 pm - 3:30 pm 3D Anatomy of the Orbit and Skull Base [2 CME]**Tucson Ballroom***Moderator: Tonya Stefkko, MD**Faculty: Juan C. Fernandez-Miranda, MD*

This symposium will take attendees on a tour of the anatomy of the skull base and orbit, using 3D projection and glasses. The review will include the bones, vasculature, nerves, and soft tissue structures contained in and around the orbit, sphenoid bone, clivus, and paranasal sinuses.

Upon completion of this course, participants should be able to: 1) Describe the relationship of the internal carotid artery to the structures of the anterior visual system and cranial nerves; 2) Describe the relationship of the cavernous sinus and superior orbital fissure (and their contents) to their surrounding structures; 3) List the indications for transcranial and ventral approaches for various orbital and parasellar pathology; and 4) Review the indications and complications of periorbital approaches to skull base pathology (eyebrow, lateral canthal, blepharoplasty, transcaruncular, etc.).

2:00 pm – 4:30 pm	Consortium of Pediatric Neuro-Ophthalmologists Meeting (CPNO) <i>Facilitator: Grant Liu, MD</i>	San Luis
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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.

4:00 pm - 5:00 pm	International Relations Committee Meeting	San Pedro
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5:30 pm - 10:00 pm	Annual NANOS Reception and Banquet <i>Buses depart from Starr Circle</i>	Old Tucson
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MAXIMIZING CURRENT NEURO-IMAGING: TRICKS AND TRAPS

Christine M. Glastonbury, MBBS

*University of California San Francisco
San Francisco, CA*

LEARNING OBJECTIVES

1. Identify the routine MR sequences used in modern neuroimaging and when these, or other, sequences are critical for use in generating a differential diagnosis
2. Demonstrate the utility of key patient history or examination findings and how they might alter either the performance or the interpretation of an MR study by the Neuroradiologist
3. Identify the different vascular imaging techniques: CTA / MRA / MRV and catheter angiography and the patient and diagnostic settings which might determine an imaging preference

CME QUESTIONS

1. The most critical sequence for an acute stroke MR protocol is:
 - a. T1
 - b. T2
 - c. FLAIR
 - d. DWI
2. The most helpful MR sequence for evaluating a patient with clinical optic neuritis is:
 - a. T1
 - b. T2
 - c. FLAIR FS
 - d. T1 FS
3. In a patient with acute renal failure which is the best method to evaluate the cervical and intracranial vasculature?
 - a. CTA
 - b. TOF MRA
 - c. DCE MRA
 - d. Catheter Neuroangiography

KEYWORDS

1. MR Pulse Sequences
2. DWI (diffusion weighted imaging)
3. FLAIR (fluid-attenuated inversion recovery)
4. CTA (CT angiography)
5. MRA/MRV (MR angiography/MR venography)

INTRODUCTION

The advent of MRI in the 1980s transformed the world of diagnostic imaging with a better ability to localize neurological disease and an unprecedented ability to differentiate disease processes. Previously, the only non-invasive imaging of neurological disease was with plain radiographs and CT, which at that time was a single detector scanner with significantly longer scan times and with poor spatial resolution. X-rays and CT were supplemented with catheter neuroangiography which prior to the development of CT had been used to localize lesions by demonstrating mass effect through displacement of vessels. There have been many important developments in the field of MR imaging since the 1980's, both in MR equipment and in scanning techniques, making those earliest scans seem of very poor quality by comparison.

This session will serve to introduce the current key sequences that are used for routine MR neuroimaging. We will emphasize the critical roles specific sequences may play in diagnosis and common pitfalls when ordering or reviewing scans. We will also review vascular imaging with MR angiography (MRA) and venography (MRV) and when CT angiography (CTA) is the preferred diagnostic tool.

MR scanners can be extremely uncomfortable for patients who may find the experience claustrophobic and loud. Even with the advent of significantly faster imaging times as compared to the early days of clinical MR, it is quite difficult for many patients to lie still. Fortunately when imaging the brain, breathing and swallowing result in very little motion artifact. It is nonetheless important that MR protocols (specific series of sequences designed for one exam) are short enough to minimize patient discomfort and motion. Most of our routine protocols require around 40 minutes of imaging time, with the exception of rapid stroke protocols designed to diagnose stroke and large vessel occlusion in an acute emergent setting. The routine sequences used for imaging the brain are T1, T2 weighted,

FLAIR, DWI and some form of susceptibility-weighted sequence, such as GRE/T2*/SWI. Fat saturation may be applied to T1, T2 or FLAIR imaging and improve conspicuity of pathology. Gadolinium contrast may or may not be administered depending on the clinical concern and the patient's preceding history, such as malignancy or immune deficiency where the chance of pathology best illustrated with contrast is high.

T1-WEIGHTED IMAGING

T1-weighted images characteristically result in high signal intensity of fat-containing structures. The presence of T1 high signal (or "T1 shortening") however, has a differential and there are 9 different causes of this signal: Fat (including fatty marrow), methemoglobin (from breakdown of deoxyhemoglobin in hemorrhages), proteinaceous fluids (for example in proteinaceous cysts such as a sellar Rathke cleft cyst), calcium, melanin (in melanoma metastases), thyroglobulin (in thyroid cysts), paramagnetic elements such as copper and manganese and also gadolinium contrast agents. Slow flowing blood may also result in high T1 signal intensity.

The T1-weighted sequence is often referred to as the anatomical sequence, and when it comes to orbital and skull base imaging, fat is your friend. Fat, being so uniformly hyperintense, allows clear delineation of other soft tissue contours so that a mass can be readily recognized. In the brain the fatty myelin results in smoothly hyperintense white matter tracts (including the optic nerves) as compared to the less intense cortex and deep gray structures.

FSPGR

The fast spoiled gradient recalled acquisition in the steady state (SPGR) sequence produces a T1-weighted image. This rapidly acquired sequence can be performed with very thin slices (typically 1mm) with high contrast resolution, allowing for excellent spatial resolution and 3D reformatting capabilities. The rapid acquisition also minimizes vascular pulsation artifacts. The most frequent use of this sequence is for the evaluation of the whole brain for cortical and/or hippocampal abnormalities in the case of seizures, but this sequence is also used elsewhere in the body for high spatial and high contrast resolution imaging.

T2-WEIGHTED IMAGING

T2-weighted imaging is to T1 as Ginger Rogers is to Fred Astaire—an inseparable couple. While T1 is often considered the anatomical image, the T2-weighted image is often considered the pathology image. High signal intensity on T2 indicates increased tissue water which frequently accompanies pathological processes. Fat is intermediate to mildly bright on T2, but fluids such as CSF and vitreous are

very high intensity and remain so even when the sequence parameters are modified so that signal declines from all other tissues such as muscles. The cerebral white matter appears darker than the cortex and deep gray nuclei on T2-weighted images. Edema or acute inflammation as in optic neuritis will result in increased T2 signal intensity.

During the earliest phase of a hemorrhage, oxygenated blood will have fluid-like properties and be bright on T2-weighted images and correspondingly intermediate to low signal on T1 weighted images. When the blood becomes deoxygenated it will drop in T2 signal intensity, while the T1 signal is not changed (first 1-2 days). As the deoxyhemoglobin converts to intracellular methemoglobin, the T1 signal becomes bright while the T2 signal remains low. This change occurs generally within the first week of a parenchymal hemorrhage (days 2-7). As the red cells swell and disintegrate, methemoglobin is released, becoming extracellular methemoglobin which has high signal intensity on both T1 and T2-weighted images (days 7-14 or more). After 14 days, hemosiderin may be found in the periphery of a cerebral hematoma which has low signal on both T1 and T2, while centrally high T2 fluid-like signal may be found.

FIESTA/CISS

Just as FSPGR is a sequence designed to create thinner but still high quality (high signal to noise, SNR) T1-weighted images, so there are sequences designed to allow thin and ultra-thin slices that are T2 weighted. These are most commonly known as CISS (constructive interference in the steady state) and FIESTA (fast imaging employing steady-state acquisition), which reflect two of the different magnet manufacturers Siemens and GE respectively. Submillimeter imaging is routinely obtained, and can be done with 3D capabilities so that reformatting may be produced in multiple planes. These images allow excellent high-contrast resolution such as between the T2 bright cerebrospinal fluid (CSF) and the thin cranial nerves in their cisternal segments. These sequences also allow depiction of very thin walls of cystic structures such as intraventricular cysts and bands obstructing ventricular CSF flow.

FLAIR

Fluid attenuated inversion recovery (FLAIR) is a type of T2 weighted sequence that attenuates or negates the fluid (eg CSF) signal making it dark, while preserving the other T2 characteristics of the brain. This is most advantageous when there are focal areas of periventricular or cortical T2 hyperintensity which may be more subtle to detect, such as in demyelinating plaques or small peripheral infarcts. Loss of bright CSF signal increases the conspicuity of such lesions, effectively increasing the sensitivity for detection of subtle disease. When CSF is contaminated with cellular debris (such as hemorrhage, pus and carcinomatosis) the

fluid signal is not attenuated resulting in focal /diffuse areas where CSF remains bright, making FLAIR a good sequence for detection of such pathology. It is important to remember, however, that fluid motion can result in failure of attenuation of CSF intensity, which is most often seen in the cerebellopontine angles, the aqueduct and foramen of Monro, resulting in hazy intermediate to high signal here. This flow-related artifact is significantly minimized with 3D FLAIR sequences which also have the advantage of multiplanar thin-slice reformations. Many of our brain imaging protocols, such as those used for demyelinating disease, depend on 3D FLAIR to allow best evaluation of the whole brain and optic nerves. 3D FLAIR with fat-saturation (FS) improves conspicuity of the intraorbital segment of the optic nerve by attenuating the bright signal of both optic sheath CSF (with FLAIR) and orbital fat (with FS).

FAT-SATURATION (FS)

While fat works as an excellent intrinsic contrast by outlining and defining normal structures, its reliably bright signal intensity on T1 and T2 weighted images can obscure contrast enhancement and T2 hyperintense tissues. When evaluating the orbits with T2 weighted, FLAIR or post contrast T1-weighted sequences, negating or nulling the fat signal increases the contrast between orbital fat and the optic nerve, thus allowing more ready detection of subtle optic nerve enlargement, hyperintensity or enhancement. Similarly, we use FS on post contrast T1-weighted images when evaluating skull base or deep face pathological processes and particularly perineural tumor spread, in order to increase conspicuity of subtle enhancement.

FS can be technically performed in different ways, either as STIR (short tau inversion recovery) or as CHESS (chemical selective), which is usually referred to as "FS". STIR is less susceptible to pulsation artifact than FS, but FS results in images with better spatial resolution. FS also ensures that the tissue that has lost signal intensity is truly fat, rather than another tissue with similar signal intensity as fat. Using FS increases the overall time for an imaging sequence, although this is generally negligible for T2 weighted sequences.

SUSCEPTIBILITY WEIGHTED IMAGING: GRE/T2*/SWI

T2* ("T2 star") refers to the loss of signal in a T2-weighted sequence due to susceptibility effects of the imaged tissue and inherent inhomogeneity of the magnetic field. When performing a T2 sequence, specific pulses are employed to minimize T2* signal loss. In contrast to this, gradient recalled-echo (GRE) sequences are designed to exploit this signal loss. That is, the GRE sequence is designed to find areas of susceptibility within the tissue being imaged, such as paramagnetic blood products (deoxyhemoglobin, ferritin and hemosiderin) and diamagnetic calcifications. A 'side-

effect' of using GRE, however, is that field inhomogeneities such as those that occur at air (paranasal sinus)--tissue (skull base) interfaces also result in signal loss, producing a dark 'halo' that frequently obscures structures and masses adjacent to the skull base.

For routine brain imaging at our institution SWI (susceptibility-weighted imaging) has largely replaced the GRE sequence. The 3D SWI is a high-spatial resolution sequence with post-processing that produces a sequence superior in its sensitivity to paramagnetic blood products. SWI is an essential component of a post-traumatic study when small hemorrhages from axonal injury or cortical contusions may be found. It is also ideal for the detection of otherwise unapparent superficial siderosis, where prior hemorrhages have resulted in a thin layer of hemosiderin deposition on the pial surface of the brain and along cranial nerves.

DIFFUSION WEIGHTED IMAGING (DWI)

Diffusion-weighted imaging (DWI) is a rapidly-performed gradient echo sequence that relies on the normal phenomenon of molecular motion better known as 'Brownian motion'. Tissues in which there is loss of this random molecular motion are said to have restricted diffusion and result in bright signal intensity on DWI trace images. Because tissues that have inherently bright T2 signal may also be bright on trace images, loss of signal must be present on the corresponding attenuation diffusion coefficient (ADC) images. Bright signal on trace images without signal loss on the ADC image indicates intrinsic T2 hyperintensity and is often referred to as "T2 shine-through". It is imperative, therefore, that DWI trace images always be read with the corresponding ADC images.

Loss of Brownian motion may occur from a number of different pathologies. The most common use of DWI is for the detection of acute infarcts, with DWI usually positive within four minutes of the ischemic event; *DWI is the most critical sequence for any acute ischemic brain protocol*. The inhibition to molecular motion in stroke is proposed to be due to cellular swelling which is also referred to as cytotoxic edema. While false negative studies were initially described in the posterior fossa where there are more skull base artifacts, the development of significantly better spatial resolution and 2-plane imaging (axial and coronal) has meant that such false negative studies are extremely rare.

Cerebral infections can also result in restricted diffusion. Acute encephalitis, such as in Creutzfeldt-Jakob (CJD) and HSV-1 Encephalitis, results in characteristic patterns of restricted diffusion; again cellular swelling is proposed as the mechanism of this signal hyperintensity. Cerebral abscesses and subdural empyemas will also show restricted diffusion, proposed to be due to the macromolecular composition of such collections restricting molecule motion. Some pathological masses are also

characteristically restricted on diffusion, such as epidermoid cyst and cholesteatoma. For this reason DWI is a critical sequence whenever these diagnoses are entertained. Densely cellular tumors such as cerebral lymphoma and the highest grade focal components of glioblastoma multiforme (GBM) frequently also have restricted diffusion; so do active areas of demyelination such as with multiple sclerosis and neuromyelitis optica (NMO).

As alluded to earlier, there are artifacts that can make imaging difficult with DWI. This sequence is extremely sensitive to variations in the local magnetic field (resulting in susceptibility artifacts). Such variations occur at the interface of air and bone and air and soft tissue such as around the paranasal sinuses, skull base, temporal bone and sella. For this reason, 2-plane imaging and thin slices can be helpful to evaluate these areas. Blood products may result in falsely positive DWI, a phenomenon most problematic in post-operative neurosurgical patients where it may be difficult or impossible by MR to differentiate a post-operative extra-axial seroma / hematoma from an infected collection.

GADOLINIUM ADMINISTRATION

Gadolinium (gad) chelates have been used for a quarter of a century as the intravenous contrast agent for MR imaging. The basic principle of their use is that gadolinium shortens the T1 relaxation time of tissues, meaning that such tissues become markedly brighter on T1-weighted images. Gadolinium is excreted renally but is not nephrotoxic, making gad-enhanced MR the study of choice over contrast-enhanced CT in patients with renal failure, as iodinated contrast is nephrotoxic.

An association between the use of gadolinium contrast and nephrogenic systemic fibrosis (NSF), a progressive systemic fibrosing disorder, was first made public by the FDA in 2006, with cases found in patients with severe acute or chronic renal failure (estimated glomerular filtration rate (eGFR) < 30). It is thought that NSF results from inflammation induced by the gadolinium ion when it is dissociated from its chelating agent and circulating for prolonged periods in the body. Gadolinium is now contraindicated for patients with eGFR <30. At our institution, when the eGFR is in the range of 30-45, we often give a reduced gadolinium dose but prefer not to give gad unless it is essential for diagnosis. In all our patients, we give a macrocyclic gad compound, which has higher binding affinity between the ion and chelate, to minimize the possibility of free gad ions.

A small number of studies have raised the possibility of teratogenic effects of MRI exposure in early pregnancy based on mice and chick embryos. While there is no evidence currently of harm in humans, it is generally considered good practice to avoid MRI when possible in pregnancy. MR should be particularly avoided during the first trimester pregnancy but remains preferable

to any studies using ionizing radiation. Gadolinium is contraindicated during pregnancy because of the persistence of gadolinium in the fetal-amniotic fluid circulation. Lactating women who receive iodinated contrast or gadolinium can continue breastfeeding without interruption.

More recently, a phenomenon has become apparent of “gad staining” where residual gadolinium accumulates in the brain and bones of patients following multiple gad doses. At the time of writing this, in August 2015, the mechanism and the significance of gad staining is unknown. It occurs in patients with normal renal function but has not yet been reported with macrocyclic gad agents. I will update you at NANOS in March 2016 with the current literature and FDA recommendations.

VASCULAR IMAGING – MRA, MRV AND CTA

There are many different ways to view the intracranial and neck vasculature. Prior to the advent of multidetector CT, catheter angiography was the only method available to evaluate or search for intracranial aneurysms. Single detector CTs, were the only scanners available widely until the early 1990’s, when dual detectors were created. In 1998, 4-detector CT was introduced. (We now typically use 64 detector scanners!). Multidetector scanners allow thinner slices and faster imaging with the ability to produce multiplanar reformats from these thinner slices. These new capabilities revolutionized our ability to noninvasively evaluate carotid and intracranial vessels. With contrast injection, it is now possible to evaluate from the aortic arch to the circle of Willis with 0.625mm slices in 3-4 seconds. The entire neck and head vasculature can then be reformatted in any plane with 3D reconstructions. This capability allows rapid imaging of the brain for stroke and other causative lesions. CTV is not a separate sequence or protocol. During the time that the circle of Willis is imaged by CT, the dural venous sinuses will enhance and be evident on whole brain imaging.

Vascular imaging with MR was initially done with non-contrast imaging. The original method exploited the phenomenon of signal intense protons flowing into a slice that had been made devoid of signal, a method known as time-of-flight (TOF) MRA. It can be performed as a 2D (larger volume) or 3D (smaller volume, more detailed imaging) study. Intracranially we use a more complex multiple overlapping thin slice acquisition (MOTSA) MRA to evaluate the circle of Willis. The addition of contrast to MRA increases the sensitivity for detection of small vessels and allows a much greater volume of coverage, although it results in venous ‘contamination’ of the image and thereby generally makes evaluation of aneurysms more difficult. In order to take advantage of the detail and greater volume of coverage that can be had with a contrast-enhanced study, we do dynamic contrast enhanced (DCE) MR. This is a GRE-based sequence where

the same volume of tissue is imaged rapidly many times during the injection of contrast. This method separates out the arterial and the venous phase of enhancement so that each can be evaluated separately. It also allows determination of arteriovenous shunts and altered direction of flow such as with subclavian steal syndrome.

SO WHICH MODALITY SHOULD BE USED AND WHEN? CTA OR MRA?

There is almost never an absolute agreement on this point, but there are scenarios where one modality has greater merits. MRA and CTA are close to equivalent when screening for intracranial aneurysms. The choice of modality is not always obvious. In the emergent setting of a subarachnoid hemorrhage it is routine to obtain a CT head and then a CTA. Catheter angiography for diagnosis and/or treatment is often also performed. In the setting of a screening study, such as with headache or family history, non-contrast MRA is typically selected to avoid radiation and contrast injection. When a patient presents with a third nerve palsy, particularly if there is pupillary involvement, MRA with MR brain is the preferred modality since it allows evaluation of other potential causes of oculomotor palsy (it is possible to evaluate the midbrain, cistern and cavernous sinuses to the orbit).

MRA and CTA appear to be similar in accuracy for neck artery dissections although CTA is preferred by radiologists over MRA for evaluation of vertebral artery dissections because of ease of finding subtle dissections. Conversely MR has the advantage of greater sensitivity and accuracy for the detection of the intracranial complications of dissection such as stroke. All radiology departments should have protocols to evaluate suspected stroke and dissection. Sometimes the acuity of onset and the rapid need to evaluate the patient will dictate a choice of CT as the imaging modality. In patients younger than 50 years, keeping in mind the age of many with trauma or spontaneous dissection, MR may be the preferred modality in order to avoid the ionizing radiation from CT. If the patient has renal failure, where neither iodinated nor gadolinium contrast can be given, MRA would be the clear imaging modality of choice.

WHAT ABOUT CTV VERSUS MRV?

There are several different types of 2D and 3D MR venography (MRV) sequences to evaluate the cerebral dural veins. None is ideal for cortical venous demonstration and the visual perception of a vessel that is not shown (the 'missing' vessel) can be extremely difficult. In the author's experience, any MRV sequence is best supplemented with a post-contrast 3D SPGR of the whole brain, where solid enhancement of normal vessels and non-enhancing (even tiny, cortical) thrombosed vessels are much more readily evident. Similarly, post-contrast CT of the brain (as thin a slice as possible) is comparable to post-contrast brain MR imaging for the detection of venous thrombosis.

In summary, routinely available imaging sequences, when correctly applied together, allow reasonably rapid and highly sensitive evaluation of the brain for most neurological disorders. The key to obtaining the highest quality imaging study that might answer the precise clinical question that you have, is to pose the question properly in the imaging requisition form. This allows a neuroradiologist to subtly alter the protocol when necessary from, for example, a 'routine brain' to a "demyelinating brain and orbits", or to a "headache, aneurysm" protocol. In the author's university hospital practice, the advent of electronic medical records (EMR) has increased the ability to anticipate clinicians' needs and answer more precisely the clinical concern. Ideally, better communication between teams might make this even easier.

CME ANSWERS

1. d. DWI. This is the most critical sequence due to its sensitivity for the detection of acute ischemia within 4 minutes of the event. For this reason it is typically the first sequence performed on the patient in the emergency setting.
2. c. FLAIR FS. The addition of FS to the FLAIR sequence increases conspicuity of signal abnormality of the optic nerves as it increases contrast between the nerves and orbital fat. This is often performed as a 3D sequence to allow multiplanar reformations. FLAIR also allows excellent whole brain evaluation for cerebral demyelinating plaques.
3. b. TOF MRA. This non-contrast technique allows both 2D and 3D evaluation of the neck vessels and 3D evaluation of the intracranial arteries. Intravenous iodinated contrast used for both CTA and catheter angiography is contraindicated in a patient with acute renal failure as it will worsen the renal function. Gadolinium contrast agents should also not be given in ARF due to the potential to develop nephrogenic systemic fibrosis.

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TO INFINITY AND BEYOND: EXPLORING THE REALM OF ADVANCED IMAGING

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LEARNING OBJECTIVES

1. Discuss and elaborate on different advanced imaging technologies with emphasis on their clinical applications.
2. Discuss contraindication to MR imaging and issues with gadolinium administration.

KEYWORDS

1. Diffusion Weighted Imaging
2. Diffusion Tensor Imaging
3. Tractography
4. Dual Energy CT
5. Parallel Imaging

CME QUESTIONS

1. Elimination of T2 effects from diffusion weighted images by mathematical division results in generation of:
 - a. ADC maps
 - b. Exponential ADC maps
 - c. Low b images
 - d. High b images
2. What is accurate about parallel imaging?
 - a. Ability to scan two body parts simultaneously
 - b. Ability to scan with high Tesla and low Tesla strength
 - c. Ability to accelerate imaging acquisition time
 - d. Ability to scan in a parallel universe
3. Which is not true about dual energy CT?
 - a. Better material characterization enables better separation of different elements
 - b. Special hardware and software requirements required for implementation
 - c. Better fat suppression due to higher sensitivity to fat
 - d. Can generate virtual non-contrast images from contrast enhanced study

INTRODUCTION

While the advent of cross sectional imaging enabled accurate anatomic analysis of internal organs without the need for open or invasive procedures, the need for obtaining physiologic information that can be combined with anatomic data for a more comprehensive analysis of tissue pathophysiology has spurred the development of various CT, MRI and nuclear medicine-based techniques. Some of these techniques have already been vogue for a decade or more (e.g., diffusion weighted imaging) while others are in the translational stage. The objective of this presentation is to discuss these techniques with emphasis on their clinical applications.

ADVANCED TECHNOLOGY IN PRESENT DAY USE

GRADIENT ECHO, SPOILED GRADIENT ECHO, SUSCEPTIBILITY WEIGHTED IMAGING, FIESTA

T2 weighted Gradient echo and spoiled gradient echo have been used since the early stages of MR development to identify regions of magnetic field inhomogeneity, specifically with attention to recognition of brain hemorrhages. While T2 weighted gradient echo (also called T2*) lacks an 180° refocusing pulse, the spoiled gradient echo refers to using 'spoiler gradients' to negate any residual transverse magnetization between each pulse. There are so many different names and abbreviations devised by different vendors to differentiate and market their products, sometimes called the 'acronym jungle'.

Susceptibility weighted imaging (SWI) is a 'super-GRE' sequence that incorporates both magnitude and phase information as opposed to GRE that only has magnitude information. SWI has been shown to improve visualization

of brain hemorrhages, differentiate hemorrhage from calcification and identify venous versus arterial flow in arteriovenous malformations.

FIESTA is a vendor-specific (General Electric) acronym that refers to a type of sequence called CISS in general terms (other vendor-specific terms include VISTA [Philips], balanced-FFE [Philips] and TrueFISP [Siemens]). This is a T2/T1 weighted sequence that accentuates signal from fluid containing structures and suppresses most other structures. There is excellent contrast between cranial nerves where they transit through the cisterns and the CSF space itself. This sequence can also be helpful in delineating the small ducts within the salivary glands in MR sialography.

DIFFUSION WEIGHTED IMAGING (DWI)

DWI is a molecular imaging technique that evaluates the motion of water molecules in human tissues and provides a different type of contrast than T1 or T2 weighted images. The results of DWI acquisition can be displayed in different ways: low b image, high b image (commonly called the diffusion image), ADC (apparent diffusion coefficient) map and exponential ADC (eADC) map. The 'b' value in DWI refers to the degree of diffusion sensitization with higher numbers implying greater sensitivity to smaller degrees of water molecular movement.

A combination of high signal on the high b image with low signal on the ADC map is referred to as 'restricted diffusion'. When there is high signal on the high b image but normal signal on the ADC map, this is referred to as 'T2 shine through' (reflecting the contribution of T2 property of the tissue to the DWI image). Occasionally, it may be difficult to determine the signal abnormality on the ADC map, in which instance evaluation of the eADC map can help because these maps are essentially DWI images in which the contribution of T2 properties have been mathematically removed. However, it is not advisable to rely only on or start with eADC maps because these maps are mathematically generated and hence appear more pixelated compared to high b DWI images.

Restricted diffusion is commonly seen in acute ischemic stroke due to cytotoxic edema that results in decreased water molecular motion in brain tissues. However, restricted diffusion is not unique to acute ischemic stroke and can also be observed with other conditions such as abscess (due to increased viscosity), optic neuritis, active demyelinating plaques (acute inflammation), malignant tumors (due to increased cellularity), herpes encephalitis and Creutzfeldt-Jakob disease. False negatives can occur with smaller acute ischemic strokes, especially in the brainstem. Interpretation of DWI images needs always to be performed in conjunction with conventional T1 and T2 weighted images as well as the ADC maps in order to minimize false positives and negatives.

DIFFUSION TENSOR IMAGING (DTI) AND TRACTOGRAPHY

While DWI evaluates magnitude of water molecular diffusion, DTI evaluates both the magnitude and directionality of water diffusion in human tissues. DTI takes longer to acquire than DWI (three directions of investigation of water motion in DWI, more than 6 for DTI and often 15 or more). DTI is able to generate two types of maps for analysis: diffusivity or ADC maps (magnitude images), and fractional anisotropy (FA) maps, which demonstrate the degree of directionality of water diffusion in each voxel. The degrees range from 0 (representing spherical diffusion with no directionality) to 1 (representing only one direction). Disease processes that cause axon and myelin sheath loss (multiple sclerosis) result in increased free water diffusion, measured as increased diffusivity and decreased number of restricted directions to water motion, measured as decreased FA. Many studies of the role of DTI in brain disorders ranging from traumatic brain injury to demyelinating disorders to neuropsychiatric diseases have shown that the DTI-derived parameters can be used to distinguish different disease populations and in some instances stratify disease severity. However, these are group studies and there is yet no consensus or major guidelines about the applicability of this technique in an individual patient to identify a particular disease. This technique could also be useful longitudinally in the follow-up of patients with chronic diseases such as multiple sclerosis, as it is more sensitive to demyelination and remyelination than conventional T2 or FLAIR sequences.

Utilizing the FA information from DTI, the preferential direction of a white matter tract in any chosen voxel can be constructed. Repeating this process in a consecutive manner across different directions in relationship to the primary voxel of interest enables depiction of different white matter tracts. This technique termed "tractography" identifies the relationship of important tracts to pathologies such as brain tumors and guides pre-operative planning.

MR SPECTROSCOPY (MRS)

MRS is a metabolite imaging technique based on quantification of non-water resonances in different human tissues. In the brain, the important spectra to identify are N-acetyl aspartate (NAA, a neuronal marker), choline (a membrane turnover marker), and creatine (a marker of energy metabolism and an internal standard). Difficulty with standardization of acquisition techniques and in comparing results from different scanners and institutions has reduced the initial excitement about this method and decreased the clinical applicability of this technique to a short list of indications, such as Canavan disease (significantly elevated NAA), recurrent brain tumors (increased choline to NAA ratio), and abscess (increased lactate and lipids). Also, comparing the ratios of these metabolites across different time points in the same patient and across different patients or scanners is fraught with difficulties in clinical interpretation.

MRS often requires the presence of a radiologist onsite to help guide the placement of voxels for both single voxel and multivoxel techniques as this placement can essentially determine the spectral peaks and influence the final results to a great degree. Lack of adequate sensitivity and specificity to various diseases makes it imperative to interpret MRS information along with conventional imaging sequences for an accurate analysis.

SPECT AND PET

Single photon emission computed tomography (SPECT) utilizes radio-isotopes injected into the bloodstream to evaluate tissue metabolism. ^{99m}Tc - HMPAO (hexamethylpropylenamine oxime) is a tracer that is taken up by brain tissue proportional to blood flow. In contrast, positron emission tomography (PET) typically evaluates glucose metabolism by studying the distribution of fluorodeoxyglucose. These techniques are complementary, with major applications in epilepsy, dementia and brain tumors. Newer agents in PET imaging are capable of evaluating neurodegenerative diseases such as Parkinson disease.

PARALLEL IMAGING

Acquisition time remains a major issue in MR imaging and influences the ability to obtain high quality images without motion artefact. In contrast to faster and stronger imaging gradients that are typically used for shortening acquisition time, parallel imaging uses the inherent spatial sensitivity of phased-array coils to provide some of the spatial information in the image that would otherwise be obtained in the traditional manner of Fourier transform MR imaging. In simpler terms, parallel imaging allows a reduction in the number of phase-encoding steps, an important factor that determines acquisition time, while generating images of good quality and spatial resolution. This technique is now routinely used by all major vendors in most magnets. The names for the specific techniques are vendor-specific (ASSET [GE], GRAPPA [Siemens], SENSE [Philips], RAPID [Hitachi], etc.). In most commercially available applications, this technique increases the acquisition speed by factors of 1.5 to 3. Gains higher than this are, however, difficult to achieve due to artefacts and signal-to-noise ratio considerations.

DUAL ENERGY CT

Dual energy CT (DECT) utilizes information obtained from x-ray spectra of two different energies to create virtual monochromatic images and material density images where the contribution of different elements (such as iodine, water, etc.) to the CT image can be selectively highlighted or suppressed. CT vendors employ different techniques to achieve the dual energy effect. There can be two separate x-ray tubes emitting different energies, one tube that oscillates rapidly between two energy peaks multiple times in a second, or one tube with two separate sandwich detectors. Each of these configurations has its own advantages and disadvantages with none considered superior to the others. DECT technology requires upgrading

the hardware on the existing scanners or purchase of a new scanner with the updated technology (it is not a simple post processing step). While there have been questions about radiation dose with DECT, recent studies have shown that it can be performed with dose neutrality compared to conventional CT or even lower doses in some instances.

Applications of this technology include reduction of beam hardening (which continues to be a major problem in the posterior fossa), metal artefact reduction (especially with implanted hardware or dental amalgam), and differentiation of hemorrhage and iodine staining after stroke thrombolysis, differentiation of benign and malignant head and neck tumors, and laryngeal cartilage invasion from cancer and reactive cartilaginous changes.

EMERGING TECHNOLOGIES

COMPRESSED SENSING

Compressed sensing (CS) is a mathematical framework that reconstructs data from highly undersampled measurements. To accelerate the acquisition time, CS can and has been applied to MRI and on diverse MRI methods. CS allows acquisition of only the important coefficients of the signal during the acquisition and utilizes concepts of transform sparsity and compression to generate the requisite images. This technique enables shortening of MR acquisition time (thereby reducing motion artefact) and can allow multiple sequences to be acquired within a reasonable time frame for better tissue characterization.

MYELIN IMAGING

Although DTI studies white matter tracts in the brain, it may be possible to directly measure myelin content using recent advances in imaging such as myelin-water ratio and inhomogeneous magnetization transfer ratio. Being able to directly measure myelin content can be very helpful in stratifying disease severity in multiple sclerosis and other diseases that result in demyelination.

MR FINGERPRINTING (MRF)

Instead of acquiring qualitative MR images that are contrast “weighted” due to a mixture of (magnetic) tissue properties, MRF takes a different approach to data acquisition, post-processing and visualization and uses a pseudo randomized acquisition that causes the signals from different tissues to have a unique signal evolution or ‘fingerprint’ that is simultaneously a function of the multiple material properties under investigation. The processing after acquisition involves a pattern recognition algorithm that matches the fingerprints to a predefined dictionary of predicted signal evolutions and can be translated into accurate quantitative maps of the magnetic parameters of interest (T1, T2, proton density, diffusion). MRF may thus offer multiparametric imaging with high reproducibility, and has a high potential for multicenter/multivendor studies.

PHASE CONTRAST CT

Phase-contrast CT is an x-ray–based imaging modality in which the images are generated by using the phase shift of x-rays passing through matter rather than their x-ray attenuation to generate tissue contrast. Some early studies are promising and suggest that phase-contrast CT can yield higher contrast in biologic soft tissue than absorption-based x-ray imaging. Recently, grating-based phase-contrast CT has been shown to be able to extract the phase-shift information when conventional x-ray tubes are used, making it the most promising candidate to bring phase-contrast CT to clinical application.

MISCELLANEOUS

FUNDAMENTALS OF MR ACQUISITION

Signal to noise ratio (SNR) increases linearly with increase in Tesla strength. However, due to other constraints, the benefit when moving from 1.5 T to 3T is not doubled but is around 40%. SNR is directly proportional to slice thickness and the type of radiofrequency (RF) coils, which contain the hardware elements of signal acquisition. There are essentially two types of RF coils in MR imaging: volume coils (which surround the anatomy of interest either completely or partially) and surface coils (which are placed as close to the imaged anatomy as possible). The overall signal depends on two components--coil elements that are responsible for signal generation and channels that refer to the receiver pathway. The advent of higher elements and channels (up to 32 channels) in the last decade has significantly helped accelerate image acquisition and acquire higher resolution images within a reasonable time.

CONTRAINDICATIONS TO MRI

MRI utilizes a magnetic field that is 1000s of times stronger than the earth's magnetic field (1.5 or 3 Tesla compared to 25 to 64 microteslas). This difference implies that ferromagnetic objects will experience a strong magnetic field when placed in the magnet. Therefore, patients with metallic objects (shrapnel, bullet fragments, implants) may experience significant torque and heating of tissues when within the magnet. Some of these effects are, however, only relative contraindications to MRI. The need for the MRI has to be assessed based on location of the metal, type of metal and type of scan required. In addition, cochlear implants and pacemakers have long been considered absolute contraindications due to problems of device malfunction from the strong magnetic field. A recent exception to this has been the 'pacemaker protocol' followed at a few major institutions where the pacemaker is turned off for the short duration of the scan under EKG and cardiology surveillance. The pacemaker is turned back on at the conclusion of the MRI scan. Recent introduction of FDA approved MRI compatible pacemakers can help future generation of patients get better access to medically indicated MRIs without the need for switching off the pacemaker.

Gadolinium is required for a majority of neuroradiology indications, but it is prudent to weigh the risks and benefits in patients with poor renal function. Although gadolinium is contraindicated when the GFR is below 30, especially due to the risk of nephrogenic systemic fibrosis, the risk-benefit ratio should be carefully considered when the GFR is between 30 and 40.

CME ANSWERS

1. b
2. c
3. c

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North American Neuro-Ophthalmology Society

42nd Annual Meeting

February 27 – March 3, 2016
JW Starr Pass Marriott • Tucson, Arizona

Program Schedule

THURSDAY, MARCH 3, 2016

6:30 am - 12:00 pm	Registration/Help Desk	Arizona Foyer
6:30 am - 7:30 am	Breakfast	Arizona Ballroom
7:30 am - 9:30 pm	Ocular Motility [2 CME] <i>Moderators: Matthew J. Thurtell, MBBS, FRACP and Eric R. Eggenberger, DO, MSEpi</i>	Tucson Ballroom

This symposium will provide a practical update on central ocular motility disorders, including nystagmus and other ocular oscillations. The focus will be on ocular motility disorders that are relevant to neuro-ophthalmic practice.

Upon completion of this course, participants should be able to: 1) Recognize ocular motility disorders due to cerebral and basal ganglia disease; 2) Recognize ocular motility disorders due to cerebellar disease; 3) Recognize ocular motility disorders due to brainstem disease; and 4) Recognize nystagmus and other ocular oscillations.

		<u>PAGE</u>
7:30 am - 7:55 am	Ocular Motility Disorders Due to Cerebral and Basal Ganglia Disease, <i>Jason J. S. Barton, MD, PhD, FRCPC</i>	415
7:55 am - 8:25 am	Ocular Motility Disorders Due to Cerebellar Disease, <i>David S. Zee, MD</i>	429
8:25 am - 8:45 am	Ocular Motility Disorders Due to Brainstem Disease <i>Eric R. Eggenberger, DO, MSEpi</i>	433
8:45 am - 9:05 am	Nystagmus and Other Ocular Oscillations, <i>David S. Zee, MD</i>	439
9:05 am - 9:30 am	Cases for Panel/Audience Discussion, <i>Matthew J. Thurtell, MBBS, FRACP</i>	
9:30 am - 10:00 am	Coffee Break	Arizona Ballroom
10:00 am - 12:00 pm	Sports-Related Concussion: The Eyes Have It! [2 CME] <i>Moderators: Laura J. Balcer, MD, MSCE and Gabriella Szatmary, MD, PhD</i>	Tucson Ballroom

The symposium will provide the audience with insight into the latest research in the field of acute sports-related concussion. The speakers will describe the practical neuro-ophthalmological tests that can be applied at the sideline to allow for early diagnosis and prognosis. Newly-recognized neuro-ophthalmological findings, such as potential biomarkers, will be described and shown how they are incorporated into clinical trials.

Upon completion of this course, participants should be able to: 1) Identify key signs and/or symptoms that the patient exhibits that could lead to early detection of diagnosis; 2) Discuss the possible findings on examination and set up proper and timely diagnostic test(s) and treatment; 3) Demonstrate the correct way to examine a patient immediately following a closed head injury; 4) Debate the advantages and disadvantages of diagnosing closed head injuries at the sideline; 5) Organize a plan of how this information could be applied in a clinical setting; 6) Determine if this information would be more useful in a clinical setting after being applied at the sideline; 7) Visualize the patient's injury and symptoms that may be present at the sideline compared to the symptoms that may be present at a clinical setting; and 8) Reflect on the above information to determine if the findings on the sideline would be beneficial in diagnosing the patient prior to being seen in the clinical setting.

10:00 am - 10:25 am	The NCAA Experience: Why Do We Need Vision? , <i>Brian Hainline, MD</i>	<u>PAGE</u> 445
10:25 am - 10:45 am	Capturing Eye Movements: Foundation for Neuro-Ophthalmic Assessment in Concussion , <i>Janet C. Rucker, MD</i>	451
10:45 am - 11:00 am	Sideline Testing for Sports-Related Concussion: What is the Evidence? , <i>Laura J. Balcer, MD, MSCE</i>	459
11:00 am - 11:10 am	Perspectives of a Neuro-Ophthalmologist on the Sideline , <i>David I. Kaufman, DO</i>	471
11:10 am - 11:30 am	Bringing Technology to the Sideline: New Data from the Pupil and OCT , <i>Randy Kardon, MD, PhD</i>	475
11:30 am - 11:45 am	Emerging Issues in Concussion , <i>Steven L. Galetta, MD</i>	485
11:45 am - 12:00 pm	Q&A	

OCULAR MOTILITY DISORDERS DUE TO CEREBRAL AND BASAL GANGLIA DISEASE

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LEARNING OBJECTIVES

1. Describe how focal cerebral lesions affect the generation of pursuit, saccades, and fixation, and what this tells us about the organization of ocular motor control in the brain
2. Describe how visual and attentional disorders from brain damage alter ocular motor behaviour
3. Review how eye movement paradigms can help to reveal the underlying mechanisms of visual dysfunction

CME QUESTIONS

1. Which lobes of the cerebral hemispheres contain the eye fields for saccades?
2. Where do hemianopic patients fixate when they bisect a line?
3. When a patient with pure alexia reads, how does the number of fixations change when the word contains more letters?

KEYWORDS

1. Saccade
2. Pursuit
3. Hemianopia
4. Hemineglect
5. Agnosia

INTRODUCTION

Where we look determines what we see. Because human vision varies greatly with retinotopic location, with high spatial resolution limited to the fovea, humans have evolved a sophisticated ocular motor system, much of it aimed at stabilizing vision on objects of interest, despite the fact that we are mobile creatures and live in dynamic environments. Thus fixation serves to hold our gaze on a stationary object, while the vestibular and optokinetic systems work together to stabilize that gaze while our bodies or heads are in motion. If the object is moving,

the smooth pursuit system will use information about the object's trajectory to keep gaze on the object. Any failure of these systems to keep gaze directed at the object will create a position error signal that will trigger a corrective saccade. Finally saccades also have the function of shifting gaze to new objects of interest, following which all the systems mentioned will act to stabilize gaze on the new object.

In this manner, all the different components of the ocular motor system work together with a common goal in real life. In the laboratory, we tend to isolate each component with artificial paradigms, and this has yielded a tremendous number of insights on the structure and function of ocular motor control. However, their common aim means that dysfunction of any of these will lead to the same result: sub-optimal vision.

It is also true that what we see determines where we look. Every snapshot our visual system takes of the world generates a decision about whether to maintain the current fixation or to make a saccade to a new location. The outcome of perceptual processing is critical for this decision. Have I seen enough of the currently fixated object to understand what it is and what it means to me? At the same time, is there something in the peripheral field that needs me to focus attention and my fovea upon it? Perception is all about making decisions about the world, and such decisions lead to ocular motor and other responses that characterize our interaction with that world. Thus, impairments in perception can also alter our ocular motor behaviour.

In a discussion of the cerebral disorders of eye movements, one can thus review both the evidence for impairments of the response system due to brain damage, as well as the changes in eye movements that follow perceptual disorders. This chapter will not be discussing the eye movements in specific disease states that affect cortex: for the most part, eye movements do not make a critical contribution to diagnosing such disorders and differentiating them from other conditions.

A. CEREBRAL OCULAR MOTOR SYSTEMS

SACCADES

Measuring saccades.

Saccades are voluntary eye movements that shift fixation of the fovea rapidly from one object to another. Their characteristics are their accuracy, latency, and velocity. Cortical lesions generally affect latency and accuracy more than velocity.

The standard saccadic test has the spot that the subject is currently fixating disappear and a new target appear somewhere in their peripheral field, with instructions for the subject to look quickly and accurately at the new target. Their response is called a *visually guided saccade*.

This simple task can be elaborated in many ways to reveal different aspects of the saccadic control system, and it is worth reviewing these first, because many studies of cerebral control of saccades have used more complex paradigms to make inferences.

For a start, there is a distinction between an *exogenous* saccade to a suddenly appearing target, and an *endogenous* saccade prompted by instructions and made to a target that is already there. The former is said to be more reflexive and the latter more volitional. Also, the temporal relationship between the disappearance of the fixated spot and the appearance of the new target can be varied. In the *gap* task, the fixated spot disappears first, typically by about 200ms, resulting in shorter saccadic latencies, an effect attributed to both earlier disengagement of attention from the fixated spot as well as the disappearance serving as a warning cue. In the *overlap* task, the target appears before the fixated spot disappears, which prolongs latencies, and this is attributed to the persistence of attention at the fixation spot.

To generate *memory-guided saccades*, the target appears and disappears while the fixation spot remains on, only disappearing several seconds later. To do this correctly, the subject must a) inhibit the tendency to make anticipatory saccade and b) use spatial working memory to remember the location of the target.

The *double saccadic target* paradigm^{1,2} flashes two targets sequentially before a saccade is made. If the second target appears long before the saccade, only one saccade is made, to the second target. If the saccade follows the second target closely, then two saccades are made, to the first and then the second target. To be accurate, the size of the second saccade must take into account the change in the second target's retinal coordinates after the first saccade is made. Thus this reveals how saccadic programming is updated by eye position data.

Complex sequences of several targets test the ability of the saccadic system to generate and store a spatiotemporal plan of a sequence of movements.

The *antisaccade*^{3,4} has subjects make a saccade not towards a suddenly appearing target but in the opposite direction. Subjects must both not make a reflexive visually guided saccade, and execute a novel unpractised one. There is usually a small error rate of looking at the target, and an increased latency of around 60ms for antisaccades compared to visually guided saccades (sometimes called prosaccades).

Even more can be done. The *global effect* has subjects make saccades to a target while a distractor also appears nearby. This causes the saccade to land at a position between the target and distractor, an effect that is attributed to spatial averaging of the two locations by the superior colliculus. On the other hand, distractors along the path of the saccade can cause the saccade's trajectory to curve away from the distractor. Saccades can be performed with *rewards or penalties* for performance, to determine the neuro-economic factors of performance.⁵

Functional imaging of saccades.

In monkeys, the *frontal eye field* codes the vectors of saccades directed contralaterally. Numerous studies show that in humans it is located in a region extending from the middle of the precentral gyrus, between the mouth and hand regions, to the posterior part of the middle frontal gyrus,⁶⁻⁹ in Brodmann areas 4 and 6, not the area 8 of monkeys.¹⁰ It is activated by horizontal and vertical saccades, by saccades to auditory targets, and even by saccades with the eyes closed or by just thinking about making saccades.

The *supplemental eye field*, in the posterior part of the superior frontal gyrus, is particularly active during memory-guided saccades^{11,12} or complex saccadic sequences.¹³ Other anterior regions active during memory-guided saccades include the cingulate, insula and dorsolateral prefrontal cortex.^{11,12,14}

A *parietal eye field*, which has strong connections to the frontal eye field in monkey,^{15,16} is located in the human intraparietal sulcus.^{17,18}

Subcortically, the basal ganglia or thalamus were found to be active during visually guided saccades in some studies^{12,13} but not others,¹¹ while memory-guided saccades increase activity in the putamen, substantia nigra and thalamus.^{11,14}

For antisaccades, most studies show greater activation in not only the frontal eye field, supplemental eye field, parietal cortex, putamen and thalamus, but also the dorsolateral prefrontal cortex.^{12,19,20}

Summary of lesion data.

While functional imaging has revolutionized the study of cerebral function, lesion studies still make important contributions to understanding the role of different regions, which will be discussed in detail. To summarize here, it has been suggested that the parietal eye field triggers reflexive visually guided saccades while the frontal eye field

is involved with saccades requiring more volitional control, such as memory-guided saccades and antisaccades,²¹ although the following data show this formulation may be simplistic. The parietal eye field performs the sensorimotor transformations that translate stimulus location into the goal for saccades: lesions here lead to hypometria and trouble with updating saccade plans in the double-step saccade paradigm. The supplemental eye field plays a role in the temporal organization of saccades, and their lesions cause errors on the memory-guided tasks and saccadic sequences, and delays in the double-step paradigm. The dorsolateral prefrontal cortex is important in spatial memory and suppressing reflexive saccades: lesions lead to delays and errors in visual memory-guided and double-step saccades, and antisaccade errors. Finally, it should be noted that unilateral lesions of any of these regions lead to only subtle abnormalities that often require eye movement recordings and special tasks to reveal deficits; however, bilateral lesions of frontal or parietal regions can lead to obvious clinical defects.

Lesions of the frontal eye field.

The latencies of visually guided saccades are minimally affected by unilateral lesions^{22, 23} unless there is additional damage to white matter of the anterior limb of the internal capsule or near the frontal horns, in which case contralateral saccades are delayed.²⁴ This suggests an effect of interrupting converging outputs from several cortical regions. Latency delays from more limited lesions are more obvious with complex tasks, as with the overlap paradigm, memory-guided saccades and antisaccades.²⁵

In accuracy, contralateral saccades of various types are hypometric.^{25, 26} One patient made accurate second saccades in the double-step paradigm,²⁵ indicating that such lesions do not affect the spatial updating of saccades for current eye position. Whether the starting position of the saccade is in contralateral or ipsilateral space has no effect:²⁵ thus deficits are related more to saccade direction than to eye position, consistent with the frontal eye field coding saccades as vectors.

Scanning patterns show that damage to the frontal eye field reduces the time spent searching the contralateral side of complex scenes,^{23, 27} an intentional type of hemi-neglect that is associated with mild neglect signs on line bisection and shape cancellation.²⁷

Lesions of the supplemental eye field.

Patients with left-sided lesions cannot perform a sequence of saccades correctly after a short delay.^{27, 28} With the double step paradigm, the latencies of second saccades directed contralaterally are prolonged.²⁷

Lesions of the dorsolateral prefrontal cortex.

These have inconsistent effects on visually guided saccades.²⁹ Bilateral delays and inaccuracies are found with memory-guided saccades.³⁰ On the double-saccade paradigm, patients may fail to initiate second saccades directed contralaterally.²⁷ During the antisaccade task,

lesions of right or left dorsolateral prefrontal cortex impair the ability to suppress reflexive saccades to targets in either hemifield, but don't affect antisaccade latencies.^{22, 29}

Lesions of the parietal eye field.

Unilateral parietal eye field lesions increase the latency of visually guided saccades, mainly contralaterally,^{27, 31, 32} sometimes bilaterally.²⁴ Similar effects can occur with lesions of the posterior internal capsule, which may serve to transmit information from the parietal eye field.²⁴ A similar result has been found with memory-guided saccades.³⁰ In addition to latency effects, a mild contralateral hypometria has been found.³¹

More complex saccadic effects can be found. The monkey lateral intraparietal area uses extra-retinal information about eye movements to update retinotopic maps of target location to ensure that saccadic plans take into account changes in eye position.¹⁶ On the double-step saccade paradigm, humans with parietal eye field lesions make amplitude errors on a second saccade to an ipsilateral target after a first saccade to a contralateral target.³¹ This suggests lack of extra-retinal information about contralateral eye movements.

Some but not all patients with parietal lesions lose the ability to reduce saccadic latencies when the tasks are predictable.³³

Bilateral parietal lesions.

Abnormal saccades with bi-parietal injury have long been described with 'visual disorientation' or Bálint's syndrome,³⁴⁻³⁷ but the literature is not precise in detailing the saccadic abnormality. In fact, there may be several dissociable elements.

First, bilateral lesions can cause severely inaccurate saccades,^{35, 38, 39} to visual or tactile targets, so that gaze wanders in search of a target until stumbling accidentally upon it. Second, once the target is fixated, they may have difficulty maintaining fixation,³⁵ an impersistence of gaze. Third, some may maintain fixation excessively, leading to *difficulty initiating saccades* to new objects.^{34, 36} Some attribute this to *fixation spasm*⁴⁰ but others suggest a disorder of volitional saccadic generation, or '*ocular motor apraxia*','³⁴ based on the fact that patients can generate spontaneous random saccades but not saccades to command or visually guided saccades.

Combined bilateral frontal and parietal lesions.

This combination impairs saccades in monkeys far more than bilateral ablations of either area alone.⁴¹ In humans a similar combination of lesions has been reported as Bálint's syndrome^{36, 42} or acquired ocular motor apraxia, without optic ataxia or simultanagnosia.^{43, 44} The abnormalities are severe: the eyes are often immobile, with no saccades to command or to visual targets, though sometimes saccades to unexpected noises.⁴² Gaze shifts are accompanied by head thrusts.⁴⁴ As well, optokinetic responses, pursuit, and convergence may be absent.

SMOOTH PURSUIT

The smooth pursuit system responds to motion of a small target across the retina by generating eye velocities that try to match the velocity of the target. If the match is successful the velocity of the target's retinal image will be reduced to zero. Thus smooth pursuit is a negative feedback system: velocity traces of pursuit reveal the small oscillations around mean eye velocity characteristic of negative feedback.⁴⁵

Measuring smooth pursuit.

The ratio of eye velocity to target velocity is pursuit gain, the main measure used to characterize pursuit. Indirectly, one can also measure the number and size of catch-up saccades, which occur when pursuit velocity does not match target velocity and the eye falls behind: this is what is observed at the bedside.

The most common test has the subject track a target that is following a predictable, constantly motion. This is usually a sinusoidal path but can be a 'triangular' path, in which the target moves at constant speed back and forth. In addition to gain, one can characterize performance by noting the phase, whether the oscillations of the eye are exactly in time with those of the target, or slightly ahead or behind. This type of pursuit is considered a *steady-state response*, and can be measured at various frequencies, amplitudes and speeds.

Less frequently used is the step-ramp paradigm. After a central fixation spot disappears, a target appears in a peripheral location (the step) and immediately moves at a constant velocity and direction (the ramp). The pursuit system has a latency of about 130ms, so the eye does not begin to move until then. Then, for the next 130ms, the pursuit seen is responding to a target velocity seen before the eye started to move. This is called *open-loop pursuit*. After that point the velocity of the target's image on the retina will be reduced by the movement of the eye: this is called *closed loop pursuit*.

Variations on these methods have been used. Predictive aspects can be reduced during sinusoidal tracking by using trajectories summed from several superimposed sinusoidal motions. Step-ramp paradigms can use targets with predictable or unpredictable steps and ramps.⁴⁶

Functional imaging of pursuit.

In monkeys, area V5 (middle temporal, MT) and area V5a (medial superior temporal, MST). respond to visual motion and show activity during pursuit. In humans, a visual motion area is located in lateral occipito-temporal cortex, in the junction between Brodmann areas 19 and 37⁴⁷ and pursuit-related activity has been demonstrated in this region.^{48, 49}

There are also pursuit-related responses in the frontal eye fields in monkeys, and there is evidence of this in humans too,⁵⁰ in a region more lateral and inferior in the frontal eye field than that activated during saccades.⁵¹

Pursuit is associated with greater activity in the lingual gyrus and dorsomedial cuneus, probably related to visual motion.⁵²

Directional pursuit defects after cerebral lesions.

Directional defects impair pursuit of targets moving in a specific direction, regardless of location in the visual field. They can often be observed clinically. Like all cerebral pursuit defects, they are asymptomatic.

Most directional defects are *ipsi-directional*, towards the side of the lesion. These were first noted with hemispherectomies,^{53, 54} then in cases with parietal and occipito-temporal lesions⁵⁵⁻⁵⁷ and finally in large series of patients with unilateral occipito-parietal lesions.⁵⁸⁻⁶⁰ While those studies used predictable pursuit paradigms, a study with unpredictable step-ramp targets showed ipsi-directional defects in pursuit initiation with lesions of the junction of areas 19/37/39.⁶¹

Ipsi-directional defects, sometimes with milder contra-directional defects, are also reported with lesions of the frontal eye field, supplemental eye field, or dorsolateral prefrontal cortex.^{25, 59, 62} Some claim that ipsi-directional pursuit defects correlate with damage to the supplemental eye field, and bi-directional defects with lesions of the frontal eye field.⁵⁸ Ipsi-directional pursuit defects may also arise from lesions of the posterior limb of the internal capsule,^{58, 59, 63, 64} affecting descending cortical output to brainstem nuclei.^{65, 66}

The origin of ipsi-directional defects is of interest. It is unlikely it results from the superimposition of a nystagmus upon the pursuit response.^{53, 63} It is not secondary to a perceptual defect, as impairments in motion perception are not found in most patients with decreased ipsi-directional smooth pursuit.⁶³ Rather, one study with step-ramps suggested a velocity bias that causes both an increase in pursuit initiation contra-directionally and a decrease ipsi-directionally.⁶⁷

A few patients have *contra-directional* pursuit defects.^{58, 68, 69} This has been attributed to hemi-neglect or hemianopia,⁶⁸ though other studies dispute this.^{60, 63} Contra-directional defects have been reported with both occipito-parietal and frontal lesions.

Bi-directional defects can occur with frontal, parietal and thalamic lesions and have been attributed to attentional dysfunction.⁵⁸

Are there hemispheric differences? Some found that right-sided lesions caused more pursuit defects,^{60, 62} but others did not.⁶⁸ Others believe that right-sided lesions cause more severe ipsi-directional defects.⁵⁸ Yet others believe that left-sided lesions caused ipsi-directional defects and right-sided ones bi-directional ones.⁵⁶ Clearly, there is no settled answer.

Retinotopic pursuit defects after cerebral lesions.

These impair pursuit of targets moving in any direction, but confined to specific regions of the contralateral hemifield. Thus they are revealed only with step-ramp tests. They are analogous to retinotopic defects for motion perception and pursuit initiation seen in monkeys with V5 lesions. In humans these are hard to find because of the frequency of hemianopia associated with lesions in this occipital area. One study⁶⁰ found a retinotopic pursuit defect in one patient with a lesion in area 19/37 and both ipsi-directional and retinotopic pursuit defects in two patients with lesions of Brodmann areas 39/40, while another⁶¹ found a retinotopic defect in one patient with a lesion in areas 21/22.

Craniotopic pursuit defects after cerebral lesions.

This is an impairment of pursuit when the eyes are located contralaterally of midline and occurs only with lesions of the frontal eye field.⁷⁰ All also had ipsi-directional pursuit defects, and some had ipsilateral gaze deviation and impaired contralateral saccades.

FIXATION

Zero eye movement is still an eye movement. Less is known about fixation than about saccades or pursuit. Some cells in monkey area 7 of the parietal cortex discharge during fixation of interesting targets.⁷¹ The frontal eye field shows activity when a saccade is countermanded or suppressed.⁷² Human functional imaging studies show fixation-related activity in the frontal eye field,⁶ dorsolateral prefrontal cortex,¹¹ supplemental eye field and anterior cingulate cortex.⁷³

Spasm of fixation.

This is an impairment in shifting fixation.^{40, 74} Modern ocular motor recordings define this as increased saccadic latencies on the overlap paradigm, but normal latencies on the standard task, when the fixation spot disappears at the same time the target appears.⁷⁵ Spasm of fixation may result from cerebral damage that disinhibits the pars reticulata of the substantia nigra, which in turn inhibits the superior colliculus. The lesions responsible are not well defined, but could include the frontal eye field.

Impersistence of fixation.

Patients with lesions of the supplementary motor area have difficulty suppressing saccades to suddenly appearing targets in the contralateral field.⁷⁶ Ventrolateral frontal lesions have the same effect, but with targets in either hemifield.⁷⁶ A similar problem may lie behind the high antisaccade error rate associated with such lesions in another study.⁷⁷ Lesions of dorsolateral prefrontal cortex lesions have also been linked to high antisaccade error rates^{22, 29} and anticipatory saccades in memory-guided paradigms.⁷⁸

Square wave jerks are a type of saccadic intrusion. A small saccade of a few degrees shifts gaze away from the fixation target, and then another returns it after about 200ms. This recurs somewhat randomly. Normal subjects make less

than eight square wave jerks a minute. It is well known that these are increased in cerebellar and extrapyramidal disorders, but this also happens with cerebral lesions, with which they correlate more with size than location.⁷⁹

A different kind of fixation impersistence is a small amplitude jerk *nystagmus* with the slow phase drifting contralaterally, in some patients with asymmetries in pursuit or vestibulo-ocular responses following unilateral cerebral lesions.⁵³ The slow phase is only a few degrees per second, insufficient to degrade resolution or cause symptoms. It may represent an imbalance of tonic activity in the pursuit system.

VERGENCE

As with fixation, little is known about the cerebral control of vergence. Monkey area V5a has cells tuned to stereodisparity,⁸⁰ but it is not known if lesions here impair vergence. Unilateral or bilateral lesions of the homologous area LS in cats do impair the amplitude and velocity of vergence, with unilateral lesions impairing the response in the contralateral eye more.^{81, 82} The lateral intraparietal area⁸³ and a region just anterior to the frontal eye field⁸⁴ contain neurons with vergence responses. In humans, one PET study found responses to stereodisparity in peristriate cortex, the parietal lobe and prefrontal cortex,⁸⁵ and vergence responses have recently been demonstrated in both frontal and parietal eye fields.⁸⁶

Some patients with parietal damage reportedly have an exotropia that is attributed to loss of convergent tone.^{87, 88}

OPTOKINETIC AND VESTIBULAR-OCULAR RESPONSES

These two systems work together to stabilize gaze during head motion. Their control systems are located primarily in the brainstem and cerebellum, but these are also associated with cerebral activity. Primate single-cell recordings have shown vestibular activity in the parieto-insular vestibular cortex,^{89, 90} area 7a, the cervical region in area 3a, area 2v, and the visual posterior sylvian area.^{91, 92} These areas also respond to optokinetic stimuli⁹³. Area V5a contains neurons that respond to optic flow stimuli.⁹⁴

Functional imaging during vestibular or optokinetic stimulation.

In humans, caloric stimulation of semicircular canals increases blood flow in the superior temporal region⁹⁵ and galvanic stimulation, which may stimulate the otoliths, activates a human homologue of parieto-insular vestibular cortex in the parieto-temporal region, as well as the central and anterior intraparietal sulci.⁹⁶

Optokinetic responses activate numerous cortical regions that respond to motion perception, pursuit or saccades, as well as parieto-insular vestibular cortex.⁷³ Optic flow stimuli without the response activates a medial parieto-occipital area but de-activates the parieto-insular vestibular cortex, suggesting reciprocal inhibition between visual and vestibular cues to self motion.⁹⁷

Effects of cerebral lesions on vestibulo-ocular responses.

Older studies reported that posterior temporal lesions caused reductions in the slow phase of caloric-induced nystagmus towards the lesion, independent of asymmetries in optokinetic responses.⁹⁸ However, in hemi-decorticate subjects, similar ipsi-directional reductions in the sinusoidal vestibulo-ocular reflex were accounted for by a superimposed nystagmus during fixation that was attributed to pursuit imbalances.⁹⁹ Ocular motor signs of otolith dysfunction such as torsional tilt and skew deviation are not seen with cortical lesions, though lesions of the parieto-insular cortex cause a contraversive tilt of the subjective visual vertical.^{100, 101}

Thus traditional measures of vestibular ocular responses are unaffected by cerebral lesions. However, more subtle effects can be seen in other paradigms. When saccades are made to targets while the head is freely moving, vestibular information is needed to maintain saccadic accuracy. With a memory-guided paradigm designed to test this, errors emerged with targets contralateral to lesions of the parieto-insular vestibular cortex.⁷⁸

Effect of cerebral lesions on optokinetic responses.

Decreased gain of ipsi-directional slow phases of optokinetic nystagmus have long been described after parietal lesions,^{98, 102} but recent studies show that these are correlated with pursuit defects and linked to damage to the parietal^{55, 99} or frontal eye fields.²⁵ Similarly, asymmetries in visual enhancement of the vestibulo-ocular reflex or cancellation of this reflex are correlated with asymmetries in pursuit.^{55, 99} An older poorly documented case exists of a dissociation between preserved pursuit and impaired optokinetic slow phases after bilateral middle cerebral artery infarctions.¹⁰³

B. EYE MOVEMENTS IN PERCEPTUAL AND ATTENTIONAL DISORDERS

Eye movements are a response to the environment, and hence reflect many other factors in that interaction, including perception, attention, intention, motivation, etc. Not surprisingly failures in those domains can be reflected in anomalous ocular motor behaviour.

HEMIANOPIA

Fixation and saccades in hemianopia.

In hemianopic patients, the point of central fixation is shifted slightly into contralateral space^{104, 105} {Reinhard, 2014 #4295}. This coincides with perceptual shifts of center, as revealed in line bisection tasks,^{104, 106, 107} which may represent a normal centrally directed bias in hemifield space.¹⁰⁸

When cued that targets will appear in random locations in their blind field, hemianopic subjects make a series of small searching saccades until the target is found.^{109, 110} This

can be used as a bedside test for functional hemianopia.¹¹¹ Interestingly, a similar series of small saccades is used by these patients towards auditory stimuli, implying that hemianopia influences a common motor program for any type of contralateral target, possibly at the level of the superior colliculus.¹¹² With predictable auditory or visual stimuli, however, patients learn the location and can make accurate single saccades.^{110, 112-114} With time some patients develop a more efficient strategy for randomly placed targets, making one very large contralateral saccade that will place the target in the seeing hemifield, then an ipsilateral saccade to it.¹¹⁰ Children do not develop this adaptive strategy naturally.¹¹⁵ Some rehabilitative approaches try to foster this 'search hypermetria'.¹¹⁶

Also curious, hemianopia prolongs the latencies of both manual responses and saccades to moving or stationary targets in the ipsilateral (seeing) field,^{53, 67, 110, 112, 117, 118} possibly due to altered interhemispheric cortical connections,¹¹⁷ or to loss of a facilitation of saccadic triggering in the superior colliculus.¹¹²

Ocular motor search patterns in hemianopia.

Some studies found that chronic hemianopia does not affect scanning of drawings,^{113, 119} but these used fairly coarse parameters. A more fine-grained analysis found that hemianopic search showed a gradient of fixations increasing towards contralateral space, opposite to what is seen in hemineglect.¹²⁰ This indicates an adaptive gradient that increases visual exploration on their blind side. Studies with simulated hemianopia in healthy subjects show that this adaptive gradient develops very quickly, within about 7 trials after onset, and then is slowly refined to become more efficient.¹²¹ This adaptation is relevant for daily life: hemianopic patients with a larger horizontal span of fixations that is shifted more to the blind side do the best on driving simulators, and such ocular motor behaviour is more important than the extent of the hemianopia.¹²² This is consistent with prior observations by other groups that safer hemianopic drivers make more exploratory eye and head movements to their blind side,^{123, 124} a fairly intuitive result.

During *line bisection*, healthy subjects concentrate fixations around the center of the line.^{104, 125, 126} Hemianopic patients have two peaks of fixations, one at the end of the line on their blind side and a central peak offset slightly contralaterally.^{104, 125, 126} The slight contralateral offset of the central peak parallels the observation of a contralateral line bisection bias in hemianopia.^{106, 107}

Hemifield defects involving the central 5 degrees impair *reading*.¹²⁷ With languages written left to right, left hemianopia affects the ability to find the beginning of the next line. Instead of a large return saccade, they show a series of leftward saccades, hunting for the beginning of the line, and sometimes ending on the wrong line.^{127, 128} Right hemianopia is more problematic, since one can no longer see what is coming up on the line to efficiently plan where

to move the eye next.¹²⁹ These subjects move along the line with many small saccades, and often have to make small leftward saccades to check what they are reading.^{127, 128, 130} This makes reading with right hemianopia slow,^{127, 130} but this can improve with practice.^{127, 131}

Attempts at improving the life of hemianopic patients can be divided into those that believe they can restore function and shrink the field defect, a controversial claim, and those that aim to improve the strategic adaptation to the deficit.¹³² Among the latter, there are promising results that training of search and reading can make the eye movements during these processes more efficient.^{131, 133, 134}

HEMI-NEGLECT

Unilateral hemi-neglect is an abnormal spatial bias in attention. Abnormal eye movements have long been recognized in this disorder: some have even asserted that the altered eye movements caused hemi-neglect.¹³⁵ However, abnormal ocular search is likely secondary to defects in orienting and attention, not primary.¹³⁶

Saccades in hemi-neglect.

With standard saccadic tests, hemi-neglect patients frequently fail to make saccades to contralateral targets: this is true even with predictable sequences.^{109, 113, 137} After recovery, hemi-neglect patients may still show prolonged latencies on the overlap task for contralateral saccades, perhaps indicating a weak ability of the target to facilitate disengagement from attention at the fixation spot.¹³⁸

Problems with saccades to contralateral targets may reflect failures of sensory attention or motor intention:¹³⁷ experiments to dissociate these have been done. To test sensory attention, one study had patients maintain fixation at center and press a key instead of making a saccade when targets appeared.¹³⁹ Another used an antisaccade paradigm to see if subjects did not make ipsilateral saccades to contralateral targets, or vice versa.¹³⁷ Both studies found evidence of failure of sensory attention for contralateral targets. Also, there was a gradient of inattention, from left-most to right-most space.¹³⁹

Hemineglect patients also have difficulty suppressing unwanted saccades. In the antisaccade task, patients made erroneous saccades, initially more to ipsilateral targets and then, as contralateral sensory attention improved, more with contralateral targets.¹³⁷ A test of steady fixation in the presence of distractors found that hemineglect patients had trouble suppressing saccades to ipsilateral targets.¹³⁹ This occurred after parietal lesions but was more severe with combined frontal and parietal lesions.

Ocular motor search in hemi-neglect.

Not surprisingly, hemineglect reduces exploration of the contralateral side of letter or symbol arrays.^{119, 140} Their search shows a horizontal gradient, even within ipsilateral hemispace,¹²⁰ consistent with neglect theories of biased attentional vectors.^{141, 142} Decreased contralateral

hemispatial search also occurs with line drawings, scenes and photographs^{113, 143, 144} or even while searching in the dark.^{145, 146} The latter technique has been used with body tilts to show that the neglect bias follows body rather than gravitational coordinates.¹⁴⁷ What may be surprising is that sometimes there is also a vertical asymmetry in hemineglect search.¹⁴⁸ Also, what search these patients do perform is inefficient, with re-fixations of areas already searched, as if they hadn't registered having already been there.¹⁴⁹

During *line bisection*, hemineglect patients show a consistent rightward shift of all horizontal scanning parameters.¹⁰⁴ However, there is considerable inter-subject variation. Some patients fixate most often on an ipsilateral position and don't fixate anywhere contralateral to this. Though their coexistent hemianopia means that they never saw the part of the line contralateral to the frequently fixated point, they nevertheless mark it as line center, a 'line completion effect' for something they haven't actually seen.^{126, 150} Other patients do make contralateral fixations but these do not appear to influence the markedly ipsilateral deviation of their bisection, as if they had never made those fixations.^{104, 151}

Reading is one of the most complex perceptual tasks. Left hemi-neglect can cause *neglect dyslexia*, manifest by reading errors restricted to the left side of the page and/or the left side of individual words.¹⁵² Recordings in one patient during reading showed the ocular counterpart to the failure to read the left side of pages: return leftward sweeps made after reaching the ends of lines failed to extend past the midline.¹⁵³ The authors concluded that this resulted from an attentional bias referenced to an environmental rather than a retinotopic frame. However, we have noted reading patterns in which the left-most point fixated in a line moves progressively rightwards as the patient moves down the page (Figure 10), which might result from a combination of retinotopic and environmental neglect biases.

BLINDSIGHT

Blindsight is the presence of remnant visual function despite the subject's denial of perception, usually after lesions of striate cortex or the optic radiations. This could represent residual functioning of the superior colliculus,¹⁵⁴ direct tectal projections to the pulvinar and extra-striate regions that bypass striate cortex,¹⁵⁵ or, in the case of blindsight colour perception, projections from lateral geniculate neurons to extrastriate cortex.¹⁵⁶

To summarize the following, the data for residual ocular motor function in blindsight is tenuous. Correlations for saccadic localization are weak or non-existent. There is no convincing evidence that practice can improve this, or that any such ability is functionally useful. The evidence for blindsight optokinetic or pursuit responses is even less impressive.

Blindsight saccades.

Early hypotheses about blindsight centered on the role of the superior colliculus, and thus studies naturally focused on saccadic localization.¹ The first study¹⁵⁴ found a weak correlation between saccadic size and target position in four patients with incomplete hemianopia. Patient D.B. had a weak correlation of saccades with targets, but only for targets between 5 and 25°, ^{155, 158} a result mainly driven by saccades to the target at 5°, which was a portion of the visual field that later recovered.¹⁵⁹ Interestingly, a later study of this patient did not find saccadic localization when targets varied in both horizontal and vertical position.¹⁶⁰ Nevertheless, another study¹⁶¹ found some saccadic localization in two patients with cortical hemianopia, for targets with eccentricity of less than 30°, and another for targets of 5° and 8° eccentricity, though saccades to the blind side were smaller in amplitude and delayed.¹¹⁸

Other studies found that only patients with conscious residual vision localized targets with saccades.^{162, 163} Another did not find any saccadic localization in three hemianopic patients.¹¹⁰ A larger study found a weak correlation of saccadic amplitude with target position in only 2 of 10 patients.¹⁶⁴

It has been suggested that saccadic localization might improve with training, as in monkeys.¹⁶⁵ In humans, the accuracy of saccadic search (as opposed to initial saccades) was weak or non-existent in six subjects but improved with training.^{166, 167} This probably represents learning of an adaptive strategy rather than development of blindsight, though.

Hemi-decorticate patients show what is possible without striate and extrastriate cortex.¹⁶⁸ found that two hemianopic infants were more likely to look to their blind hemifield when a target was presented there than when there was no target at all, indicating some rudimentary subcortical target detection.

An alternate strategy to study blindsight is to see how saccades to seen stimuli are affected by additional stimuli in the blind field. Saccades deviate away from distractors placed along their trajectory, and one study found that two of five hemianopic patients showed such a deviation even though the distractor was in their blind field.¹⁶⁹ In the global effect, if the distractor is close to the target, the saccade lands at a position between the distractor and the target, which is attributed to spatial averaging in the superior colliculus. Curiously, two hemianopic patients displayed a paradoxical global effect, with saccadic endpoints deviated away from rather than towards distractors in their blind field.¹⁷⁰ Another study showed that antisaccades prompted by targets in the ipsilateral

field and directed to the blind contralateral side were more accurate when a probe was simultaneously flashed at the goal location in the blind field.¹⁷¹

On the other hand, there are negative findings. In the ocular motor distractor effect, distractors far away from the target or saccadic trajectory tend to increase the latency of saccades: blind distractors did not have any influence in hemianopic subjects in one study.¹⁷² Also, the normal beneficial influence of concurrent visual stimuli on the accuracy of saccades to auditory targets, was not found in seven hemianopic patients.¹⁷³

Blindsight optokinetic responses.

Four children with cortical blindness were shown to have optokinetic nystagmus,¹⁷⁴ though this is tempered by the fact that two may have had some residual vision. In the two with congenital cortical blindness, the optokinetic responses elicited by monocular stimulation showed the temporo-nasal asymmetry characteristic of the brainstem optokinetic system.¹⁷⁵ In adults, one man with cortical blindness recovered some optokinetic responses after five months,¹⁷⁶ but others have not found this in another cortically blind patient¹⁷⁷ or in the blind hemifield of hemianopic patients.¹⁷⁸

Blindsight pursuit responses.

Pursuit initiation to focal moving targets was not present in adult patients with chronic lesions confined to the medial occipital lobe.¹⁶⁴ One study has also looked at whether blind-field stimuli can influence pursuit of a visible target. Pursuit of two extra-foveal targets is better than that of one, but when the second target was in the blind field of a hemianopic patient, the gain of pursuit was not increased.¹⁷⁹

VISUAL AGNOSIA

In contrast to what we know about hemianopia and hemineglect, there is less information about how higher level visual disturbances affect eye movements. It is clear that healthy subjects differ widely in the way they scan complex visual stimuli,^{180, 181} though a given subject will show regularities in their preference to fixate certain features and to make certain sequences.^{180, 182} While, the variability poses a challenge for uncovering abnormal behaviour, some interesting results have been reported.

General visual agnosia.

Subjects with this lose the recognition of objects at a very basic level. Knowledge of what objects look like serves as a top-down influence on how we organize the visual inputs served forward from the striate cortex, helping us determine what is object and what is background, which components belong to object 1 and which to object 2, and so on. Understanding what these objects are and where they typically occur in natural scenes is inevitable reflected in how we scan the environment. There is a balance between salience, the ability of low-level properties such as colour, contrast and motion to attract attention, and

1 Indeed, in monkeys with striate ablations, saccadic localization of contralateral targets is lost after a muscimol injection of the superior colliculus.¹⁵⁷ Kato R, Takaura K, Ikeda T, Yoshida M, Isa T. Contribution of the retino-tectal pathway to visually guided saccades after lesion of the primary visual cortex in monkeys. *Eur J Neurosci*. 2011;33(11):1952-60.

relevance, the importance of elements of the scene to the subject's current objectives and tasks. One experiment looked at fixations made by healthy subjects and a subject with visual agnosia as they engaged in a task searching scenes for specific objects.¹⁸³ While healthy subjects made fixations to regions relevant to that task, the patient with visual agnosia was more likely to be guided by salience. Hence, in the absence of object knowledge to organize the interpretation of scenes, low-level properties are what primarily drive fixations. Nevertheless, other experiments do show that some top-down influences remain in these subjects.^{184, 185}

Prosopagnosia.

This is a more selective problem in which patients lose the ability to recognize familiar faces. In two patients scanning of faces was similar to that of healthy subjects, and their scanning was more idiosyncratic for familiar than for unfamiliar faces,¹⁸⁶ an effect that has been interpreted as evidence of guidance by pre-existing knowledge of what familiar faces look like. However, another experiment found that the fixation sequences used to scan faces was more chaotic in prosopagnosia,^{187, 188} consistent with disruption of an internal schema for faces. Also, some prosopagnosic subjects fail to perceive information from the upper face, and scanning studies have shown a similar lack of fixations to the upper face in one patient.¹⁸⁹ Patients with developmental prosopagnosia also showed an abnormal tendency to scan the external contours rather than the internal features of faces.¹⁹⁰ Both of these suggest loss of the knowledge of what is most informative in faces.

Pure alexia and developmental dyslexia.

There is a large body of data on the eye movements during reading,¹⁹¹ but surprisingly little data for pure alexia. One study of two patients¹⁹² showed that the number of fixations within a word can be used to document the word-length effect characteristic of this disorder.¹⁹³ Also, fixation number and duration correlated with the frequency and imageability of the word, indicating residual linguistic influences.

Finally, it might be worth noting some of the findings reported in developmental dyslexia, though this disorder does not likely stem from the same dysfunction as pure alexia. As has been summarized,^{191, 194} like poor readers and young readers, dyslexic subjects make longer and more fixations, shorter saccades, and more regressive saccades when reading. Some have suggested that this may indicate an ocular motor origin for dyslexia. However, the results of non-reading studies of vergence and saccades in dyslexia have been mixed,^{195, 196} and currently it seems more likely that the eye movements are a reflection of linguistic dysfunction, not its cause.¹⁹⁷ Likewise, similar findings can be produced by perceptual difficulty in reading: when healthy subjects read upside-down, the same set of fixation and saccadic abnormalities results.¹⁹⁸ For these reasons, training of eye movements is not likely to improve dyslexia.

CME ANSWERS

1. Frontal lobe (frontal eye field) and parietal lobes (parietal eye field)
2. At the middle and the contralateral blind end of the line
3. The number of fixations increases (the word-length effect).

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OCULAR MOTILITY DISORDERS DUE TO CEREBELLAR DISEASE

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LEARNING OBJECTIVES

1. Describe the compartmentalization of functions within the cerebellum
2. Demonstrate an appreciation of both the immediate and long-term effects of cerebellar disease
3. Describe topical diagnosis of cerebellar eye signs

CME QUESTIONS

1. All of the following are common features of dorsal vermis lesions except:
 - a. Saccade dysmetria
 - b. Saccade slowing
 - c. Esodeviations
 - d. Pursuit deficits
2. All of the following are common features of nodulus lesions except:
 - a. Abnormal patterns of head-shaking nystagmus
 - b. Periodic alternating nystagmus
 - c. Saccade dysmetria
 - d. Positional nystagmus
3. Structural lesions of the fastigial nucleus in humans commonly produce:
 - a. Bilateral saccade hypermetria
 - b. Ipsiversive saccade hypometria with contraversive saccade hypermetria
 - c. Contraversive saccade hypometria with ipsiversive saccade hypermetria
 - d. Skew deviation

KEYWORDS

1. Saccade
2. Nystagmus
3. Pursuit
4. Cerebellum
5. Skew

INTRODUCTION

The cerebellum plays a central role in the control of every type of eye movements. It has both immediate, on-line functions to make each individual movement accurate, and long-term, adaptive functions to keep ocular motor responses correctly calibrated for optimal motor behavior. Here we take an anatomical approach to the types of eye movement disorders that appear with lesions within specific parts of the cerebellum. We present a summary diagram to aid in the localization of eye movement disorders associated with cerebellar disease.

VESTIBULOCEREBELLUM: FLOCCULUS/PARAFLOCCULUS (TONSILS)

The flocculus and paraflocculus (or tonsil) together with the caudal portions of the cerebellar vermis (nodulus and uvula) are part of the archicerebellum, also called the vestibulocerebellum. Lesions of the flocculus/paraflocculus impair many ocular motor functions. First, smooth tracking of a moving target, either when the head is still or moving (VOR cancellation suppression) can be impaired. A second cardinal feature of lesions of the flocculus/paraflocculus is impaired gaze holding with the eyes drifting centripetally after eccentric eye movements, resulting in a gaze-evoked nystagmus. Thus the flocculus/paraflocculus functions in the control of the brain stem circuits (nucleus prepositus and medial vestibular nuclei for horizontal movements and superior vestibular nuclei and interstitial nucleus of Cajal for vertical eye movements) that convert (mathematically integrate) velocity into position commands for all types of conjugate eye movements; the ocular motor integrator. The paramedian tracts and their associated neurons may also be part of this integrator network, and there are rich interconnections between the cerebellum and these structures. A third distinctive feature of lesions in the flocculus/paraflocculus is downbeat nystagmus, in which the eyes drift up (slow phase) and are brought back to the fixation target by a corrective downward saccade (quick phase). This form of nystagmus can be linked to the damage of physiologic 'up-down' asymmetry of the floccular Purkinje cells (with predominant downward facilitation) resulting in upward slow drift or the tonic inhibition by the flocculus upon the upward VOR (by inhibitory projections to the superior vestibular nucleus), and lack of corresponding projections from the flocculus to the brain stem structures that mediate downward vestibulo-ocular responses. The upward drift waveform is variable from subject to subject and occasionally may be velocity

increasing. These variable waveforms suggest that for the vertical integrator the flocculus/paraflocculus has a more subtle, modulator role, possibly related to the long-term adaptation capability of an individual animal. In other words, based upon the animal's own ocular motor history (e.g., trauma or disease) and genetic makeup, the inherent brain stem vertical neural integrator could be relatively leaky or relatively unstable, and the cerebellar lesion then unmasks the 'default' behavior (3,4-Diaminopyridine (3,4-DAP) and 4-Aminopyridine (4-AP), potassium channel blockers, can diminish downbeat nystagmus associated with cerebellar lesions. Rebound nystagmus is also typically seen in patients with cerebellar syndromes. Rebound nystagmus is short-lived and occurs when the eyes are returned to the central position following sustained eccentric gaze. The rebound nystagmus beats oppositely to the prior gaze-evoked nystagmus, i.e., the slow phase is toward the prior eccentric gaze position. Similar to gaze-evoked nystagmus, rebound nystagmus is linked to the gaze-holding neural integrator controlled by the vestibulocerebellum. In extreme cases the mechanism producing rebound nystagmus becomes unstable leading to a centripetal-beating nystagmus on eccentric gaze in which slow phases are directed outwards. Postsaccadic drift, a brief drift of the eyes lasting several hundred milliseconds following each saccade, is another feature of the floccular/parafloccular syndrome. The postsaccadic drift reflects a mismatch between the pulse (phasic) and the step (tonic) components of innervation that produce saccades. The flocculus and paraflocculus are not critical for generating a compensatory response to head rotations since the VOR is still present after a lesion there but its amplitude and direction may be incorrect. This implicates the flocculus and paraflocculus in the long-term adaptive mechanism that keeps vestibular responses accurate.

During rotation of the head around an earth-vertical axis, patients with diffuse cerebellar lesions may show a dynamic upward bias so that the eyes move up as well as horizontally, producing a 'cross-coupled' VOR. There are also inappropriate torsional components and the responses in the two eyes are disconjugate. A release of inhibition upon anterior semicircular canal pathways within the brain stem (which produce upward slow phases) is a possible explanation. In line with this hypothesis, patients with cerebellar disease have an asymmetric vertical VOR with higher gain for downward head impulses (consistent with increased anterior semicircular canal stimulation). These results implicate the cerebellum, and likely the flocculus/paraflocculus, in generating movements of each eye that have the correct amplitude and direction for perfect VOR compensation.

VESTIBULOCEREBELLUM: NODULUS/VENTRAL UVULA

These structures mainly contribute to the control of the rotational and the translational VOR. Though pursuit deficits, especially vertical, may also be seen with lesions in this region. Lesions in the nodulus/ventral uvula commonly lead to spontaneous downbeat nystagmus and periodic alternating nystagmus. The nodulus/ventral uvula projects directly to the brain stem velocity storage mechanism which depends upon Purkinje cell inputs for its proper actions. The velocity storage mechanism has several functions. First it extends the duration of the VOR response beyond that expected from the mechanical properties of the cupula-endolymph system within the semicircular canals. This perseverating (integrating) action slows the decay of nystagmus that normally occurs during a constant-velocity rotation in the dark. Secondly, during sustained 'off-vertical axis' rotation of the head, when there is an imposed changing linear acceleration due to the continuous reorientation of the head relative to the pull of gravity, the velocity-storage mechanism modulates the direction of compensatory slow phases, reorienting the axis of eye rotation towards earth vertical. It thus serves an orienting function so the brain can know the position of the head relative to the pull of gravity, as well as determine whether a sensed linear acceleration of the head is from gravity or an imposed translation of the head (Am I tilted or am I translating?).

Lesions of the nodulus/uvula alter the velocity-storage mechanism for the horizontal VOR and increase the duration of vestibular responses to a constant-velocity input around an earth-vertical axis (i.e., the VOR time constant is increased). Lesions of the nodulus/uvula also disrupt the spatial orientation function of the velocity-storage mechanism; the VOR no longer reorients the axis of eye rotation toward upright during off-vertical axis rotation. With nodulus/uvula lesions, there is also a loss of the normal habituation of the time constant of the VOR to repetitive stimulation as well as loss of tilt suppression of post-rotary nystagmus, the phenomenon by which the decay of post-rotary nystagmus is hastened with pitching the head down immediately following the end of a constant-velocity rotation. Periodic alternating nystagmus (PAN), a horizontal jerk nystagmus that changes direction every few minutes, may appear following lesions of the nodulus and its adjacent paravermal region. PAN reflects the combined actions of a (1) disinhibited brain stem vestibular velocity-storage mechanism (due to loss of inhibition from Purkinje cells in the nodulus that project to the vestibular nuclei) and (2) an intact adaptive mechanism that acts to null any sustained unidirectional nystagmus, thus allowing PAN to change direction. Because Purkinje cell inhibition is mediated through GABA_B receptors, treatment with baclofen (a GABA_B agonist) disengages the velocity-storage mechanism and stops PAN. Memantine may also be of use in treating this disorder.

Note that as for rebound nystagmus, the adaptive mechanism that leads to the reverse of the direction of PAN is intact or possibly increased after lesions in the cerebellum. Downbeat nystagmus is also reported with nodulus and uvula lesions. The slow-phase velocity of this nystagmus may be independent of orbital position (i.e., nystagmus does not change intensity with up and down gaze nor increase with lateral gaze), and may be suppressed with visual fixation. Changing the orientation of the head with respect to gravity may also alter the nystagmus. Thus the downbeat nystagmus with nodulus/uvula lesions could be due to a bias in the vestibular system (either the t-VOR or r-VOR mechanisms) and need not reflect changes in the gaze-holding neural integrator. Several other characteristic findings with lesions in this region include a “cross-coupled” post head shaking nystagmus (e.g., after horizontal head shaking there is a vertical nystagmus), an immediate strong reversal of horizontal head-shaking induced nystagmus and a horizontal positional nystagmus (usually apogeotropic (beats to the sky whether left ear down or right ear down)).

DORSAL VERMIS AND FOR (FASTIGIAL OCULOMOTOR REGION): SACCADDES

The dorsal vermis (lobules V–VII, also called the oculomotor vermis; OMV) and the underlying posterior fastigial nucleus (also called the fastigial oculomotor region; FOR) is especially important for the control of saccades. Lesions in the OMV cause changes in the accuracy, latency, trajectory, and dynamic properties (speed and acceleration) of saccades. Purkinje cells in the OMV discharge before saccades, and stimulation of this same area can elicit saccades). Transcranial magnetic stimulation (TMS), functional magnetic resonance imaging (fMRI), and mapping of lesions supports a role for the participation of the OMV in the generation of saccades. The OMV also plays an important role in saccade adaptation, a mechanism that detects errors in motor performance and updates saccade commands to accurately move the eye toward a target. OMV lesions impair adaptation of saccade amplitude. Neurons in the FOR also discharge in relation to saccades and supply a presaccadic burst for contraversive saccades and a ‘braking’ discharge, late during the saccade, for ipsiversive saccades. Thus, each FOR acts to facilitate contraversive saccades and contributes to the termination of ipsiversive saccades. Consequently, unilateral lesions (only possible experimentally using neuronal toxins because the axons from one FOR immediately course through the other before exiting the cerebellum through the superior cerebellar peduncle) in the FOR cause ipsiversive saccadic hypermetria (overshoot) and contraversive hypometria (undershoot) and bilateral FOR lesions cause bilateral hypermetria. Purkinje cells in the OMV behave similarly to those of the FOR, though, as predicted from their inhibitory nature, their ‘sign’ is opposite. Thus, each side of the vermis acts to facilitate ipsiversive saccades and contributes to the termination of contralateral saccades. Accordingly, OMV

lesions lead to hypometric ipsiversive and hypermetric contraversive saccades and bilateral lesions in OMV cause hypometric saccades in both horizontal directions. Vertical saccades show ipsipulsion (oblique trajectory toward the side of inactivation) with experimental lesions of the FOR Ipsipulsion is also a feature of Wallenberg’s syndrome, presumably due to a functional lesion of the FOR resulting from interruption of the climbing fiber input (within the inferior cerebellar peduncle) to the OMV and a consequent increased inhibition by Purkinje cells upon the underlying FOR. Other areas, such as the interposed nucleus (emboliform and globose) and paraflocculus (tonsils), may also be important in the generation of vertical saccades. The central role of the cerebellum in the control of saccades is reflected in the different ways it can influence the trajectory of the saccade but how does the cerebellum modulate the brain stem circuits that generate saccades? There are many targets in the brain stem by which the cerebellar output, via the FOR, could influence saccades including excitatory burst neurons (EBN) for saccade initiation and inhibitory burst neurons (IBN) and omnipause neurons (OPN) for saccade termination. Projections to the fixation zone of the rostral pole of the superior colliculus are another route by which the FOR could help bring the saccade to an end. Of all these, the projections to IBN seem most important functionally, as the FOR acts mainly to stop the saccade.

DORSAL VERMIS AND FOR (FASTIGIAL OCULOMOTOR REGION): PURSUIT

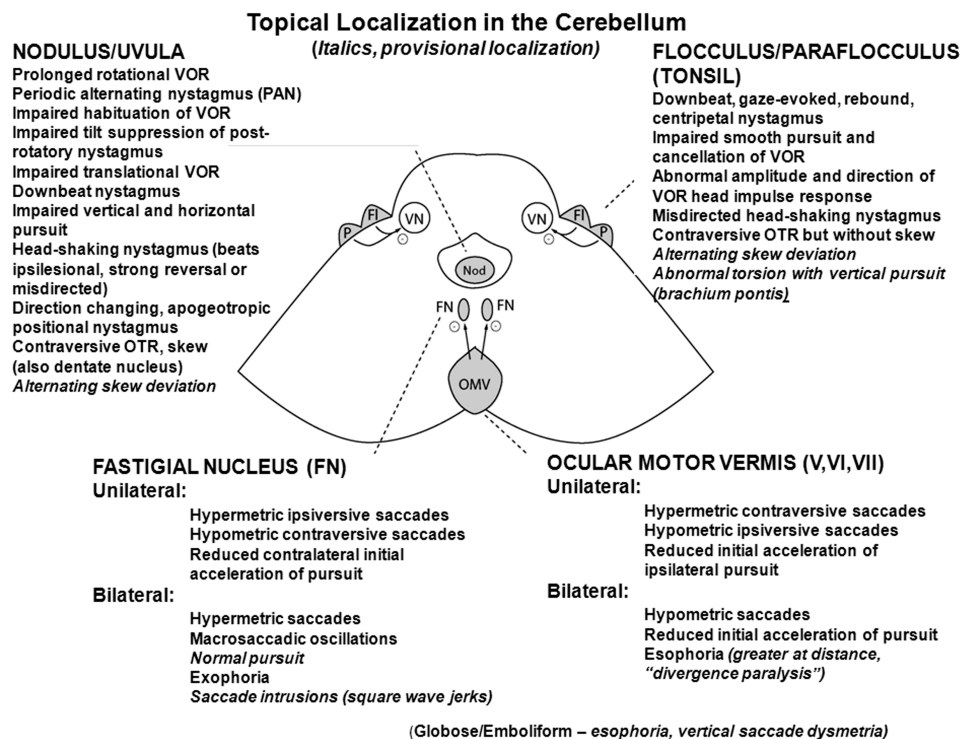
The OMV and FOR also participate in the generation of pursuit eye movements. Electrical stimulation of the OMV in monkeys can enhance contraversive or impair ipsiversive pursuit, and transcranial magnetic stimulation of the skull over the posterior cerebellum in humans can influence pursuit eye movements in the same pattern. There are neurons in the FOR that discharge early during contraversive pursuit and late for ipsilateral pursuit, analogous to activity associated with saccades. Thus, each FOR can facilitate contraversive pursuit and can contribute to the termination of ipsiversive pursuit. Purkinje cells in the OMV probably behave in a similar way to those of the FOR, though, as predicted from their inhibitory nature their ‘sign’ is opposite. Each side of the vermis would act to facilitate ipsiversive pursuit and contribute to the termination of contralateral pursuit. The pursuit deficits reported after experimental lesions in the OMV and the FOR are largely in accord with the physiological findings. With a lesion in the FOR contralateral pursuit is impaired, and with a lesion in the OMV ipsilateral pursuit is impaired. Vertical pursuit is little affected following OMV lesions whereas FOR lesions reduce downward pursuit more than upward pursuit. Bilateral lesions of the OMV in monkeys produce horizontal pursuit deficits in both directions though bilateral FOR lesions leave pursuit relatively intact; this is also seen in patients with bilateral

FOR lesions. These findings suggest the pursuit deficit is due to imbalance between opposing drives of the two FOR. Therefore, with bilateral FOR inactivation, and no FOR imbalance, the pursuit movements remain intact. Lesions of OMV and FOR mainly affect eye acceleration during the initial period of pursuit (the first 100 ms of tracking after a target has started moving or has changed its speed) and have a smaller effect during the sustained tracking period. As noted above, the flocculus/paraflocculus contribute to smooth pursuit. One possible division of labor between these two regions is that the OMV/FOR is more concerned with the initiation and termination of the preprogrammed initial 'open-loop' portion of pursuit (when retinal slip is high), and the vestibulocerebellum is more concerned with pursuit during sustained tracking.

CEREBELLUM AND BINOCULAR CONTROL

Patients with cerebellar damage sometimes show a skew deviation, a vertical misalignment of the eyes that cannot be attributed to a simple ocular muscle weakness. Most commonly the abducting eye is higher as the patient looks from far right to far left. The source of the skew may be

an imbalance in otolith-ocular reflexes and patients with cerebellar skew deviation have reduced and disconjugate counterroll gains that depend on the direction of the head tilt. Note that a skew deviation is commonly observed in Wallenberg's syndrome but this is probably attributed to involvement of the caudal portions of the vestibular nuclei in the brain stem. The dentate nucleus has been also implicated in cerebellar skew deviation based on MRI/CT lesion analysis. Patients with cerebellar lesions can also show misalignment of the eyes during the r-VOR and during saccades. An esotropia (the eyes turn inward), sometimes attributed to a divergence paralysis since the esodeviation is usually greater at distance, also occurs in cerebellar disease and probably reflects involvement of the dorsal vermis. Patients with acute cerebellar lesions can show impaired slow but relatively intact fast vergence. Moreover, divergence, but not convergence, can be affected particularly with the lesions in the OMV. Patients with vestibulocerebellar lesions may also show a divergence-beating nystagmus (convergent slow phases with divergent quick phases). These abnormalities hint at an excess of convergence tone with some cerebellar lesions. In sum, the cerebellum is involved in almost every facet of the control of eye movements and a careful examination of the different subclasses of eye movements in patients with cerebellar disease provides precise localizing diagnostic information.



CME ANSWERS

1. b. Saccade Slowing
2. c. Saccade Dysmetria
3. a. Bilateral Hypermetria of Saccades

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OCULAR MOTILITY DISORDERS DUE TO BRAINSTEM DISEASE

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LEARNING OBJECTIVE

1. Review brainstem anatomy and its relevance to clinical presentations

CME QUESTIONS

1. The interstitial nucleus of Cajal serves as the:
 - a. Neural integrator for vertical gaze
 - b. Torsional burst cell locale
 - c. Center of vestibular function
 - d. Conduit from the abducens to the oculomotor nuclei
 - e. Region most related to auditory function
2. The rostral interstitial nucleus of the MLF (riMLF):
 - a. Lies within the pons
 - b. Contains excitatory burst neurons generating vertical and torsional saccades
 - c. Is a subnuclei of the oculomotor nucleus
 - d. Innervates vergence motor neurons
 - e. Serves as the neural integrator
3. Parinaud dorsal midbrain syndrome may produce all the following EXCEPT:
 - a. Lid retraction (Collier sign)
 - b. Limitation of vertical gaze
 - c. Convergence retraction “nystagmus”
 - d. Contralateral hemiparesis
 - e. Light-near pupil dissociation

KEYWORDS

1. Brainstem
2. Eye Movements
3. Saccades

INTRODUCTION

The brainstem is a complex series of nuclei and interconnections divided into 3 primary component, midbrain, pons and medulla. The conceptual framework of a house serves as a model to teach the brainstem anatomy. The attic is the “Mickey Mouse” shaped midbrain, overlying the 1st floor “bridge” of the pons, and the “butterfly” basement of the medulla. These 3 structures share rich connections with the cerebellum (the “garage” of the posterior fossa house).

MIDBRAIN

ANATOMY

The midbrain is the attic of the house. Axial imaging reveals the familiar Mickey Mouse configuration with cerebral peduncle (pyramidal tract) ears and cerebral aqueduct mouth. Within the midbrain, key neuro-ophthalmic structures include the nuclei of CN3 & 4, riMLF, INC, posterior commissure, superior colliculus and the red nucleus.

KEY FEATURES/STRUCTURES

CN3

CN3 (oculomotor nerve) is responsible for the majority of extraocular muscle control, including superior, inferior, and medial rectus, levator palpebrae, and pupil sphincter muscles. The **nucleus of CN3** is a complex conjoined structure within the dorsal midbrain.

From the nucleus, CN3 fascicles emerge ventrally and diverge, running through the red nucleus and substantia nigra prior to converging and exiting via the medial aspect of the cerebral peduncle into the interpeduncular fossa, then piercing dura to enter the cavernous sinus, where they reside in the superior lateral region. The nerve enters the orbit via the superior orbital fissure to innervate its target muscles.

Central Caudal Nucleus

This single CN3 subnuclei innervates the levator palpebrae muscles.

Edinger Westfall (EW) Nuclei

The EW subnucleus of CN3 is a V-shaped structure providing parasympathetic innervation to the ciliary ganglia, controlling pupil constriction and accommodation.

Superior Rectus CN3 Subnuclei

This CN3 subnuclei CROSSES to innervate the contralateral superior rectus; note the evolutionary parallel with its fellow superior globe muscle (superior oblique) and CN4 crossing.

These unique features provide a set of constraints for nuclear CN3 palsies, including:

Bilateral levator sparing or affliction (which may be asymmetric)

Ipsilateral CN3 paresis with contralateral superior rectus involvement

Bilateral pupil affliction or sparing

Fascicular Organization

The fascicle of CN3 is organized into a recognizable pattern even within the midbrain. Within the cerebral peduncle, the fibers running from medial to lateral appear: pupil – inferior rectus – lid – medial rectus – superior rectus – inferior oblique. Rare lesions of the peduncle may selectively involve one aspect of the fascicle.

CN4

The trochlear nuclei reside in the dorsal midbrain and give rise to CN4 fascicles which emerge DORSALLY and cross before turning ventrally, wrapping around the cerebral peduncles and entering the cavernous sinus in the lateral wall region. The nerve enters the superior orbital fissure to innervate the superior oblique muscle.

A trochlear nuclear lesion is identical to a CN4 fascicle lesion (NB, crossing fibers within the superior medullary velum). Rarely, an intrinsic dorsal midbrain lesion produces the combination of CN4 palsy and an RAPD.

Interstitial Nucleus of Cajal (INC)

The INC is the neural integrator for vertical gaze. The INC projects to the ocular motor nuclei via the posterior commissure, and selective dysfunction of this nucleus results in vertical gaze evoked nystagmus; in practice, many lesions that restrict vertical gaze involve the INC in part, highlighting the nuclei's role in additional vertical gaze function. Unilateral INC lesions produce the ocular tilt reaction with ipsilesional torsional fast phases.

Rostral Interstitial Nucleus of the MLF (riMLF)

The riMLF lies dorsomedial to the red nucleus and rostral to the INC, and contains excitatory burst neurons generating vertical and torsional saccades. These neurons send fibers to innervate yoked muscle pairs, bilaterally to elevator muscles, but unilaterally to depressor muscles; additionally, there are neurochemical differences distinguishing upward from downward saccadic eye movements. The right riMLF drives clockwise torsional fast phases, while the left riMLF performs counterclockwise fast phases. The paired riMLF receive blood from the thalamo-subthalamic paramedian artery, which often involves a single artery of Percheron providing the basis for infarction as the most

common riMLF lesion. The riMLF may also be involved in degenerative tauopathies such as progressive supranuclear palsy (PSP). Unilateral lesions of the riMLF should produce ipsitortional fast phase defects; however, such restricted lesions are rare. Infarction within this territory often involves the INC or bilateral riMLF. The latter produce loss of downward or all vertical saccades.

Posterior Commissure

The posterior commissure involves not just projections from the INC, but also axons from the nuclei of the posterior commissure, which appear to function in vertical gaze and eyelid function. Lesions within this clinically produce the dorsal midbrain syndrome.

Superior Colliculus

While superior colliculus function in nonhuman primates has been well established to participate in saccades, such lesions in isolation in humans are exceedingly rare.

CLINICAL SYNDROMES:

Weber

Ipsilateral CN3 + contralateral hemiparesis = midbrain peduncle pyramidal tract region

Nothnagel

Ipsilateral CN3 + ipsilateral ataxia = superior cerebellar peduncle region

Benedikt

Ipsilateral CN3 = contralateral tremor/chorea = red nucleus/substantia nigra region

Claude

Ipsilateral CN3 + contralateral ataxia = dentatorubralthalamic cerebellar crossing fiber region

These eponyms have often been used in the descriptions of varying combinations of midbrain CN3 deficits, and accordingly lack specific value. While the clinical features and related anatomic localization is important, the specific eponym often is not.

Parinaud Dorsal Midbrain Syndrome

Lesions of the dorsal midbrain often produce Parinaud syndrome, with various components typically in combination. The syndrome consists of 7 primary features:

1. Lid retraction (Collier sign)
2. Limitation of vertical gaze
3. Convergence retraction "nystagmus"
4. Vergence dysfunction
5. Square wave jerks
6. Light-near pupil dissociation
7. Skew deviation

Most patients present with a few of these features (not all); convergence retraction nystagmus is essentially pathognomonic of the syndrome, while other features may be observed in various locations. The most common pathophysiologies producing Parinaud syndrome include

neoplasms of the pineal gland, hydrocephalus, infarct, demyelination, and trauma.

Vertical 1.5 Syndrome (one-and-one-half)

Loss of all vertical eye movements in one eye, and either an upward or downward defect in the fellow eye have been termed vertical one-and-one-half syndrome; such lesions likely result from combination of INC, posterior commissure or oculomotor nuclei fascicles.

SPECIFIC DISEASES

Progressive supranuclear palsy (PSP)

PSP is a rare degenerative tauopathy with classic ocular motor implications including functions residing within the midbrain. Core features of PSP criteria include (mandatory inclusion criteria)

1. gradually progressive disorder
2. onset age ≥ 40 years
3. either vertical supranuclear palsy, or both slowing of vertical saccades and prominent postural instability with falls in the first year of onset
4. no evidence of other disease explanation

SUPPORTIVE FEATURES

1. symmetric akinesia or rigidity, proximal > distal
2. abnormal neck posture, especially retrocollis
3. poor or absent response to levodopa
4. early dysphagia and dysarthria
5. early cognitive impairment with at least 2 of:
 - a. apathy
 - b. impaired abstract thought
 - c. decreased fluency
 - d. frontal release signs

EXCLUSION CRITERIA

1. recent history of encephalitis
2. alien limb syndrome, cortical sensory deficits, focal frontal or T-P atrophy
3. hallucinations or delusions unrelated to dopamine therapy
4. cortical dementia of Alzheimer type
5. prominent early cerebellar symptoms or unexplained dysautonomia
6. severe asymmetric parkinsonian signs
7. neuroradiologic evidence of relevant structural abnormalities
8. Whipple's disease confirmed by PCR

EYE MOVEMENTS

Although eye movement abnormalities are perhaps the most distinct feature of PSP, the primary clinical aspect emphasized by the disease title, and often present early, it is important to realize that ocular motility abnormalities are occasionally late or absent. Slow vertical saccades are often the initial ocular motor abnormality. The quick phases of OKN are often slow or absent, so that a single slow phase is noted without resetting fast phases. Vertical saccades early in the disease may take an oblique course ("round the

house" sign). Horizontal saccades tend to be hypometric, but slowing in the horizontal plane often does not appear until later in the course.

Frequent or continuous square wave jerks are a characteristic PSP finding. This in combination with the parkinsonism feature of impaired blink constitutes a useful clinical sign.

WHIPPLE DISEASE

Tropheryma whippelii produces combinations of GI symptoms, arthralgia lymphadenopathy and CNS symptoms. The latter may simulate PSP with vertical gaze dysfunction leading to global ophthalmoplegia. Oculomasticatory or oculofacioskeletal myorhythmia are pathognomonic for Whipples disease; however, this occurs in the minority of patients. The diagnosis is often quite challenging, but may be made with PCR of spinal fluid or small bowel biopsy. The disease is treatable with prolonged course of antibiotics.

PONS

ANATOMY

The pons is the first floor great room of the brainstem house. The name pons is derived from the Latin literally meaning "bridge", and on axial imaging, imagine sitting in the river of the 4th ventricle, one can imagine a bridge over this river.

KEY FEATURES/STRUCTURES

CN6

The abducens nuclei contains neurons destined to innervate the lateral rectus in addition to internuclear neurons innervating the medial longitudinal fasciculus (MLF); accordingly, a lesion of the CN6 nucleus produces a ipsilateral horizontal gaze palsy (not CN6 palsy), sparing vertical gaze and vergence (vergence fibers synapse directly with the medial rectus subnuclei of CN3). The CN6 fascicle exits the pons ventrally, ascends along the clivus, then enters the cavernous sinus under Gruber's ligament in Dorello's canal. The nerve courses anteriorly in the middle of the cavernous sinus adjacent to the carotid artery. Like CN3 and 4, it enters the orbit via the superior orbital fissure, and then innervates the lateral rectus muscle.

Paramedian Pontine Reticular Formation (PPRF)

The PPRF houses several neuronal populations related to ocular motor control including excitatory burst neurons for horizontal saccades (nucleus pontis centralis caudalis), omnipause neurons (nucleus raphe interpositus) inhibiting burst neurons, inhibitory burst neurons (dorsal paragigantocellular nucleus), and the adjacent paramedian tracts (PMT) projecting to the flocculus, plus fibers conveying vestibular, pursuit and gaze holding signals to the CN6 nucleus. In general, unilateral lesions of the PPRF produce ipsilateral horizontal gaze palsies that may involve saccades or all classes of eye movement.

Bilateral pontine lesions may impair vertical saccades via loss of coordinated omnipause cell interaction with burst cells.

Medial Longitudinal Fasciculus (MLF) & Internuclear Ophthalmoplegia (INO)

MLF lesions produce internuclear ophthalmoplegia (INO), a critical neuro-ophthalmic syndrome with the fundamental finding of slowed/weak adduction; additional features include contralesional abducting nystagmus, skew deviation (often with ipsilesional hypertropia), upbeat with torsional (slow phase moves upper eye pole contralesional) or dissociated vertical nystagmus, vertical gaze evoked nystagmus (especially bilateral INOs). Numerous pathophysiologies have been reported to produce INO, most commonly including ischemic (paramedian pontine perforator endartery territory) and demyelination (~50% of MS patients), but also neoplasms, infectious, trauma, nutritional/metabolic and toxic etiologies. Wall-eyed bilateral INO (WEBINO) is a subset of bilateral INOs that present with primary position exotropia. Vergence capabilities in the presence of INOs are variable and not consistently reliable for localization purposes.

CN7

The facial nuclei resides in the dorsal pons, and sends fibers in a posterior arc (forming the facial colliculus) wrapping around the abducens nuclei to exit the pons laterally as the CN7/8 complex.

CLINICAL SYNDROMES

Gaze palsy

As mentioned previously, a lesion of the abducens nucleus produces an Ipsilateral gaze palsy; similarly, lesions of the CN6 nerve and contralateral MLF produce a gaze palsy.

Internuclear Ophthalmoplegia (INO)

The medial longitudinal fasciculus connects the CN6 nucleus within the pons to the contralateral CN3 nucleus (medial rectus subnucleus) in the midbrain, and lesions of the MLF produce an internuclear ophthalmoplegia. In contrast to classical teaching, most INOs do not have overt limitation of adduction, but rather slowed adduction speed. The best method to detect these “saccadic” INO is to elicit horizontal saccades while the examiner views the nasal bridge, attentive for adduction slowing.

1.5

The one-and-one half syndrome was originally described by Freeman et al and coined by C Miller Fisher. This lesion subtends the abducens nuclei and the adjacent MLF, producing a combination of an Ipsilateral gaze palsy and INO; the only remaining horizontal eye movement is abduction of the contralateral eye. The syndrome may be due to any one of various pathophysiologies including multiple sclerosis (MS), infarct, neoplasm or arteriovenous malformations.

8.5

The eight-and-one half syndrome simply adds CN7 to the 1.5 syndrome. These brainstem syndrome names are not relevant, but their importance lies in understanding the pontine anatomy. Recognition of an INO, CN6 palsy, gaze palsy, 1.5 and 8.5 syndromes mandates a working understanding of clinical pontine anatomy.

16.5

8.5 syndrome and cochlear (CN8) involvement with deafness. (Cummins et al).

24.5

Bilateral CN8 + 8.5 syndrome (Man et al).

Oculopalatal tremor (OPT)

OPT is related to disruption of the Guillain-Mollaret triangle, often within the pontine central tegmental tract (see inferior olive and OPT under medulla).

SPECIFIC DISEASES

MSA

Slowed saccades

Pontine diseases may be associated with slowed horizontal saccades; possibilities include genetic (SCA, Huntington, CADASIL), degenerative (PSP, DLB, Alzheimer (late), Parkinson disease (late), FTD, Neiman Pick type C, Gaucher, ALS (late), CJD), infectious (Whipple, tetanus), toxic (AED, benzodiazepine overdose), inflammatory (paraneoplastic Ma2), mitochondrial (CPEO, MELAS).

Selective saccadic palsy following cardiac surgery

Presumably impairment of bilateral PPRF function is involved in this syndrome, although no clear and consistent pathologic correlate has been found in the few cases examined.

MEDULLA

ANATOMY

The medulla is identifiable in axial imaging as the small caudal butterfly, and represents the basement of the model brainstem house.

KEY FEATURES/STRUCTURES

Vestibular Nuclei

The vestibular nucleus partially resides within the medulla; however, lesions of this structure may produce varied nystagmus including horizontal, vertical, torsional or mimic those of peripheral vestibular lesions.

NPH/MVN

The medial vestibular nucleus and nucleus prepositus hypoglossi are key structures involved in gaze holding, comprising part of the neural integrator responsible for pulse step calculations. Lesions within this region produce gaze evoked nystagmus.

Inferior Olive

The inferior olive emits climbing fibers destined for the contralateral cerebellum, and is involved in the syndrome of oculopalatal tremor.

Lateral Medulla

The lateral medulla is the site of Wallenberg syndrome, most often caused by infarct, but also possible as the result of demyelination, neoplasm, trauma, etc. The critical structures within this region correlating with symptoms include the vestibular nuclei and otolith fibers, descending tract of CN5, CN9/10, climbing fibers destined for the Purkinje cells of the cerebellum via the inferior cerebellar peduncle.

SPECIFIC DISEASES/CLINICAL SYNDROMES

Wallenberg Lateral Medullary Syndrome

Wallenberg is the most common brainstem stroke syndrome, and usually results from vertebral artery disease (more than PICA disease). Wallenberg causes a constellation of features including ipsilateral Horner, facial numbness, CN9/10 dysfunction (dysarthria and dysphagia), and contralateral body hypesthesia. Ocular features include lateropulsion with eye closure and with ipsilesional saccades (loss of climbing fiber input from the contralateral inferior olive to the Purkinje cells produce increased fastigial nucleus inhibition), impaired contralesional smooth pursuit, mixed horizontal-torsional nystagmus, and the ocular tilt reaction (contralesional hypertropia, ipsilesional head tilt and cyclodeviation of upper eye poles). Despite its commonality, lateral medullary infarcts often go unrecognized as such in the ED due to the absence of weakness.

Paramedian Medulla

NPH and MVN connect with cerebellum and control gaze holding; accordingly, gaze evoked nystagmus is typical for lesions within this area (infarct, demyelination). In addition, lesions within this area, potentially involving the paramedian tracts, may produce varied types of jerk nystagmus including downbeat, upbeat, torsional and hemi-seesaw. Medullary causes of both upbeat and downbeat may violate Alexander's law, producing nystagmus that dampens with gaze in the direction of the fast phase. There are several medullary structures which when lesioned result in upbeat nystagmus.

Medial medullary infarcts produce contralateral hemiparesis and position sense loss, tongue paralysis (either side depending upon lesion location), nystagmus (often horizontal with slow phase away from lesion side, but also upbeat and rarely downbeat occur), skew, ocular tilt reaction and possible contrapulsion of saccades (inferior olive climbing fibers destined for the cerebellum).

Oculopalatal Tremor (OPT)

Oculopalatal tremor is the delayed result of a lesion with the Guillain-Mollaret triangle (inferior olive – contralateral deep cerebellar nuclei/dentate nucleus – red nucleus/central tegmental tract). The inciting lesion is usually infarction within the central tegmental tract, but can result from various pathophysiologies including cavernoma, hemorrhage, trauma, or neoplasm within various locations including the cerebellum or superior cerebellar peduncle. This syndrome has its onset following a delay ranging from weeks to years following the acute insult.

The nystagmus is most often 2 Hz vertical pendular, but may have elliptical, torsional or seesaw components. The palatal tremor mirrors the ocular movements, and may also involve the diaphragm, larynx and rarely other motor areas. OPT is characterized by MRI-demonstrable inferior olive hyperintensity ("pimento sign"; S Johnstone, personal communication), which appears histologically as degenerative hypertrophy. The disruption of this feedback circuit may allow the inferior olive to develop an abnormal synchronous pacer-like signal creating a cerebellar derived maladaptive response. Treatment options such as gabapentin, clonazepam, memantine and anticholinergics produce modest improvement in some patients in our experience.

Progressive Ataxia with Palatal Tremor (PAPT)

A small subgroup of patients with OPT later develop progressive ataxia in addition to the oculopalatal findings. This tends to be primarily gait disabling, and in several of our patients has resulted in wheelchair bound status after progressive courses ranging from months to years in duration. We have been unsuccessful in providing any pharmacologic symptomatic treatment for this syndrome.

Wernicke

Hypovitaminosis B1 produces the classic triad of ophthalmoplegia, ataxia and confusion. In practice, eye movement dysfunction may include CN6 palsy, but also gaze evoked and upbeat nystagmus; the latter may disobey Alexander's law, implying a lesion in the NPH-MVN region.

CONCLUSIONS

The brainstem is an understandable collection of wires and nuclei, and obligatory working battle field knowledge for every neuro-ophthalmologist. The concept of brainstem as a house, with midbrain attic, first floor pons, and basement medulla helps when teaching brainstem anatomy.

CME ANSWERS

1. a
2. c
3. d

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NYSTAGMUS AND OTHER OCULAR OSCILLATIONS

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LEARNING OBJECTIVES

1. Distinguish among different types of eye oscillations; their localization and treatment
2. Describe the main types of pendular and jerk nystagmus
3. Identify the various mechanisms that cause nystagmus

CME QUESTIONS

1. Which of the following is not commonly associated with pendular nystagmus?
 - a. Multiple sclerosis
 - b. Dorsal cerebellar vermis lesions
 - c. Lesions in the central tegmental tract
 - d. Toluene intoxication
2. Of the following anatomical areas which is not commonly associated with abnormal horizontal or vertical gaze holding?
 - a. Interstitial nucleus of Cajal
 - b. Medial vestibular nucleus
 - c. Nucleus prepositus hypoglossi
 - d. Dorsal cerebellar vermis
3. Of the following locations where do lesions not commonly cause a vertical nystagmus?
 - a. Nucleus of Roller
 - b. Nucleus intercalatus
 - c. Dorsal cerebellar vermis
 - d. Cerebellar flocculus/paraflocculus

KEYWORDS

1. Pendular
2. Nystagmus
3. Jerk
4. Infantile
5. Latent

INTRODUCTION

Nystagmus is a form of ocular oscillation in which the primary disturbance is an unwanted slow-phase drift of the eyes away from the target of interest. It contrasts with the type of disturbance of fixation in which the primary offending movement is an unwanted saccade (intrusion) away from the target of interest. Here we combine a mechanistic and observational approach to develop a flow chart for the classification of nystagmus for diagnosis and treatment.

Nystagmus derives from a Greek word νυσταγμός, meaning drowsiness, nodding off to sleep or dozing. Eduard Hitzig, the 19th century German neurologist of Hitzig zones fame for the description of the unusual patterns of sensory loss in tabes dorsalis, first used the word *nystagmus* in the 19th century to describe the effects of galvanic stimulation behind the ears on the mastoids which produced a nystagmus with slow and quick phases. The eye movements were likened to a fisherman's float drifting slowly in the water and then being snatched back. Nystagmus is one of the most confusing aspects of efferent neuro-ophthalmology but if one organizes one's thoughts, keeps in mind the mechanisms by which the brain holds the eyes still, and considers the waveform of the slow phase and the appearance and pattern of the nystagmus, one can then use a flow chart to identify and classify most types of nystagmus (Figures 1 and 2). Many forms of nystagmus can now be treated with medications so identifying the type of nystagmus is necessary to guide therapy.

WHAT MECHANISMS HOLD THE EYES STILL?

1) Vestibular drives, so that any imbalance in the vestibular nuclei leads to an unwanted drift of the eyes. 2) Gaze-holding networks, which keep the eyes still after all types of conjugate eye movements (saccades, pursuit, vestibular or optokinetic). The key gaze-holding structures are the medial vestibular nucleus (MVN) and nucleus prepositus hypoglossi (NPH) for horizontal eye movements and the interstitial nucleus of Cajal (INC) for vertical eye movements. The vestibular nuclei, the paramedian tracts and nuclei (adjacent to the MLF in the rostral medulla and caudal pons one of which is also called the nucleus paraflocculus), and the nucleus intercalatus and nucleus of Roller (both part of the perihypoglossal nuclei) are all important for gaze-holding. Finally the flocculus and paraflocculus (tonsil) of the cerebellum are interconnected with these various structures and play an important role in

the neural integration that is necessary for steady gaze-holding, primarily by extending the time constant of the inherently relatively weak brainstem neural integrator. This anatomical complexity reflects the widespread nature and importance of the neural networks responsible for holding the eyes still. 3) Adaptation networks that keep eye movements calibrated. These can be affected in two ways: By direct abnormalities within the adaptation networks themselves, e.g., disease of the cerebellum in which many ocular motor learning networks reside, or indirect effects by depriving the adaptation networks of the error signals (usually visual, unwanted motion of images on the retina) that apprise the adaptation networks of the need for and the type of adaptation necessary to optimize ocular motor (and gaze-holding) performance. Other mechanistic issues that need to be considered include developmental abnormalities (both on the afferent and efferent side of ocular motor function) and ion channel function (which determines membrane stability) that can be influenced by both genetic factors and acquired disorders, for example, autoimmune disease.

WAVEFORMS AND PATTERN RECOGNITION

Naturally the qualitative appearance and quantitative characteristics of nystagmus are also guiding features for classification of nystagmus. In general, nystagmus can be divided into a jerk pattern (with alternating slow and quick phases (resetting saccades)) or a pendular pattern (with alternating slow phases approximately of equal amplitude). The velocity profile of the slow-phase waveform becomes important: most nystagmus driven by vestibular imbalance has roughly constant-velocity slow phases, most gaze-

evoked nystagmus due to impaired integration has velocity-decreasing slow phases, while infantile (congenital) nystagmus often has velocity-increasing slow phases. There are exceptions, with acquired nystagmus occasionally having velocity increasing slow phases (usually vertically). Other forms of nystagmus for which pattern identification is critical include see-saw nystagmus (both a jerk and a pendular form), divergence jerk nystagmus, convergence-retraction nystagmus, divergence-convergence pendular nystagmus, various forms of monocular pendular nystagmus, and latent (or occlusion) nystagmus in which a conjugate jerk nystagmus develops or is accentuated when one eye is occluded (with slow phases directed toward the nose of the viewing eye). This last pattern of nystagmus is associated with congenital strabismus (usually esotropia) and dissociated vertical divergence (DVD) in which the eye under cover elevates. This syndrome is also called fusion maldevelopment nystagmus syndrome. Its slow-phase waveforms are velocity decreasing.

A FLOW CHART FOR CLASSIFYING NYSTAGMUS

With these concepts in mind one can use a flow chart to recognize and classify the most common forms of nystagmus (Figure 1). Again, begin by deciding if the primary reason that fixation is unstable is because of a slow drift away from fixation or a saccadic intrusion away from fixation. If the culprit is the slow phase determine if the nystagmus is jerk with a corrective quick phase or pendular in which case the two slow phases occur one upon the other in opposite directions and are of approximately equal amplitude.

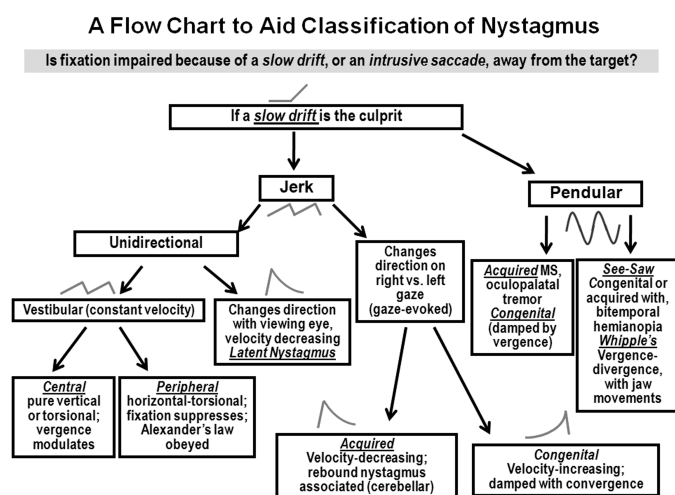


Figure 1

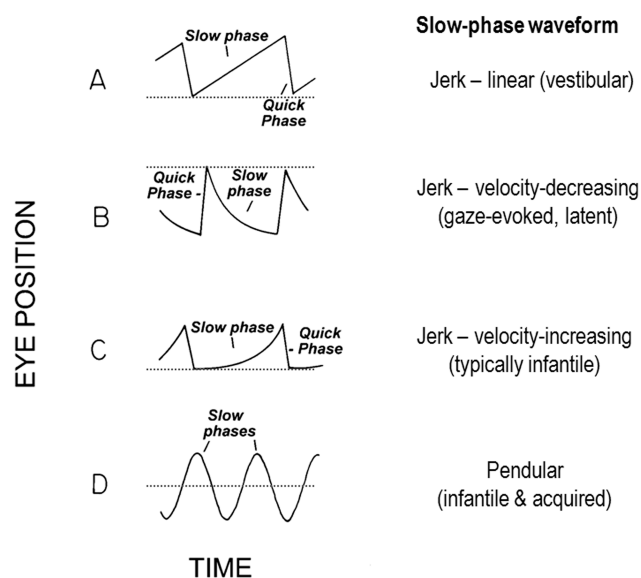


Figure 2

JERK NYSTAGMUS

If jerk, and unidirectional, consider the following: If the slow phase is of a constant velocity, the mechanism is likely vestibular whether central (e.g., vestibular nuclei or vestibulocerebellum) or peripheral (e.g., labyrinth or VIII nerve). If peripheral the nystagmus is usually suppressed by visual fixation and obeys Alexander's law (intensity of nystagmus increases when the eyes are in a position of the orbit in the same direction to which the quick phases are beating). A mixed horizontal-torsional pattern is often peripheral. If the nystagmus is pure vertical or pure torsional its cause is often central and it is often accentuated by convergence. Downbeat nystagmus in the straight-ahead position is a characteristic sign of disturbances in the posterior fossa, especially of the cranial-cervical junction (e.g., Chiari malformation) or of the cerebellum itself (especially the vestibulocerebellum (flocculus/paraflocculus (tonsil) complex and the nodulus)). Downbeat nystagmus is usually more intense on lateral gaze and with convergence. It usually, but not always obeys Alexander's law. Causes include cranio-cervical junction anomalies, cerebellar degenerations, paraneoplastic syndromes, drug intoxications and Wernicke's encephalopathy. Pure torsional nystagmus is often a sign of a lesion in the medulla (e.g., syringobulbia) or in the cerebellum. Pure upbeat nystagmus is often associated with lesions in the medulla in the region of the nucleus intercalatus and nucleus of Roller which are two of the perihypoglossal nuclei (the nucleus prepositus is a third). Wernicke's disease is another cause of upbeat nystagmus and is associated with acute bilateral vestibular hypofunction. Pure upbeat nystagmus is usually damped with convergence or may reverse to a downbeating waveform. It is often associated with a striking lid nystagmus.

Horizontal nystagmus in the straight-ahead position that is associated with a central lesion may increase in intensity when the eyes are in a position in the orbit in the opposite direction to which the quick phases are beating (anti Alexander's law) although the opposite (Alexander's law is obeyed) also occurs. If a jerk nystagmus changes direction on looking in opposite directions in the orbit (e.g., right beating on right gaze and left beating on left gaze) this is a sign of a gaze-holding deficit and reflects a central disturbance in the brainstem or vestibulocerebellum. This gaze-evoked nystagmus usually has a slow-phase wave-form that appears velocity decreasing and is often associated with rebound nystagmus (after sustained eccentric gaze, the gaze-evoked nystagmus damps but on return to the straight ahead position there is a transient jerk nystagmus (rebound nystagmus) with slow phases directed in the prior direction of eccentric gaze). It is as if the brain has developed a bias in the direction of the poor gaze holding to try and stabilize the eyes in that position, but on return to the straight ahead position the adaptive bias takes a bit of time to dissipate which is manifest as rebound nystagmus. When this adaptive mechanism that

attempts to null centripetal drift overacts on eccentric gaze the nystagmus in the eccentric position may actually begin to beat centripetally toward the straight-ahead position (centripetal nystagmus) and then on return to the straight ahead position there is a particularly strong rebound nystagmus. Occasionally gaze-evoked nystagmus becomes more intense with sustained eccentric fixation. This can be the case with myasthenia gravis and is often associated with a more pronounced rebound nystagmus. When the intensity of gaze-evoked nystagmus changes little with prolonged eccentric gaze, a congenital origin of the nystagmus is suggested.

Two forms of infantile nystagmus can be altered by the direction of gaze. In so-called infantile or congenital nystagmus (see also above), with a wave form that appears jerk; the nystagmus may change direction on looking left or right. The slow-phase waveform is often velocity increasing or even more complicated, with a number of unusual patterns. Congenital nystagmus of this type is often damped by convergence. There is often a null position in which the nystagmus is absent, and the head may be rotated to bring the eyes to that null position, producing a sometimes cosmetically unattractive head turn but in the interests of better vision. In latent nystagmus (or fusion maldevelopment nystagmus syndrome), the slow-phase waveform is velocity decreasing. Any form of congenital nystagmus that is disconjugate is a red flag for a central, structural lesion and needs to be investigated with proper imaging of the optic nerve and the brain. Convergence-retraction nystagmus is associated with lesions in the pretectum and posterior commissure in the midbrain. It is often best brought out with an attempted upward saccade, which can be a quick phase induced during vertical optokinetic stimulation. There is retraction of the orbit with the rapid convergent component which may in fact be a convergent saccade with a loss of normal reciprocal innervation producing the retraction.

PENDULAR NYSTAGMUS

If the wave form appears pendular with a predominant slow phase oscillation, consider if the nystagmus is acquired or congenital. Acquired pendular nystagmus is generally of two types: a rather smooth pendular waveform, roughly sinusoidal, or a more irregular, variable waveform. The former is typical of multiple sclerosis and other processes that primarily affect white matter (e.g. intoxications such as toluene) and is often elliptical or circular. This nystagmus often briefly stops, for a few 100 ms or so, after a saccade or a blink. This feature, which reflects the resetting of an unstable neural integrator, can be taken advantage of by patients to gain a brief period when they can see clearly without oscillopsia or visual blurring. Pendular nystagmus is often asymmetric and disconjugate, with the more intense oscillations being seen in the eye with the lower visual acuity. Neither the exact mechanism nor anatomical localization of this type of pendular nystagmus as seen in multipole sclerosis is known. Presumably the neural gaze

holding networks in the lower brainstem and cerebellum are the culprit. Memantine and gabapentin may ameliorate the nystagmus. We recently discovered that mastoid vibration may partially suppress pendular nystagmus, implicated proprioceptive mechanisms or vestibular activation as influences on pendular nystagmus.

The second major type of pendular nystagmus occurs as part of the oculopalatal tremor syndrome (OPT) associated with lesions in the Gullain-Mollaret Triangle (Inferior olive – cerebellum (dentate nucleus?) – superior cerebellar peduncle – central tegmental tract). The nystagmus may be disconjugate (the lesions in the Guillain-Mollaret triangle may also directly involve ocular motor nuclei or the MLF), vary considerably with position in the orbit, and usually has an irregular wave form with pendular and jerk components. It is often markedly accentuated or brought out by lid closure. The mechanism of this nystagmus is of considerable neurobiological interest. Lesions in the Guillain-Mollaret triangle result in deafferentation of the inferior olive which leads to olivary hypertrophic degeneration, seen on MRI as an increase in size of the inferior olivary complex with increased signal on T2 weighted imaging. With this response there is a ballooning of inferior olivary neurons so that their somas contact each other directly leading to abnormal soma to soma electrotonic (membrane to membrane) conduction via connexin 36 ion channels. This in turn, leads to increased coupling between olivary neurons and consequent synchronization of their discharge producing a barrage of inappropriate climbing fiber activity onto cerebellar Purkinje cells. It is this activity that drives the cerebellum to produce the anomalous discharge leading to the spontaneous nystagmus (and perhaps the palatal tremor as well). Theoretically, connexin blockers might alleviate this nystagmus. Memantine and clonazepam have helped some patients but this type of nystagmus is particularly hard to treat. Remember to always look carefully at the palate in patients with pendular nystagmus. PAPT (progressive ataxia with palatal tremor) is a degenerative disease in which palatal tremor occurs though nystagmus is often minimal or absent. Whipple's disease should also be considered in patients with pendular nystagmus (and palatal tremor), but especially when the nystagmus is divergent-convergent, associated with a vertical supranuclear gaze palsy, and accompanied by rhythmic movements of the jaw (ocular masticatory myorhythmia). Late-onset Alexander's disease is associated with palatal tremor [(and a very small upper cervical cord and medulla on MRI scanning (tadpole sign)].

See-saw nystagmus, as mentioned above and may be congenital or acquired. The congenital form is often associated with midline abnormalities of the chiasm, optic atrophy and pituitary abnormalities as in septo-optic hypoplasia (de Morsier syndrome). Acquired see-saw nystagmus can be pendular or jerk (hemiseesaw nystagmus) and in some instances reflects vestibular imbalance, as occurs in the ocular tilt reaction (skew, ocular counterroll, head tilt), a manifestation of utricular imbalance. Windmill nystagmus (in which there is a clock

like rotation of the nystagmus vector) is a complicated form of period alternating nystagmus in which there are, usually out of phase, oscillations of both the horizontal and vertical components of a jerk nystagmus. Windmill nystagmus is usually associated with severe retinal disease such as retinitis pigmentosa.

SACCADIC INTRUSIONS

As indicated at the beginning, fixation instability may also reflect an unwanted saccade as the initiating culprit. Saccadic oscillations may consist of back and forth, one upon the other, saccades without an intersaccadic interval (opsoclonus if multidirectional, ocular flutter if horizontal) or unwanted saccades occurring in a repetitive fashion but with an intersaccadic interval, such as square wave jerks or saccadic intrusions (Figure 3 and 4). Macrosaccadic oscillations consist of large, hypermetric saccades, separated by an intersaccadic interval in which saccadic hypermetria is the problem, so that a small enough saccade cannot be made to acquire the target. Causes for opsoclonus and flutter include paraneoplastic syndromes, immune-mediated post-infectious causes, intoxications and familial, genetic causes. A usually benign form, microsaccadic oscillations, often occurs in migraineurs. Many normal subjects can induce saccadic oscillations, often with a convergence effort. This has been called voluntary nystagmus but in fact is a saccadic oscillation rather than a nystagmus. Spasmus nutans is high frequency, shimmering, usually monocular, intermittent, typically horizontal, oscillation that begins in infancy. It is pendular like but it is not settled if it is a saccadic oscillations or a pendular nystagmus. The nystagmus is usually worse when the eye is in abduction. It may be brought out by convergence or have a convergence component. It is associated with head nodding and a head tilt. If not due to a structural lesion it largely resolves in a few years. It can be mimicked by optic nerve and more central lesions so imaging is mandatory. If there is an associated vertical component (usually upbeat) one must consider a retinal disorder. Ocular bobbing is of four types and in some cases is primarily a saccade disturbance and in others primarily a slow drift disturbance away from fixation. Its variations include typical bobbing (downward saccade, followed by upward drift), usually with a pontine lesion, reverse bobbing (upward saccade, followed by downward drift), ocular dipping or inverse bobbing (slow drift down, followed by upward saccade) and reverse dipping or converse bobbing (slow drift up, followed by downward saccade). Ping-pong gaze refers to back and forth, horizontal excursions, from far right to far left gaze occurring every one or two seconds. The wave form is one of a smooth movement (if the patient is deeply unconscious) or a series of small saccades (if the patient is somewhat awake). It probably represents release of rhythmic exploratory eye searching mechanisms and can occur with Cheyne-Stokes respirations.

Figure 3

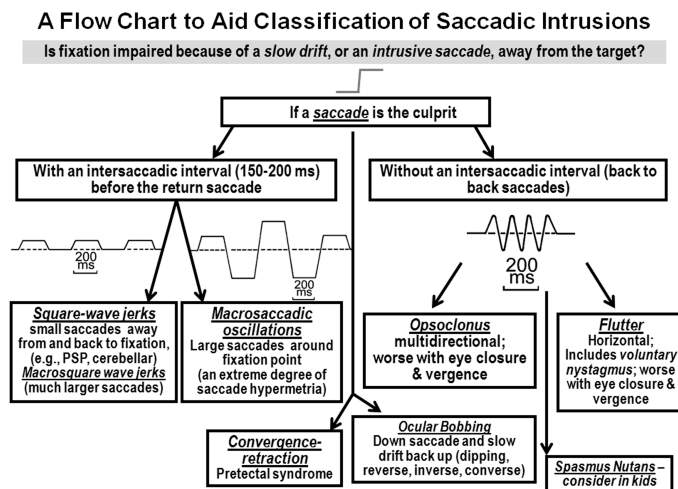
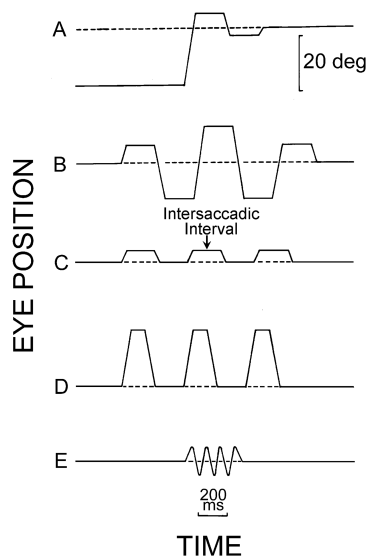


Figure 4



CME ANSWERS

- b
- d
- c

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THE NCAA EXPERIENCE: WHY DO WE NEED VISION?

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LEARNING OBJECTIVES

1. Describe the public health implication of concussion
2. Identify shortcomings in defining concussion and in defining the natural history of concussion
3. Discuss the unique opportunities for utilizing visual tracking in managing concussion

KEYWORDS

1. Concussion
2. Sport
3. Neurobiological Recovery
4. King-Devick
5. CARE Consortium

CME QUESTIONS

1. The natural history of concussion is poorly understood because:
 - a. There has never been a prospective study of concussion.
 - b. We do not understand neurobiological recovery in concussion.
 - c. Most definitions of concussion are consensus based and do not localize brain dysfunction.
 - d. B and C
 - e. All of the above
2. Neurobiological recovery differs from clinical recovery because:
 - a. Clinical recovery is primarily based on subjective criteria.
 - b. An athlete may appear recovered clinically while the brain remains in active repair.
 - c. Neurobiological recovery assesses brain physiology.
 - d. B and C
 - e. All of the above
3. King-Devick visual tracking may provide unique opportunities in concussion management because:
 - a. It assesses multiple areas of the cortex and brainstem.
 - b. It is a rapid sideline assessment tool.
 - c. It has high test-retest ability.
 - d. A and B
 - e. All of the above

INTRODUCTION

Sport-related concussion is a public health concern that has attracted considerable national attention. Despite a greater awareness of concussion, the condition is not well-defined, and we do not understand the natural history of concussion. This article provides an overview of the largest, prospective, clinical longitudinal study ever conducted in concussion, and discusses the unique role of visual tracking in managing concussion.

BODY

Sport-related concussion is a major public health concern. Up to 3.6 million sport- and recreation-related concussions occur annually, and this is likely a conservative estimate because many concussions are unreported.¹ Data suggest that there has been an increase in sport-related concussion in recent years—a trend that may be caused by a greater national awareness of this condition.² Sport-related concussion incidence varies by sport, with the greatest incidence occurring in contact-collision sports, which predispose to greater head impact vulnerability.²

Although there has been scientific interest in sport-related concussion for some time, there are three primary shortcomings with regard to understanding concussion:

1. There are numerous working definitions of concussion. The most commonly utilized definition is from the 2012 Zurich Guidelines, which follows:³

Concussion is a brain injury and is defined as a complex pathophysiological process affecting the brain, induced by biomechanical forces. Several common features that incorporate clinical, pathologic and biomechanical injury constructs that may be utilized in defining the nature of a concussive head injury include:

- i. Concussion may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an “impulsive” force transmitted to the head.
- ii. Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously. However, in some cases, symptoms and signs may evolve over a number of minutes to hours.
- iii. Concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies.
- iv. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course. However, it is important to note that in some cases symptoms may be prolonged.

This definition has some flaws because it defines concussion as a largely ‘functional’ injury, thereby discounting any physical brain changes that result from a forceful blow to the head that results in concussion symptomatology.⁴ The definition also lumps concussion into a single diagnostic category, without taking into account biomechanical or brain localization specificity. The most recent definition of concussion, which is the only evidence-based definition, follows:⁵

Concussion is:

- a change in brain function,
- following a force to the head, which
- may be accompanied by temporary loss of consciousness, but is
- identified in awake individuals, with
- measures of neurologic and cognitive dysfunction.

Although this definition is based purely on evidence-based data (and not consensus), it also lumps all concussions into a single diagnostic category, without taking into account biomechanical or brain localization specificity.

2. We do not understand the natural history of concussion. Concussion is described primarily in terms of clinical recovery based on measures of subjective symptoms and objective signs that can either be manipulated by the athlete, or that vary because of inter-rater variability.⁶ Although several prospective

studies have attempted to clarify the typical time course of clinical recovery in concussion, they focus primarily on male football and male ice hockey athletes.

The clinical recovery is usually measured by a resolution of a checklist of subjective symptoms and signs, as noted in Table 1. Symptoms are easily manipulated by athletes, depending on the desired outcome⁷. For example, if an athlete wishes to return-to-play soon, then he/she may deny symptoms. On the other hand, if the athlete is seeking more time off (e.g., to study for an exam), he/she may claim to have an increase in symptoms.

Objective measures may also be unreliable. Athletes have been known to score poorly on baseline computerized cognitive tests so that their post-concussion tests will be at or above baseline, thereby allowing early return-to-play.⁸ The Balance Error Scoring System (BESS) is a validated balance test, but scoring relies on interpretation from the observer that is based on some subjective interpretation, and performance can be affected from non-concussion effects such as a lower extremity injury.⁹

In addition to these shortcomings, there are no large-scale, multi-sport, multi-demographic studies that delineate the natural history of concussion over one-year and beyond.

3. We have not defined neurobiological recovery in concussion. Beyond clinical recovery, there may be a window of cerebral vulnerability in which brain function is in an active reparative mode. In other words, it is possible that an athlete may have a normal neurological exam and no concussion symptoms but may remain with brain physiological dysfunction or disrepair as a result of head trauma.¹⁰ All return-to-play and return-to-learn protocols following concussion are based on presumed clinical recovery, without objective measures of brain function per se.

To address these concussion knowledge shortcomings, the National Collegiate Athletic Association (NCAA) and the Department of Defense (DoD) have partnered to sponsor the NCAA-DoD Concussion Assessment, Research and Education (CARE) Consortium. This investigation is poised to investigate the dynamic time course of acute clinical and physiological recovery following sport-related concussion, and this has considerable public health implications for improving safety, injury prevention, and medical care in athletes. The CARE Consortium has three primary core focus areas:

1. Administrative and Operations Core (AOC). The AOC serves as the centralized coordination center for the clinical study by providing administrative and fiduciary oversight, support for data collection and management, bio-banking, and bioinformatics and biostatistics.

2. Longitudinal Clinical Study Core (CSC). The CSC will conduct a prospective, longitudinal, multi-site, multi-sport investigation that delineates the natural history of concussion in males and females by incorporating a multi-dimensional assessment of standardized clinical measures of post-concussive symptomatology, performance-based testing such as cognitive function and balance testing, and psychological health. The CSC will work with 30 institutions over a three-year period, and will obtain evidence-based baseline data from over 30,000 NCAA student-athletes in all sports. A rigorous post-concussion testing paradigm will be employed for any student-athlete who develops sport-related concussion. The study should capture over 800 concussions. The CSC will also serve as the foundation for more advanced research projects.
3. Advanced Research Core (ARC). The ARC will utilize the framework of the CSC and leverage existing collaborative research networks such as the NIH-sponsored TRACK-TBI project.¹¹ ARC will operate from four schools and will obtain detailed data from athletes participating in the following contact-collision sports: men's football; men's and women's soccer; men's and women's lacrosse; men's and women's ice hockey. In addition to undergoing identical baseline testing as the CSC study, athletes will also undergo baseline genetic and blood biomarker testing, will wear head sensors during practice and competition, and will undergo serial post-concussion MRI and blood studies side-by-side with the clinical post-concussion measures.

The baseline and post-concussion measures of the CSC and ARC are outlined in Table 2.

Although the NCAA-DoD CARE Consortium will provide exceptional clinical and neurobiological data, it does not provide an answer for obtaining easy-to-use, objective measures of clinical function compared to physiological function. For example, as noted in Table 3, the CSC-Level A assessment measures are noteworthy for clinical measures of neurocognitive assessment, Standardized Assessment of Concussion, postural stability via BESS, and a symptom checklist. It is difficult to complete such measures within three minutes, and they all suffer from some degree of subjective interpretation. CSC-Level B assessment measures include more objective, but more cumbersome, measures of balance and stability, and are therefore less practical. Clinical reaction time is a poorly validated but easy to utilize assessment tool. Vestibular Ocular Motor Screen has been validated within a single institution, but more widespread inter-rater reliability is unknown.¹²

King-Devick (K-D) is a two minute rapid number naming assessment that assesses eye movement (saccades, convergence and accommodation), attention and language function. Thus, K-D assesses functions of the brainstem, cerebellum and cerebral cortex.¹³ K-D is one of many emerging assessments of the visual pathways and

oculomotor movement post-concussion that hold promise for providing easy-to-use and objective measures of clinical function that correlate with neurobiology. The visual system involves pathways that have extensive connections with the cerebral cortex and brainstem, and may provide a key window into understanding both clinical function and cerebral vulnerability post-concussion.¹⁴

K-D has been validated as a reliable tool that detects concussion with high degrees of sensitivity and specificity, and high test-retest reliability.¹³ The NCAA-DoD CARE Consortium is uniquely poised to assess K-D in a much more rigorous fashion both with regard to comparing K-D to numerous clinical measures and advanced research technologies. This should provide an even better understanding of K-D vis-à-vis clinical and neurobiological recovery. The NCAA-DoD CARE Consortium is also uniquely poised to study other measures of visual function post-concussion, and active recruitment for such studies is underway.

As we move forward with a better understanding of concussion, we may be walking side-by-side with neuro-ophthalmologists as we tap into the richness, elegance and simplicity of measuring visual function as a key measure of recovery.

Table 1 – Signs and Symptoms of a Concussion.

Physical
<ul style="list-style-type: none"> • Headache • Nausea • Vomiting • Balance problems • Dizziness • Visual problems • Fatigue • Sensitivity to light • Sensitivity to noise • Numbness/tingling • Dazed • Stunned
Cognitive
<ul style="list-style-type: none"> • Feeling mentally 'foggy' • Feeling slowed down • Difficulty concentrating • Difficulty remembering • Forgetful of recent information and conversations • Confused about recent events • Answers questions slowly • Repeats questions
Emotional
<ul style="list-style-type: none"> • Irritable • Sadness • More emotional • Nervousness

Table 1 Continued

Sleep
<ul style="list-style-type: none"> • Drowsiness • Sleep more than usual • Sleep less than usual • Difficulty falling asleep

Table 2 – CSC & ARC Assessment Protocol

	Pre-Season	Acute Concussion		Sub-Acute Concussion			Post-Concussion
	Baseline	<6hrs Post-Injury	24-48hrs Post-Injury	Asymptomatic / Cleared for Return to Play Progression	Unrestricted Return to Play	7 days following Return to Play	6 Months Post-Injury
Neurocognitive and Behavioral Testing (CSC)	X	X	X	X	X	X	X
Blood Biomarker & DNA Collection	X	X	X	X		X	X
Multi-modal MRI Studies	O		X	X		X	X

Head Impact Measurement: HITS (FB) and non-helmeted sensors (FB, SCR, LAX, IH)

Table 3 – Assessment Measures

CSC – Level A	CSC – Level B
<ul style="list-style-type: none"> • Demographics <ul style="list-style-type: none"> - Age, Height, Weight, Sex, Year in School, Ethnicity, Handedness, Socio-economic status, Sport(s) played, Sport Position(s) played, Number of years/seasons of exposure for each sport • Personal and Family History <ul style="list-style-type: none"> - Neurological History - Concussion History - Education - Psychiatric/Psycho-Social History • Neurocognitive Assessment <ul style="list-style-type: none"> - Computer and/or pen/paper assessments • Neurological Status <ul style="list-style-type: none"> - Standardized Assessment of Concussion (SAC) • Postural Stability <ul style="list-style-type: none"> - Balance Error Scoring System (BESS) • Symptoms <ul style="list-style-type: none"> - SCAT3 symptom list and Brief Symptom Inventory (BSI)-18 	<ul style="list-style-type: none"> • Advanced Postural Stability <ul style="list-style-type: none"> - NeuroCom Sensory Organization Test (SOT) - Sway-Balance • Clinical Reaction Time • Oculomotor/Oculovestibular Tests <ul style="list-style-type: none"> - King-Devick Test - Vestibular Ocular Motor Screens (VOMS) • Quality of Life Measures <ul style="list-style-type: none"> - Short Form Health Survey (SF-12) - Hospital Anxiety and Depression Scale (HADS) - Satisfaction with Life Scale

CME ANSWERS

1. d
2. e
3. e

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CAPTURING EYE MOVEMENTS: FOUNDATION FOR NEURO-OPHTHALMIC ASSESSMENT IN CONCUSSION

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LEARNING OBJECTIVES

1. List the common clinical neuro-ophthalmologic signs in traumatic brain injury (TBI)
2. Recognize the difficulties and controversies surrounding clinical evaluation of ocular motility in concussion (mild TBI) and post-concussive syndrome
3. Critically analyze quantitative ocular motor literature on abnormal saccades in concussion

CME QUESTIONS

1. What is the most common neuro-ophthalmologic sign in concussion?
 - a. convergence insufficiency
 - b. abducens palsy
 - c. slow saccades
2. Which saccade type is predominantly controlled by the frontal lobes?
 - a. express saccades
 - b. memory-guided saccades
 - c. reflexive saccades
3. Which of the following have most often been reported as abnormal in concussion?
 - a. antisaccades
 - b. reflexive saccades
 - c. quick phases of optokinetic nystagmus

KEYWORDS

1. Concussion
2. Convergence Insufficiency
3. Antisaccades
4. Memory-guided Saccades
5. King-Devick Test

INTRODUCTION

Concussion, a major societal concern, results from biomechanically-induced alteration of brain physiology. Underlying cerebral dysfunction is primarily manifested through clinical symptomatology and standard methods of assessment for structural pathology (clinical examination and neuroimaging) are often unrevealing. The ocular motor system is governed by a complex and delicate network of cortical and subcortical structures. Given its widespread distribution, including a high load of circuitry in the frontal lobes which is prone to injury, it is highly likely to be affected by concussion. Resulting ocular motor dysfunction, particularly of saccade subtypes may, indeed, prove to be a sensitive measure of detection, a marker of biological injury, a sensitive outcome measure for clinical trials, and possibly a predictor of recovery.

INTRODUCTORY OVERVIEW: CLINICAL EFFERENT DYSFUNCTION IN TRAUMATIC BRAIN INJURY (TBI)

Ocular motor deficits are a common result of traumatic brain injury of any degree, from mild to severe, and can span the range of localizations from extraocular muscle involvement due to orbital trauma to intracranial cortical supranuclear dysfunction due to hemorrhage or diffuse axonal injury.¹⁻¹⁰ Studies have varied in their inclusion criteria with regard to visual symptoms and severity of head injury, the overall focus of the study (all ocular involvement versus only neuro-ophthalmic versus only afferent or efferent dysfunction), the duration between injury and examination, and the presence or absence of other neurological or neuroimaging defects. Despite this variability, there is general consensus that ocular motor cranial nerve palsies are the most common efferent neuro-ophthalmologic defect in head trauma, with oculomotor (third) and trochlear (fourth) nerve involvement more common than abducens (sixth) nerve involvement.^{2,5-7,9,11-13} Ocular motor cranial nerve injury is typically followed in frequency by convergence insufficiency of presumed supranuclear origin.^{1,3,5,7,9,14}

EFFERENT DYSFUNCTION IN MILD TBI: THE CLINIC

Detailed neuro-ophthalmological studies evaluating the frequency of ocular motor deficits in patient populations with isolated mild TBI are limited; however conclusions can be drawn from broader neuro-ophthalmologic studies in generalized TBI cohorts ranging from mild to severe. Oculomotor (third) nerve paresis and multiple simultaneous ocular motor nerve injuries have been associated with more severe head injury as determined by other neurological or neuroimaging deficits, such as corticospinal tract injury, intracranial hemorrhage, or basilar skull fractures.^{5,9,12,15} The presence of ocular motor nerve involvement, in general, is also associated with more severe head trauma as judged by lower initial Glasgow Coma Scale scores, higher rates of neuroimaging abnormalities, and higher frequency of inpatient rehabilitation.^{12,16} In contrast, convergence insufficiency¹⁴ and isolated ocular motor cranial neuropathies can occur in the setting of mild TBI, especially unilateral abducens (sixth) and unilateral or bilateral trochlear (fourth) nerve paresis.^{12,17}

The majority of the information discussed so far is derived from studies performed between the 1980's and the early 2000's in the neuro-ophthalmology or ophthalmology clinical setting, with motor vehicle accident and assault as the two most common mechanisms of injury. A shift in the origin of clinical publications of ocular motor and visual assessment in TBI has occurred over the past decade, as attention has been drawn in clinical settings and in the media to military and sports populations experiencing prominent visual symptoms following TBI, including in large populations with mild TBI / concussion. These later publications based in the optometric and rehabilitation literature are summarized here.

This body of literature often refers to a "post-trauma vision syndrome" after TBI, in which "...vision imbalances can occur between...focal and ambient visual processes that can affect balance, posture, ambulation, reading, attention, concentration, and cognitive function in general."¹⁸ In 2007, initial reports of military patient evaluations in inaugural Veterans Affairs inpatient Polytrauma Rehabilitation Centers (PRC) and outpatient Polytrauma Network Site (PNS) clinics were published.^{19,20} PRC patients typically had multiple and life-threatening injuries. In contrast, PNS patients were diagnosed with mild TBI, usually associated with a blast event. Updated results of 108 PRC and 125 PNS patients were published in 2009²¹. These programs, devised to meet the needs of Iraq and Afghanistan conflict combat survivors, many of whom sustained blast exposures and suffered from emotional trauma and physical injuries, revealed a high prevalence of TBI and post-concussion symptoms. In addition, via initial optometric visual screening processes, they had a high burden of visual symptomatology. A questionnaire assessment of visual clarity, photosensitivity, binocularity, and visual and cognitive symptoms during reading revealed a high burden of visual symptoms in

75% of patients,^{19,21} including prominent photosensitivity. Further, examination of visual function in these studies, including ocular motor range, binocular alignment, convergence, saccades, and smooth pursuit resulted in report of ocular motor dysfunction in the majority. The breakdown was as follows: convergence dysfunction in 40-48%, pursuit and/or saccadic dysfunction in 23-29%, strabismus in 6-19%, and fixation insufficiency in 7-13%.¹⁹⁻²¹ Ocular motor deficits were similar between the inpatient PRC and outpatient PNS cohorts, with exception of more frequent diplopia in the inpatient cohort.²¹ It was determined likely that disorders of binocular visual function may account for self-reported reading difficulties in 57-63% of the patients, though it is acknowledged in these papers that cognitive, perceptual, or attentional factors may also play a role in symptom burden. It is further noted that vision therapy is frequently employed to address functional deficits, along with visuospatial training and techniques to improve scanning and perception.^{21,22}

A four-tiered optometric approach to evaluation of visual issues in mild TBI has been proposed to include 1) the basic optometric vision examination (e.g., refractive status, binocular status, ocular health status), 2) oculomotor-based vision problems (e.g., fixation, saccade, pursuit, vestibular, optokinetic systems), 3) non-oculomotor-based vision problems (e.g., shift in spatial 'sense of straight ahead', photosensitivity, motion sensitivity, dizziness, visual information processing dysfunction), and 4) non-vision-based problems (e.g., depression, cognitive and behavioral issues, postural problems).²³ Ocular motor deficits similar to those seen in military populations by optometrists have also been reported in civilian populations with TBI who have undergone optometric assessment.²⁴

A high prevalence of mild convergence insufficiency is found across neuro-ophthalmologic, optometric, and rehabilitation literature in mild TBI in civilian and military populations.^{1,3,5,9,14,21,25-27} Outside of this uniform feature, several controversies have arisen with regard to the inter-relationships between visual symptoms and examination findings. *First*, there are likely to be differing opinions with regard to how much visual and physical symptomatology directly relate to convergence insufficiency. It has been suggested that convergence insufficiency may result in blurred vision, diplopia, eyestrain, headaches, loss of concentration, having to reread or read slowly, difficulty in remembering what was read, and visual fatigue.²⁵ Some of these are classic symptoms of convergence insufficiency, but others could originate from headache disorders or other neurocognitive or psychiatric issues triggered by mild TBI, as similar visual symptoms may also be present in mild TBI patients who lack convergence insufficiency. *Second*, controversy exists with regard to the frequency and significance of non-vergence dynamic ocular motor abnormalities, most notably of saccades. With regard to saccades, it has been published that assessment may be labelled as abnormal if the saccades do not appear smooth

and accurate or if the subject is unable to perform the task.²⁸ However, given the visual and physical discomfort elicited by the ocular motor examination in many mild TBI patients, there is no evidence that inability to comply with testing indicates true saccadic dysfunction. Assessment for mild saccadic dysfunction and determination of its significance at the bedside is clinically challenging. Studies to date in the Veterans Affairs PRC and PNS patient populations now report a frequency of pursuit or saccadic dysfunction ranging between 5 to 60%, with low and high percentages found in both more severe PRC populations and in milder TBI PNS populations.^{20,27,29-31} This may reflect the presence of different study populations in each publication, but variability could also exist due to differences in inter-examiner determination of whether a clinical saccade is normal or abnormal. Further underscoring this possibility is the fact that, despite evidence of impaired saccadic behavior in mild TBI in an ocular motor laboratory setting, studies have shown that these subjects have no abnormalities of saccades on clinical examination.^{32,33} *Third*, there is a large discrepancy between the prominence of visual symptomatology in mild TBI and the frequency of abnormalities on clinical visual and ocular motor assessment. This had led to assumptions that elicitation of visual and physical symptoms by the ocular motor examination implies corresponding ocular motor deficits on examination,^{34,35} which may not be the case in many patients with mild TBI.

EFFERENT DYSFUNCTION IN MILD TBI: THE EYE MOVEMENT LABORATORY

Ocular motor recordings allow quantification of various saccade behavioral features, such as latency (time between target onset and saccade onset), velocity, amplitude, duration, accuracy, directional errors, and positional errors. Outside of the laboratory and in simplistic terms, we typically utilize two main types of saccades: volitional purposeful saccades that are largely governed by frontal lobe saccade centers and reflexive

saccades that are largely governed by parietal saccade centers. In the laboratory, in addition to studying volitional and reflexive saccades as broad categories, saccade behavior can be altered via manipulation of the timing of onset and offset of fixation and saccade visual targets. A number of other saccade types can then be generated in a controlled setting. Comprehensive coverage of this topic is far beyond the scope of this syllabus, but a few saccade types heavily utilized in mild TBI research will be briefly described. These include memory-guided saccades, antisaccades, self-paced saccades, and reflexive saccades (Table 1). Smooth pursuit and vestibular eye movements have also been studied in mild TBI,^{36,37} but the discussion here will be restricted to saccades.

Before compiling the research results, it is worthwhile to ask the question *why is it worth it to study detailed saccade behavior in the laboratory in mild TBI?* There are at least four important answers to this question: 1) improved detection of structural injury in highly symptomatic patients with a heavy burden of visual and other symptomatology, 2) exploration of underlying neuroanatomic deficits, 3) for potential future use as outcome measures in clinical trials, and 4) as potential markers for assessment of recovery. Patients who sustain mild TBI may develop a protracted post-concussive syndrome,^{38,39} with few to no findings on standard physical examination and brain MRI. As has been seen in multiple studies in the above clinical section, the majority of these patients have a very high burden of incompletely understood visual symptoms. Further, physicians may be biased towards the possibility of secondary gain in the form of disability or litigation as the most prominent mechanism underlying post-concussive deficits. While this may be true in some individuals, studies assessing this question have found a minimal role of secondary gain in patient outcomes^{40,41} and organic injury likely due to diffuse axonal injury⁴²⁻⁴⁴ can be identified with more detailed evaluation methods, such as neuropsychological testing,⁴⁵ positron-emission tomography⁴⁶ and functional MRI, and via ocular motor recordings.

Table 1. Examples of Saccade Types

Memory-guided	A subtype of volitional saccades generated to the remembered location of a previously displayed visual target when the target is no longer visible.
Antisaccades	A subtype of volitional saccade generated intentionally in the direction opposite to a visual target. Require not only intentional generation of a saccade in the opposite direction, but also suppression of a saccade to the visual target.
Self-paced	Volitional saccades made between two continuously present targets without verbal commands.
Reflexive	Saccades involuntarily generated to an unexpected novel visual target, such as to an object unexpectedly appearing in the peripheral vision.

Extensive cortical and subcortical networks are involved in the planning and execution of saccades, including the frontal eye fields (FEF), the dorsolateral prefrontal cortex (DLPFC), the supplementary motor area (SMA), and the cingulate eye fields (CEF). The diffuse nature and complexity of this network render it susceptible to injury in mild TBI. Frontal and antero-temporal brain regions are the most common sites of focal lesions after closed head injury.⁴⁵ When MRI fails to disclose pathology, functional assessment of frontal cortex may be sought

with exploration of saccades paradigms heavily indicative of frontal function, such as memory-guided saccades and antisaccades.⁴⁷⁻⁵² However, the complexity of this network and how each structure controls each saccade parameter is complex. Localization of a saccadic abnormality to a specific neuronal population may be challenging. Table 2 outlines a simplified schema of the role played by individual structures in generation of specific saccade types. The results of published studies of saccades in adults with mild TBI are summarized in Table 3.

Table 2. Simplified schema of the role of cortical structures in saccade subtype deficits

Memory-guided saccades ^{51,53-56}	FEF, DLPFC, PPC play a role. FEF and DLPFC lesions reduce accuracy and increase response errors. DLPFC and PPC are reciprocally connected – lesions in either affect memory-guided saccades. Lesions in SMA cause errors in sequences of memory-guided saccades.
Antisaccades ^{33,49,57,58}	FEF triggers correct antisaccade. DLPFC inhibits reflexive misdirected saccades.
Self-paced saccades ^{33,59}	May be due to FEF lesions or lesions in connections between FEF or DLPFC and SC.
Reflexive visually-guided saccades	Governed by PEF.

Abbreviations: FEF frontal eye fields, DLPFC dorsolateral prefrontal cortex, PPC posterior parietal cortex, SMA supplementary motor area, SC superior colliculus, PEF parietal eye fields.

Table 3. Saccades in mild TBI (mTBI)

<i>Study</i>	<i>Number of subjects</i>	<i>Time since injury</i>	<i>Memory-guided saccades</i>	<i>Antisaccades</i>	<i>Self-paced saccades</i>	<i>Simple reflexive saccades</i>
2000 Crevits ⁶⁰	25 mTBI – no alcohol 6 mTBI – alcohol 27 controls	Within 24 hours	á latencies and errors only in mTBI with alcohol	á latencies and errors only in mTBI with alcohol		
2002 Heitger ³²	30 mTBI 30 controls	Within 9 days	á latencies and errors* Worsened performance with longer sequences of saccades			
2004 Heitger ³³	28 mTBI 28 controls	Within 16 days	á errors â accuracy	á latencies and errors â accuracy	Longer inter-saccade intervals Fewer saccades	No difference
2006 Heitger ⁶¹	37 mTBI 37 controls	1 week and 3, 6, 12 months	Improved but ongoing deficits at all intervals	Improved but ongoing deficits at all intervals		
2007 Pearson ⁶²	12 boxers	Within 12 hours before match, within 7 minutes of match, and days later				á latencies** Resolved within days

Table 3 Continued

Study	Number of subjects	Time since injury	Memory-guided saccades	Antisaccades	Self-paced saccades	Simple reflexive saccades
2007 Kraus ⁶³	20 mTBI 19 controls	Mean 65 months		á errors		No difference
2009 Heitger ⁶⁴	36 PCS 36 prior mTBI with good recovery	140 days for PCS 163 days for prior mTBI	Poorer performance in PCS***	Poorer performance in PCS	Poorer performance in PCS	No difference
2014 and 2015 Johnson ^{65,66}	9 mTBI ^ 9 controls	Acutely within 7 days and 30 days post-injury	Acutely: á errors â accuracy 30 days: á errors	Acutely: á errors â accuracy 30 days: á errors â accuracy	Acutely: Fewer saccades 30 days: Fewer saccades	

PCS = post-concussive syndrome

*Memory-guided saccade sequences with 2-3 steps were tested, rather than single memory-guided saccades

**Possibly different from 2004 Heitger and 2007 Kraus due to inter-subject vs. intra-subject comparisons

***Abnormal saccades of all types were more likely to be present in PCS with higher symptom burden

^In 2014 study, 9 subjects. In 2015 follow up study, 7 subjects. Ocular motor testing was performed simultaneously with fMRI, which showed increased areas of activation in mTBI.

EFFERENT DYSFUNCTION IN MILD TBI: FUTURE PROGRESS

The King-Devick test, a task of rapid number naming, has been well-validated as a sensitive sideline measure for concussion detection.⁶⁷ This test functions as a pseudo-reading task, which broadly captures aspects of afferent visual function, attention, language, visual fixation, and saccadic eye movements. Slowing of the total time to read the three test cards occurs in acute concussion; however the explanation as to why this occurs remains forthcoming. Possibilities include saccadic slowing, increased duration of fixations, increased blinking, increased overall numbers of saccades due to backtracking or inaccurate saccades, excessive saccadic intrusions superimposed upon otherwise normal eye movements, and attentional and cognitive deficits. Future research avenues include bridging the sidelines, the clinic, and the laboratory with assessment of ocular motor behaviour during rapid number naming and with assessments for correlations between laboratory abnormalities of saccades, concussion severity, and recovery.

CME ANSWERS

- a
- b Memory-guided saccades are predominantly controlled by the frontal lobes. Express saccades are generated at the level of the superior colliculus. Reflexive saccades are controlled by the parietal lobes.
- a

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SIDELINE TESTING FOR SPORTS RELATED CONCUSSION: WHAT IS THE EVIDENCE?

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LEARNING OBJECTIVES

1. Determine the usefulness of vision-based testing for sideline assessment
 2. Calculate the published evidence that supports the role for rapid number naming as a vision-based sideline test
 3. Describe how meta-analysis techniques are helpful in combining study results and strengthening the evidence base
 4. Determine reasons why performance measures, such as rapid number naming, timed tandem gait, and brief cognitive tests can capture more concussions on the sidelines than traditional neurological examinations
3. The advantages of a meta-analysis to examine current evidence for sideline or other diagnostic tests include all *except*?
 - a. Ability to combine data and calculate a weighted average score
 - b. Capacity to determine the degree of heterogeneity across published studies
 - c. Opportunity to review the available literature using systematic methods
 - d. Potential for publication bias of studies with positive results

KEYWORDS

1. Concussion
2. Vision
3. Sideline Testing
4. Rapid Number Naming (King-Devick Test)
5. Meta-analysis

CME QUESTIONS

1. The currently used sideline testing battery, SCAT3, does not include which of the following testing areas?
 - a. Balance
 - b. Cognition
 - c. Vision
 - d. Symptom checklist
2. Which of the following is *false*?
 - a. Vision based testing of rapid number naming can detect 100% of concussions on the sidelines
 - b. A composite of balance, cognition and vision testing has the greatest ability to identify concussed athletes
 - c. Based on the meta-analysis, the average time for an athlete to complete the King-Devick test is about 40 seconds
 - d. Published studies show that King-Devick test time worsening is associated with a 5x greater risk of concussion

INTRODUCTION

Concussion is defined as a complex pathophysiological process affecting the brain from an impulsive force transmitted to the head or from a direct blow to the head, face, neck or elsewhere on the body that results in a new neurological sign or symptom.¹ Increasing public awareness of the incidence of concussion, estimated at 4 million per year, and the possible long-term consequences on brain function are becoming a growing concern for participants in contact and collision sports.² The development of a range of sideline screening tests has occurred in response to the concussion epidemic. The visual system is important in the diagnosis of concussion, particularly since ~50% of the brain's pathways are dedicated to vision. The efferent visual pathways are particularly vulnerable to injury in the acute setting of concussion^{34,43-46} and may be assessed through visual performance measures such as rapid number naming tasks. The King-Devick (K-D) test is a 2-minute rapid number naming assessment in which an individual reads numbers aloud quickly from test cards or a computer-based application. The K-D test requires eye movements (saccades, convergence and accommodation), attention and language function. These tasks involve the integration of

functions of the brainstem, cerebellum, and cerebral cortex. In the setting of concussion, the K-D test has been studied across several cohorts and throughout a variety of contact sports, including boxers and mixed martial arts (MMA) fighters, collegiate athletes in contact sports, amateur rugby players, elite professional hockey players, high school level football and youth contact sport athletes.^{29,30,47-56} The purpose of this talk is to present results of a meta-analysis and systematic review of all studies of the K-D and other rapid sideline tests of balance and cognition test across athletic event types. We will also summarize the literature examining the K-D test as a rapid sideline tool to aid in the detection of concussion.

WHAT IS THE EVIDENCE, AND WHY DO WE NEED A META-ANALYSIS OF SIDELINE TESTING DATA?

During concussion, linear and rotational accelerations of the brain occur relative to the skull producing pressure and shear forces throughout the brain tissue.⁶ This may lead to tissue damage and diffuse axonal stretching, and in turn, lead to diffuse axonal injury (DAI), which can cause disruption of cortical and subcortical pathways producing neurobehavioral dysfunction.^{6,7} Exposure to repetitive concussion or sub-concussive impacts is now recognized as having possible long-term neurological consequences, including neurodegenerative disease.^{2,8-10} The general lack of radiological signs after concussion on conventional MRI and CT have often left medical professionals to rely primarily upon clinical signs and symptoms to diagnose concussion.¹¹⁻¹⁶ In the acute or sideline setting, there is a need for testing that can be quickly administered to help confirm the diagnosis of concussion—or more importantly, given the simple clinical definition, to force critical thinking regarding a potentially meaningful neurologic event.

The development of a range of sideline screening tests has occurred in response to the concussion epidemic. Sideline tools such as the Sports Concussion Assessment Tool, 3rd Edition (SCAT3) include a Symptom Checklist and the Standardized Assessment of Concussion (SAC). The SAC is a cognitive component of SCAT3 that has also been incorporated into the Military Acute Concussion Evaluation (MACE). To test balance, the SCAT3 includes a modified version of the Balance Error Scoring System (BESS),¹ while the Child-SCAT3 relies upon the more recently developed timed tandem gait test. While both balance and neuro-psychological testing have been shown to be

effective in the assessment of concussion, there remain opportunities for improving the ability to consistently capture all concussive events quickly.¹⁷⁻²¹ Balance function can be affected by fatigue²¹⁻²³ and previous injury.^{18,24} The SAC has largely been validated using earlier concussion definitions, which required alteration of mental status, loss of consciousness, or post-traumatic amnesia.^{25,26} As such, the reported sensitivities of these measures may have been greater than those that could result when applied using more broad definitions of concussion. Furthermore, since concussive symptoms often go unreported at the high school or collegiate levels, there is a need for sensitive and quantitative concussion tests that can be used to support clinical or lay-witness suspicion of an event.^{27,28} Recent work has demonstrated that the addition of a rapid, simple vision-based performance test to cognitive and balance-based sideline tests enhances the ability to detect concussions at youth and collegiate levels of play.^{29,30}

The visual system is important in the diagnosis of concussion for a number of reasons (**Figure 1**,³¹⁻³³). These pathways travel from the eyes to the visual cortex with extensive connections made with countless areas in the frontal, parietal and temporal lobes. Cortical areas engaged in saccadic function include the frontal eye fields, dorsolateral prefrontal cortex (DLPFC), supplementary motor area, posterior parietal cortex, middle temporal area and striate cortex.³⁴⁻⁴⁰ These areas are responsible for the planning, initiation and execution of coordinated saccades such as those needed for reading and rapid number naming.^{36,41} The DLPFC also plays a crucial role in the control of saccades through the suppression of unwanted eye movements (antisaccades).^{37,40,42} Other subcortical structures involved in eye movements include the thalamus, superior colliculus, cerebellum and other structures within the brainstem.⁴¹ The interdependency of the neural activity between these areas illustrates the importance of their functional integrity for proper eye movement function. Additionally, these complex circuits involve cognitive processing such as memory, attention, and language function.³⁵ Pathology at any of these various levels in a functional pathway will result in errors of performance.³⁵ Given that the network of visual and eye movement pathways is widely distributed throughout the brain, saccade testing is well suited to examine the neurophysiologic effects of concussion.

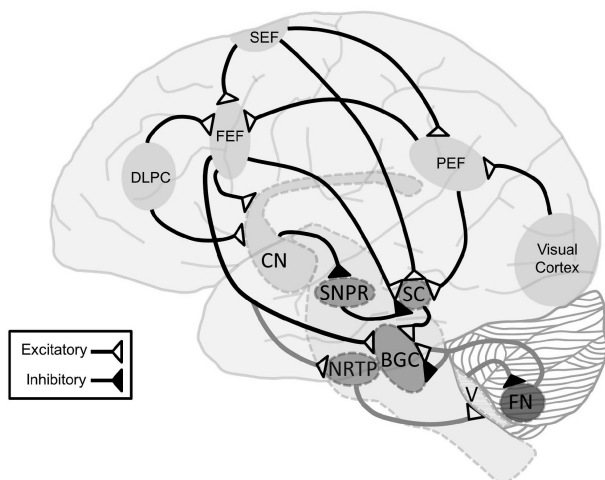


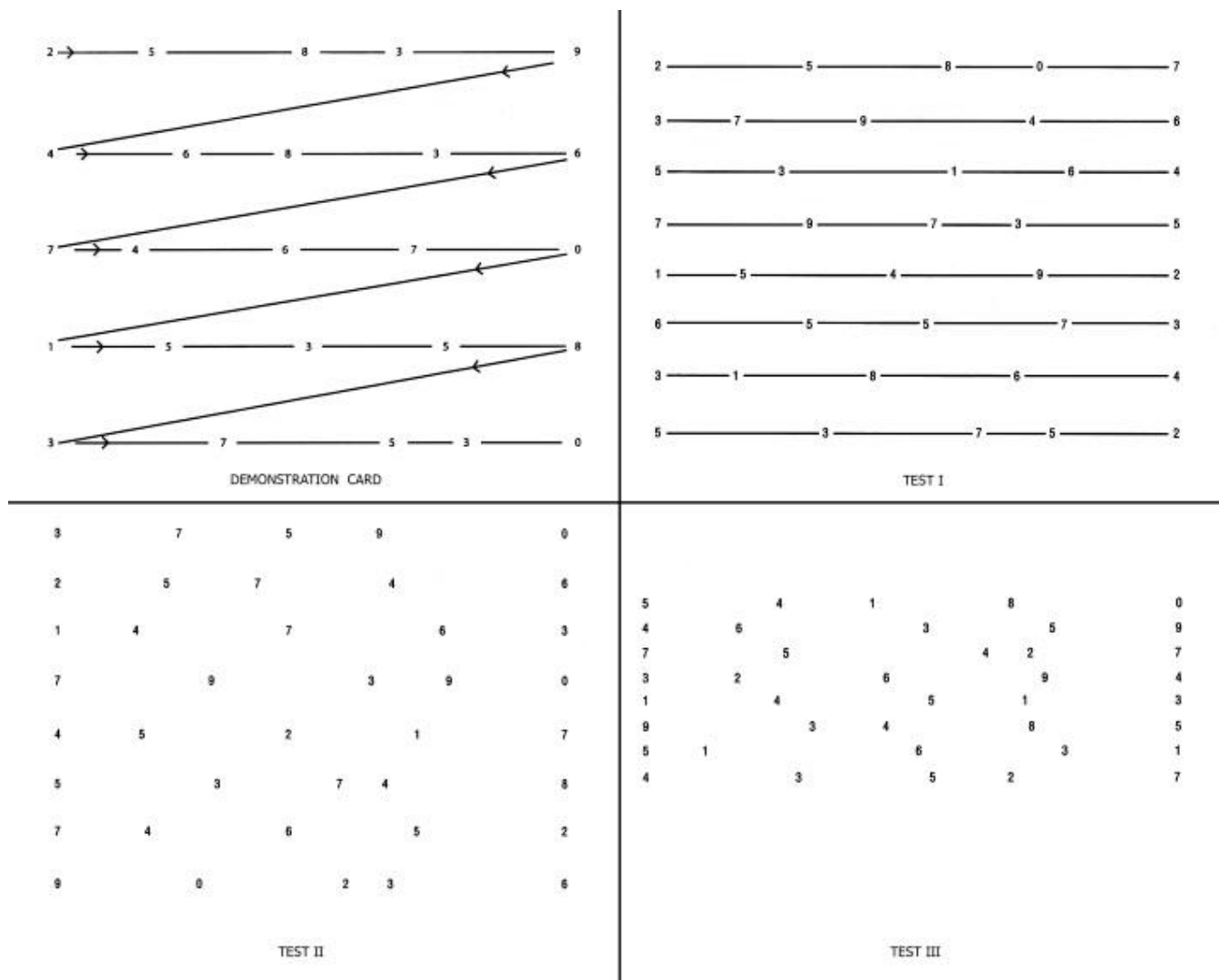
Figure 1. Major cortical areas involved in control of eye movements and visual processing, with projections illustrating saccade generation in black. Saccades are initiated by signals sent from the frontal, parietal, or supplementary eye fields (FEF, PEF, SEF) to the superior colliculus (SC), which then projects to the brainstem gaze centers (BGC). In parallel, the FEF also initiates saccades via direct connections to the BGC. In the indirect pathway, the substantia nigra pars reticulata (SNPR) inhibits the SC, preventing saccade generation. To turn off this inhibition, the frontal eye fields are activated prior to a saccade which then inhibits the SNPR via the caudate (CN). The saccade pathways are a multi-distributed network, but the FEF primarily generates voluntary or memory guided saccades, the PEF—reflexive saccades, the SEF—saccades in coordination with body movements as well as successive saccades, and the dorsolateral prefrontal cortex (DLPC)—antisaccades, the inhibition of reflexive saccades and the advanced planning of saccades. Cerebellar projections (shown in blue) fine-tune the saccades, given that cerebellar lesions can lead to saccadic dysmetria. The nucleus reticularis tegmenti pontis (NRTP) receives projections from the FEF and the superior colliculus (projection not shown) and in turn projects to the cerebellar ocular vermis (V). The vermis inhibits the ipsilateral caudal fastigial nucleus (FN) which then projects to the BGC to enhance saccades moving to the contralateral side and tamp down saccades moving to the ipsilateral side, likely via both inhibitory and excitatory connections.^{33,70,71}

The efferent visual pathways are particularly vulnerable to injury in the acute setting of concussion^{34,43-46} and may be assessed through visual performance measures such as rapid number naming tasks. The K-D test is a 2-minute rapid number naming assessment in which an individual reads numbers aloud quickly from test cards or a computer-based application (**Figure 2**). The K-D test requires eye movements (saccades, convergence and accommodation), attention and language function. These tasks involve the integration of functions of the brainstem, cerebellum, and cerebral cortex. Performance on the K-D test has been shown to correlate with suboptimal brain function in concussion,^{29,30,47-56} Parkinson's disease,⁵⁷ multiple sclerosis (MS),⁵⁸ amyotrophic lateral sclerosis (ALS),⁵⁹ sleep deprivation,⁶⁰ and hypoxia.^{61,62} Patients with Parkinson's disease and those with ALS have been found to have slower (worse) K-D times than healthy controls.^{57,59} In one study of astronaut trainees with experimentally induced hypoxia, mean K-D times were found to be 54.5 seconds compared with 46.3 seconds for controls ($p=0.02$).⁶¹ Investigation of the K-D test in an MS cohort showed K-D scores that were significantly worse than disease-free controls, accounting for age ($p<0.001$). Also in the MS study, higher (worse) K-D times were associated with worse vision-specific quality of life among MS patients as measured by the 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25, $p=0.001$) and correlated with measures of MS disability in MS including the timed 25-foot walk ($p<0.001$).⁵⁸ In a study of neurology residents, those taking call with an average of two hours' sleep had smaller magnitudes of learning effect from a pre-call baseline compared to participants who did not take call over a 24-hour period ($p<0.0001$, Wilcoxon rank sum test).⁶⁰

In the setting of concussion, the K-D test has been studied across several cohorts and throughout a variety of contact sports, including boxers and mixed martial arts (MMA) fighters, collegiate athletes in contact sports, amateur rugby players, elite professional hockey players, high school level football and youth contact sport athletes.^{29,30,47-56} The purpose of this investigation was to perform a meta-analysis and systematic review of all studies of the K-D test across athletic event types, and to summarize the literature examining the K-D test as a rapid sideline tool to aid in the detection of concussion.

Figure 2. Demonstration and test cards for the King-Devick (K-D) test, a candidate rapid sideline screening for concussion based on speed of rapid number naming. To perform the K-D test, participants are asked to read the numbers on each card from left to right as quickly as possible but without making any errors. Following completion of the demonstration card (upper left), subjects are then asked to read each of the 3 test cards in the same

manner. The times required to complete each card are recorded in seconds using a stopwatch. The sum of the 3 test card time scores constitutes the summary score for the entire test, the K-D time score. Numbers of errors made in reading the test cards are also recorded; misspeaks on numbers are recorded as errors only if the subject does not immediately correct the mistake before going on to the next number.



HOW IS A META-ANALYSIS PERFORMED?

Following generally accepted methodologic recommendations, these pooled and meta-analyses were performed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement.⁶³ This checklist contains specifications for the selection and review of studies for inclusion in the meta-analysis.

SEARCH STRATEGY

The systematic literature search was begun in January 2015 and concluded in April 2015. Two independent investigators searched for relevant articles. Each investigator searched PubMed and MEDLINE using specific

key search terms including: “King Devick,” “concussion,” “sideline concussion test,” and “concussion assessment.” Additional studies were identified by checking reference lists of the retrieved studies, searching clinical trial registries, and contacting clinical experts. PubMed searches yielded 31 results and MEDLINE revealed 5 articles. After screening for duplicates there were 31 manuscripts. Articles must have included the K-D test as a baseline or post-injury measure for detecting concussion, and have been accepted for publication in a peer-reviewed journal. Abstracts were screened for those studies that met criteria, and this left 17 articles eligible for consideration of inclusion in the meta-analysis. Two published studies were

excluded because investigations were ongoing, prohibiting analyses as part of the present study. Thus, there were 15 studies (14 published texts and one article accepted for publication) included in these pooled and meta-analyses.

STUDY SELECTION

All English language published studies including data and examining the use of the K-D test for concussion from 2010 to present were included in these analyses. Publications were included if they met the following criteria:

1. The study participants were athletes
2. De-identified, participant-specific data were available for pooled analyses
3. The study examined the K-D test in the setting of sports-related concussion with baseline measurements (testing time from injury was available)
4. The study defined concussion by the standard definition of a witnessed or reported blow to the head or body followed by new neurological signs or symptoms
5. Concussions, when captured by the study, occurred within the context of a sporting event

Eligibility assessments were performed independently by two reviewers. Disagreements regarding study inclusion were discussed between the reviewers; it was planned that any further disagreements would be mediated by a third investigator. Participant-specific data, with all potential identifiers removed, were obtained for analyses that were performed at the NYU School of Medicine. Any questions regarding potential for duplicate publication of specific data were clarified with the authors of each study.

DATA ITEMS & COLLECTION

Data were pooled into a single dataset with a variable representing an identification number for each study. Variables retained in the pooled dataset included: 1) non-identifying characteristics of participants; 2) pre-season or pre-match baseline K-D test scores, in seconds; 3) other baseline concussion test scores (not available for all participants), including components of the Sport Concussion Assessment Tool (SCAT, 2nd and 3rd editions); 4) post-injury K-D test scores following concussion (not available for all participants) and for non-concussed control athletes of similar age, gender and sport; 5) K-D test scores following vigorous workout or match play in the absence of concussion (fatigue trial testing, not available for all participants); and 6) post-season K-D test scores (not available for all participants).

ASSESSMENT OF BIAS

Two reviewers worked independently to determine the validity of studies included in these analyses with regard to data collectors and outcome assessors. Some studies whose data were included were designed and executed by authors of the present study. Different study designs

were represented; for example, some studies included non-concussed control athletes who underwent K-D testing in parallel with concussed athletes for comparison of performance. The definitions of concussion and control athlete were consistent throughout the studies represented in the pooled dataset. Assessments and K-D testing were performed in all studies at the time of first recognition of a concussive event or symptoms.

There are other potential risks of bias inherent to pooled- and meta-analyses in general. Language bias was not a particular risk for our study since all published data and manuscripts were in English. Availability bias was avoided through the use of a variety of techniques to obtain articles (see Search strategy). All studies were included regardless of the direction and statistical significance of results comparing concussed vs. non-concussed control athletes.

DATA ANALYSES

The primary objectives of these pooled and meta-analyses included the following:

1. To calculate pooled and weighted estimates and measures of precision (means and 95% confidence intervals) for pre-season/ pre-match baseline K-D test scores across the 15 studies;
2. To calculate pooled and weighted estimates and measures of precision (mean and 95% confidence intervals) for changes in K-D score from baseline at the time of post-injury recognition of concussion among those studies with post-concussion data included in the pooled dataset;
3. To perform similar analyses to #2 above for non-concussed control athletes among studies with control data included in the pooled dataset;
4. To estimate sensitivity and specificity of K-D test score worsening (defined as any increase in time score from baseline) for identifying concussed vs. non-concussed control athletes using pooled analysis techniques;
5. To calculate the weighted relative risk of an athlete being concussed vs. a non-concussed control in the setting of K-D score worsening from pre-season/ pre-match baseline using meta-analysis with fixed effects models.

Stata 13.1 (StataCorp, College Station, TX) software was used to perform all statistical analyses and calculations. Data for 15 studies with de-identified participant-specific values were analyzed. Pooled analyses estimated pre-season baseline K-D scores, participant age, and sensitivity/specificity for K-D to identify concussed vs. control athletes on the sidelines (athletes who were playing the game but did not have concussion). Fixed-effects models were used for meta-analysis to calculate weighted estimates in objectives 1-3 and 5. Heterogeneity across studies in the meta-analysis was evaluated using the I^2 (I-squared) statistic. I^2 is the percentage of variation in a pooled

dataset that is attributable to heterogeneity between studies (systematic differences). A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. While there is no absolute rule for when heterogeneity becomes important, authorities in the field⁶⁴ have suggested categories of low heterogeneity for I^2 values between 25-50%, moderate for 50-75%, and high for 75% or greater. Thus, in the case of the I^2 statistic, low percentages and high p -values are the desired result.

Areas under the Receiver Operating Characteristic (ROC) curves generated from logistic regression models were estimated from the pooled dataset to examine the capacity for K-D scores to distinguish concussed vs. non-concussed control athletes based on changes from pre-season or pre-match baseline. The area under the ROC represents the discriminatory ability of a continuous test score to correctly classify any two individuals in a study with and without the disease (in this case, concussed vs. non-concussed). These areas range from 0.50 (indicating no better ability to distinguish than the flip of a fair coin) to 1.0 (perfect ability to distinguish).

WHAT ARE THE DATA SUPPORTING VISION-BASED SIDELINE TESTING?

Pre-season baseline K-D scores from 1,419 youth, collegiate, amateur and professional athletes were analyzed from among the 15 studies included in the pooled dataset. Study-specific characteristics of the athletes are presented in **Table 1**. Mean age from pooled analyses of the overall athlete cohort (all studies combined without weighting) was 18.3 years (95% CI: 18.0, 18.7), range 5-63. The weighted estimate of age from the meta-analysis was 14.8 years (95% CI: 14.1, 15.4). Pooled analysis mean pre-season baseline K-D scores were 44.5 seconds (95% CI: 43.8, 45.2), with a weighted estimate of 43.8 seconds (95% CI: 40.2, 47.5). I^2 (I-squared) values were 0.0%, $p=0.85$, indicating very little heterogeneity between studies in calculation of the weighted estimate (**Figure 3**). Stated differently, the non-significance of the I^2 test for heterogeneity suggests that the differences between the studies are explicable by random variation.

Among 112 athletes with concussion in the dataset, weighted estimates for post-injury changes in K-D score from pre-season or pre-match baseline showed a worsening (increased time) of 4.8 seconds (95% CI: 3.7, 5.8; $I^2 = 0.0\%$, $p=0.58$ —large p -value indicating very little heterogeneity and good consistency between

studies); non-concussed control athletes demonstrated an *improvement* of 1.9 seconds (95% CI: -3.6, -0.02; $I^2 = 0.0\%$, $p=0.99$). Pooled analysis values for sensitivity of the K-D test for detecting concussion on the sidelines were 86% (96/112 concussed athletes had any worsening of K-D time score from baseline, 95% CI: 78%, 92%); specificity was 90% (181/202 non-concussed control athletes had no worsening of K-D from baseline, 95% CI: 85%, 93%). Relative risk from meta-analysis of these proportions across studies was 4.92 (95% CI 3.07, 7.89; $I^2 = 0.0\%$, $p=0.87$), indicating an approximately 5 times greater likelihood of a participant being a concussed vs. a control athlete if their K-D score worsened from pre-season or pre-match baseline. Increasing age was significantly associated with decreasing K-D time scores in linear regression models for the pooled dataset.

Similar to recently published studies reporting times for the three K-D test cards, baseline scores for each card were lower (faster) with increasing age in this cohort of predominantly young athletes ($p<0.001$, linear regression models). This age effect was particularly evident for K-D test card 3, which has the greatest degree of vertical crowding of the numbers (**Figure 2**; $p<0.001$ for magnitude of correlation of score with age for test card 3 vs. card 1). Furthermore, total time scores improve (are faster) overall with age among youth (age 18 and younger), then appear stable with perhaps some increase by the end of the fourth decade.

Using the pooled dataset, the capacity for K-D scores to distinguish the concussed ($n=112$) vs. non-concussed control athletes ($n=202$) based on changes from pre-season or pre-match baseline were examined using areas under ROC curves generated from logistic regression models. The ROC area was 0.90 (95% CI: 0.85, 0.96), indicating an approximately 90% chance of correctly distinguishing concussed vs. control athlete status on the basis of change in K-D score from baseline alone. Accounting simultaneously for age, these same models yielded an ROC curve area of 0.89 (95% CI: 0.82, 0.96; $n=239$ total participants with age recorded). Among participants who underwent testing with the Standardized Assessment of Concussion (SAC) and timed tandem gait components of SCAT in addition to K-D ($n=69$), ROC areas, from models accounting for age, were 0.89 for KD (95% CI: 0.82, 0.96), 0.81 for timed tandem gait (95% CI: 0.69, 0.92) and 0.66 for SAC (95% CI: 0.53, 0.79). These differences in ROC curves were significant ($p=0.002$ by linear combination methods).

Table 1. Study characteristics and baseline rapid number naming (K-D) scores.

Study ID and Reference	N	Age at Pre-Season Baseline, years (95% CI)	K-D Test Pre-Season Baseline Score, seconds (95% CI)	Gender	Level of Play	Sport
1. Galetta KM et al., 2015 ²⁹	312	13.3 (12.8, 13.8)	54.2 (51.8, 56.6)	M/F	Youth/College	Hockey, Lacrosse
2. Galetta KM et al., 2011b ⁴⁸	217	20.3 (20.1, 20.5)	38.5 (37.7, 39.3)	M/F	College	Football, Basketball
3. Marinides et al., 2014 ³⁰	220		38.7 (37.8, 39.6)	M/F	College	Football, Lacrosse, Soccer
4. Galetta MS et al., 2013 ⁵⁰	69	24.5 (23.2, 25.8)	42.5 (41.0, 43.9)	M	Professional	Hockey
5. Munce et al., 2014a ⁷²	15	13.3 (12.9, 13.6)	49.6 (45.7, 53.4)	M	Youth	Football
6. Leong et al., 2015 ⁵³	152	19.6 (19.4, 19.8)	36.3 (35.4, 37.3)	M/F	College	Football, Basketball
7. Leong et al., 2014 ⁵²	34	25.8 (22.9, 28.6)	41.0 (38.1, 43.9)	M/F	Amateur	Boxing
8. Galetta KM et al., 2011a ⁴⁷	42	27.2 (24.2, 30.1)	43.3 (41.3, 45.3)	M	Amateur	Boxing
9. Dhawan et al., 2014 ⁵⁴	140	15.5 (15.3, 15.7)	44.5 (43.5, 45.4)	M	Youth	Hockey
10. King et al., 2015a ⁵⁶	68	24.5 (23.4, 25.7)	46.9 (44.8, 48.9)	M	Amateur	Rugby
11. Duenas et al., 2014 ⁵⁵	12	16.5 (15.8, 17.2)	43.0 (38.3, 47.6)	M	Youth	Football
12. Munce et al., 2014b ⁷³	22	12.8 (12.5, 13.0)	52.1 (45.3, 58.9)	M	Youth	Football
13. King et al., 2015b ⁷⁴	19		62.0 (57.2, 66.7)	M/F	Youth	Rugby
14. King et al., 2013 ⁴⁹	36	23.5 (22.1, 24.8)	49.5 (45.8, 53.2)	M	Amateur	Rugby
15. King et al., 2012 ⁵¹	61	19.3 (18.3, 20.3)	48.4 (46.7, 50.0)	M	Amateur	Rugby

K-D: King-Devick; M: male; F: female; N: number of athletes

Using the criteria of any worsening of score from baseline for K-D, and published criteria of 2-point worsening for SAC and any worsening for timed tandem gait score, the K-D worsened from baseline in 85% of concussed athletes in the pooled dataset. SAC worsened in 48% and tandem worsened in 75%; worsening of either SAC or timed tandem was observed in 89%. Importantly, however, worsening of at least one of the three tests was observed in 100% of concussed athletes, supporting the capacity for a composite of tests to capture concussions to a greater degree than tests of a single neurologic dimension.

Similar to many performance measures, the K-D test demonstrated a mild learning effect when administered over two trials at the pre-season baseline. For participants with two K-D baseline trials ($n=1,048$), the pooled analysis mean for the first trial was 49.5 seconds (95% CI: 48.6, 50.4); the second trial had a slightly faster time score 46.7 seconds (95% CI: 45.8, 47.6, $p<0.0001$, paired t-test). This translates into a learning effect of 2.8 seconds *improvement* on average between the two baseline trials (95% CI: -3.1,

-2.1) in analyses of the pooled dataset. In the meta-analysis, the weighted mean improvement was 1.8 seconds (95% CI: -3.4, -0.1, $I^2 = 0.0\%$, $p=0.98$). Despite the inherent and expected learning effects for the K-D in the absence of concussion, test-retest reliability was very high between the two baseline trials, with intraclass correlation coefficient values $ICC = 0.92$ (95% CI: 0.91, 0.94). This indicates that 92% of the variability in the dataset is between-participants, rather than between the two K-D baseline trials from the same participants.

K-D scores also *improved* following vigorous exercise in the absence of concussion. On average in the pooled dataset, K-D scores were 1.4 seconds better (95% CI: -2.1, -0.8) than the pre-season baseline among 92 participants who underwent testing immediately following active competition or vigorous exercise. The weighted estimate from the three studies with post-exercise data was similar, showing an improvement of 1.2 seconds (95% CI: -4.3, 1.8, $I^2 = 0.0\%$, $p=0.52$). Test-retest reliability in this setting was likewise high, with $ICC = 0.91$ (95% CI: 0.85, 0.97).

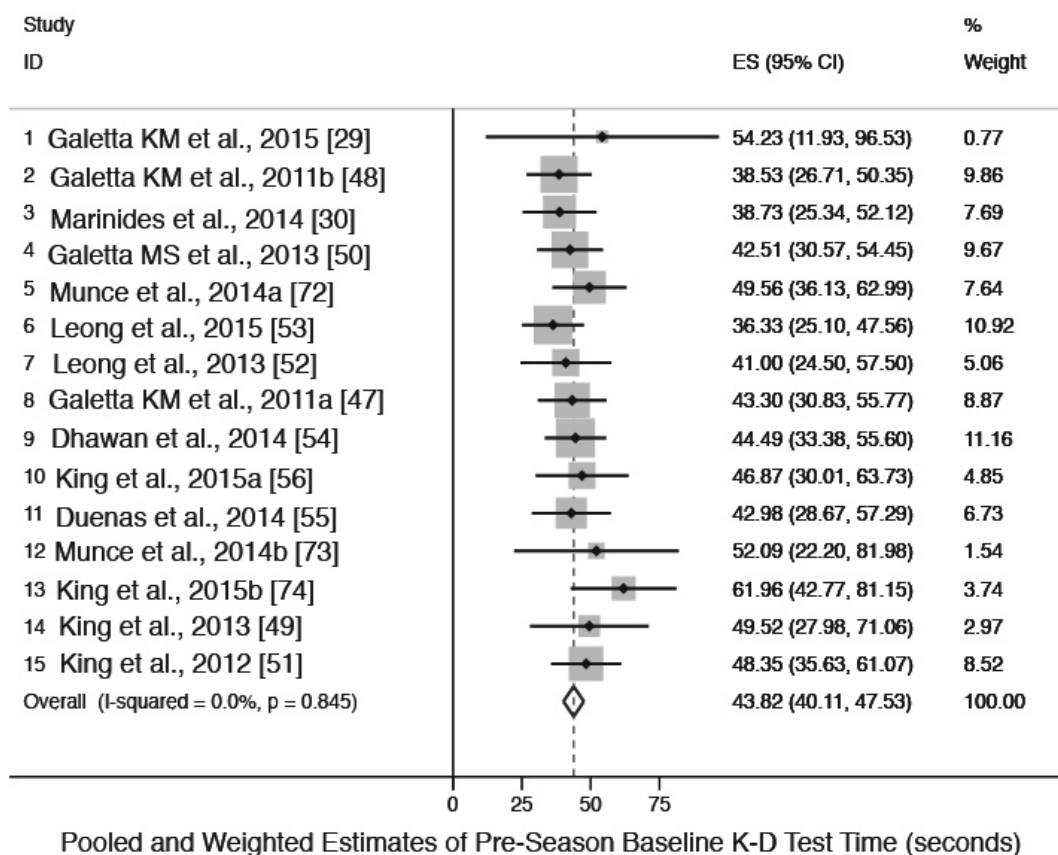


Figure 3. Distribution of pre-season baseline time scores for the King-Devick (K-D) test. Dots represent point estimates of each study mean (or effect size, ES); sizes of the gray boxes reflect the weights of the studies in the meta-analysis. Bars are 95% confidence intervals (CI). The diamond shows the weighted estimate for the mean pre-season K-D baseline score; this is determined from fixed-effects models account for study N and precision (narrowness of 95% CI). I^2 (I-squared) statistic values were 0.0%, $p=0.85$, indicating very little heterogeneity between studies in calculation of the weighted estimate. Stated differently, the non-significance of the I^2 test for heterogeneity suggests that the differences between the studies are explicable by random variation.

SO, WHAT IS THE EVIDENCE?

Rapid number naming (K-D test), a timed vision-based measure that requires the integration of eye movements and number identification demonstrates high sensitivity and specificity in distinguishing concussed athletes from controls. The test has been investigated across a variety of contact sports, including boxing and mixed martial arts (MMA), collegiate athletics, amateur rugby, professional hockey, high school level football, and youth sports.^{29,30,47-56} Collectively, these studies and the meta-analyses reported herein demonstrate that worsening of K-D scores from a pre-season or pre-match baseline is an accurate and sensitive indicator of concussion and emphasizes the importance of comparison to an individualized baseline, not normative data. In these meta-analyses, concussed athletes showed a mean worsening from baseline of 4.8 seconds (95% CI: 3.7, 5.8; $I^2 = 0.0\%$, $p=0.58$ —large p -value indicating very little heterogeneity and good consistency between studies) while non-concussed control athletes demonstrated an *improvement* of 1.9 seconds (95% CI: -3.6, -0.02; $I^2 = 0.0\%$, $p=0.99$). These weighted means, derived from multiple independent investigations, are perhaps most illustrative of the concept that any worsening of K-D score from baseline is suggestive that a meaningful neurological event has occurred.

Test-retest reliability of K-D has been investigated in multiple studies. High levels of reliability have been reported in the absence of concussion with ICC's ranging from 0.95 (95% CI: 0.87, 1.0) to 0.97 (95% CI: 0.90, 1.0) in studies of boxers and MMA fighters.⁴⁷ ICC values of 0.95 (95% CI: 0.85, 1.1) were noted among collegiate athletes.⁵² In a study examining how well sports parents could reliably administer the K-D test in boxers, equally high levels of test-retest metrics were observed (ICC = 0.90, 95% CI: 0.84, 0.97).⁵²

Collectively, these ICC values demonstrate that both medical personnel and laypersons may administer the K-D test with high degrees of reliability. Our current meta-analysis similarly demonstrated high test-retest reliability in the absence of head trauma (ICC = 0.92 [95% CI: 0.91, 0.94]). The use of the K-D test in combination with other sideline tests has been investigated. Marinides et al.,³⁰ showed that among 30 athletes with concussion, worse scores on the K-D occurred in 79%, while worsening of the SAC by 2 points was noted in 52% of concussed athletes. When the K-D and SAC were combined, their ability to detect concussion was increased to 89%, and increased to 100% when the BESS was added. In 2015, a study of the K-D test in ice hockey and lacrosse athletes at the youth and collegiate levels examined the SAC, timed tandem gait, and K-D test on the sidelines and rink-side for concussed athletes as well as non-concussed controls under the same testing conditions. Among athletes who sustained concussion ($n=12$), K-D scores worsened from baseline by an average of 5.2 seconds. In contrast, non-concussed control athletes improved on average by 6.4 seconds. In

comparing the SAC, timed tandem gait, and K-D test with regard to capacity to distinguish concussed athletes vs. non-concussed controls (based on changes from pre-season baseline to post-injury), ROC curve areas were 0.92 for K-D, 0.87 for timed tandem gait, and 0.68 for SAC ($p= 0.0004$ for comparison of ROC curve areas from logistic regression models, accounting for athlete age).²⁹

The association of age on K-D time score was also explored in a recent study²⁹ in which scores decreased (improved) with advancing age among youth athletes. In particular, the youngest athletes within the 5 to 18 year old range had significantly slower K-D times ($p<0.001$) and demonstrated, as in our cohort, the greatest improvements in score occur from ages 5 to approximately 18 years. These differences in time could potentially be explained by the brain development of youth athletes; diffusion tensor imaging MRI studies show that both white matter and grey matter changes continue in the frontal lobes throughout childhood and eye movement tasks required to perform the K-D test involve frontal eye field circuits.⁶⁵ Published literature demonstrates that saccade performance improves with development during childhood and that this is largely due to shortening of saccade reaction times, or latency. Not simply brainstem mediated (brainstem execution of saccades is stable throughout childhood), this phenomenon has been shown by functional MRI to be directly related to stronger activation in cortical eye fields, which enhances saccade preparation.^{66,67} The K-D may well be capturing these developmental changes. The increased vertical crowding that characterizes the number stimuli of K-D test card 3 may also contribute to the slower time scores among younger children. In this meta-analysis, age was also significantly associated with K-D times. Taken together, these findings support the need to perform K-D pre-season baselines at least annually, if not every playing season, among young athletes.

The Developmental Eye Movements (DEM) test, which involves a very similar paradigm to the K-D test and involves vertical saccades, has also been studied as a diagnostic tool,⁶⁸ but its use in concussion assessment has been limited. A number of new metrics and automated portable devices that can detect eye movements and other visual abnormalities have also been developed.⁶⁹ These tools can be used in conjunction with helmet mounting or with telemedicine to enable sideline detection of signs of concussion on the sidelines.

Effects of the testing environment on K-D test scores have been investigated in different studies. One important question is the potential for vigorous exercise to affect performance on the K-D test. As captured in these pooled and meta-analyses, data have demonstrated that competition alone does not worsen K-D scores from baseline, but is, rather, associated with the same mild learning effects that are observed in studies of test-retest reliability. In the absence of concussion, the present study as well as published investigations showed an average

improvement of 1.4 seconds in the setting of vigorous exercise.^{48,49,53} Other environmental factors, such as noise in the testing area, have also been examined. In a small pilot study in which participants (n=9) completed the K-D test in a quiet environment and within two loud environments (with speakers and headphones), no significant difference in K-D scores was found between the testing conditions. Further, baseline testing of athletes in some of the studies⁴⁸ occurred in a busy training room environment. Improvement in K-D times among non-concussed control athletes within the noisy game setting also suggests that K-D performance is relatively resistant to test conditions.

Construct validity of the K-D test as an instrument to capture meaningful neurologic events such as concussion has been explored with formal computerized eye movement recordings of individuals with hypoxia-induced impairment. In these studies, worsening of K-D performance was associated with changes in quantitative eye movement metrics.^{61,62} Furthermore, performance on other cognitive measures such as the SAC and a similar tool called the Military Acute Concussion Evaluation (MACE) has correlated with K-D test outcomes both at baseline and post-injury.^{29,30,47,48,50} These associations are likely due to shared anatomical aspects engaged in the execution of eye movements required for both the K-D and the SAC/MACE, such as predictive saccades and immediate memory. The dorsolateral prefrontal cortex (DLPFC), for example, is one such structure that is also vulnerable to injury in concussion (**Figure 1**). To the extent that the SCAT3 does not assess vision and eye movements, and that K-D test scores are better among those with higher scores on the SAC and MACE, these findings likely explain why the K-D complements cognitive sideline testing.³⁰ In these studies of collegiate level athletes, 10% of concussed athletes failed to show significant changes on SAC and BESS. Addition of the K-D test, however, captured all of the concussions. Similar findings were noted in the pooled dataset of the present study.

Future studies of the K-D test will include examining the underlying mechanisms and nature of eye movements during the rapid number naming task through quantitative electronic eye movement recordings. Evaluation of the capacity of KD to capture functional improvement during longitudinal recovery following concussion will be important, and will increase our understanding of the timing of visual pathway recovery over time.

CONCLUSIONS

This meta-analysis demonstrates that pre-season baseline scores are consistent across published studies, with high degrees of precision and little heterogeneity by meta-analytic techniques. The K-D test detects concussion with high degrees of sensitivity and specificity, with any worsening of time score from baseline indicating a 5 times greater likelihood of concussion. Test-retest reliability

are high, and vigorous exercise alone is associated with mild learning effects rather than worsening of scores from pre-season baseline. Among youth, collegiate and adult amateur and professional athletes, rapid number naming using the K-D test adds significantly to sideline assessment and contributes a critical dimension of vision to sports-related concussion testing.

CME ANSWERS

1. c
2. a
3. d

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PERSPECTIVES OF A NEURO-OPHTHALMOLOGIST ON THE SIDELINE

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LEARNING OBJECTIVES

1. Describe how to successfully perform as a sideline neuro-ophthalmology for a division one football team
2. Describe how the environment on the field is quite different from a clinical examination room
3. Describe how to best assist fellow sports medicine experts with your neuro-ophthalmology knowledge in the care of student-athletes

CME QUESTIONS

1. Which of the following is true in determining if a student athlete has suffered a mTBI:
 - a. Television review and analysis is the very best way to diagnose mTBI.
 - b. Change in personality or cognitive ability is important to notice.
 - c. Pupil response is always invaluable.
 - d. Arm strength is typically reduced bilaterally.
2. Which of the following is important for successful performance as a sideline neuro-ophthalmologist:
 - a. Be inconspicuous.
 - b. Do not be a distraction.
 - c. Work carefully with the athletic trainers to assess personality or cognitive changes.
 - d. It is important to have complete neurologic examination equipment available on the field including reflex hammer, tuning fork, cotton, Maddox Rod and red filter.

3. Which of the following about student athletes is true:
 - a. They will always tell the truth regarding the severity of their head injury.
 - b. If a student athlete does not express an urgent desire to go back into the game that may imply there is something seriously wrong despite your exam.
 - c. Computer assisted neuro-psych testing (ImPACT) is the fastest way to return a player to the field during a game.
 - d. Never bother to examine a student athlete within a locker room situation to determine if they have had a mTBI as it is unduly artificial regarding their ability to compete.

KEYWORDS

1. mTBI
2. Sports Concussion
3. SCAT III
4. Athletic Trainers

INTRODUCTION

Sideline neuro-ophthalmology is quite different than an office practice. There are additional sports medicine skills that must also be mastered to be effective. These skills include being inconspicuous yet calm, quick and above all accurate when called upon. Student-athletes are a very different sort of patient than typically seen as they will do anything to remain in competition if at all possible including denial of the truth. Cognitive or personality changes can be one of the primary ways to make a diagnosis of a mTBI. Interaction with athletic trainers regarding a student-athlete's cognition and personality can help diagnosis. If it is unclear if a student-athlete has a mTBI after a SCAT III or a modified neurologic examination take them inside the locker room for a more controlled environment to do the examination. Although TV replay and a variety of equipment and technology can assist in determining if a student-athlete is at risk for a concussion, it does not make the diagnosis. All of this technology must be an extension of a properly done clinical examination.

There is limited literature about how to be a successful sideline Neuro-Ophthalmologist for a Division One College Football Team.¹⁻¹⁵ What I enclose are personal observations only. These are based on art as much as science.

There are three major ideas to impart:

1. Diagnosis may be challenging, especially if you are only watching on TV.
2. Be inconspicuous and do not be a distraction.
3. When called upon be calm, ready, quick and accurate.

FIRST

You can not accurately make the diagnosis of concussion, significant neck or spine injuries from T.V. (or from the stands) except in a minority of cases. Approximately 9% of student-athletes are rendered unconscious from a concussion. Those are of course obvious. The other 91% percent may be far more difficult to diagnose.¹⁻⁷ Student-athletes coming off the field “wobbly” may actually be short of breath, have a leg injury or similar issue. On the other hand student-athletes successfully running off the field may be concussed or even have a neck injury. It takes careful vigilance, knowledge of the player’s intellectual ability and personality, multiple people looking at each play and fellow teammates to assist in finding those student-athletes that need to be carefully evaluated. Spotters, trained in concussion, watching TV replays from the booth can also be a tremendous help.¹⁻⁸

SECOND

The role of the sideline Neuro-Ophthalmologist is to actually “do nothing” until it is time to do something. The worst thing a neuro-ophthalmologist can do is be a distraction. This can include getting a penalty, saying the wrong thing at the wrong time to an athlete, referee or speaking to sideline reporters about injury, etc. You have been placed in your position on the field to secure student-athlete safety not to schmooze with Magic Johnson, the university president, cheer leaders or the players. You are certainly not there to tell the referee they have retinitis pigmentosa, end stage glaucoma or pituitary apoplexy. If the head coach calls your name that is never good. If you do not answer when called you are done. Typically, the lead team physician, athletic trainer or both will quietly but quickly ask for your opinion. In the system at MSU I do not volunteer my opinion until asked unless it is obvious there could be a major issue. Then I provide it asked or not.

THIRD

When called upon you have to be available, ready to go, quick and accurate. Realizing this, I soon began to grow fond of field goal kickers. I noticed they have a similar ambition not get in the way, be ready to go when called on, perform successfully and then disappear again. As a sideline Neuro-Ophthalmologist, you want to be able to decide if someone clearly has NOT had a concussion, if possible, within 60 to 240 seconds. That is a key. If you are unsure within this first 240 seconds or you believe it is likely they have had a concussion, then take all the time you

wish to get it right.⁷ Go to the locker room, if needed, for a proper exam if it is still unclear. If still unsure, even after an in depth, quiet and complete neurologic and neuro-ophthalmologic examination, we have an unwritten rule to disqualify the player and reassess over the next hour or two. All such players are reexamined the next day also.⁷

Regarding Equipment

I use to carry all sorts of tools to the sidelines. This included a complete neurologic examination kit, dementia cards, ophthalmoscope, reflex hammer, tuning fork, cotton balls, e-card, red filters, Maddox Rod, pen light, etc. About three years ago I decided they were all simply an encumbrance. I really never used any such equipment to make a decision in the first 60-240 seconds. If I was unsure, the exam was done in the locker room where it was quiet and controlled.

Regarding Examination

We rely on a formal but rapid neurological examination rather than the SCAT III.^{1-8, 12} We also rely a lot on history of the event, the player’s memory and description of the blow along with cognitive, personality and memory changes. Arm and leg strength, coordination, tandem gait, balance and ocular motility are all quickly checked. We favor use of a rapid doll’s head maneuver both vertical and horizontal to see if symptoms like headache, nausea or the sensation of vertigo or light headedness are accentuated. The following day we also assess with computer assisted cognitive and neuro-psychology testing.⁹⁻¹²

Regarding the Environment

The sideline is absolutely nothing like an exam room. It is really crowded on the sidelines and it is quite loud. It is hard to communicate except if you are very close to the player. There is also a surprising variety of emotion on the sidelines both positive and negative, at times simultaneously. Fans attending the game will sadly also give their opinion about a player’s condition, what your diagnosis should be and review the conception and birthing practices of the injured player’s family. All this needs to be ignored of course while you do the exam. Rarely, especially at places like Kennick Stadium at the University of Iowa, certain fans will also provide you with an opinion of your parents’ origin of birth and engage in lively discussions regarding your family tree during such examinations. It is hard to be accurate and aloof to the environment when you are being heckled by fans approximately ten feet away while doing a neurologic examination. It is a unique experience.

Regarding Truth or Dare

A player will do anything to compete. Anything. They will bargain. They will exaggerate. They will look you in the eye, promise you they are absolutely fine but actually be telling you a lie so they can go back in the game. If an athlete does not express desire to go back into the game during the exam that is a sign there may well be something significantly wrong. I do my best to ignore a player when

they are sharing with me in a friendly but raised voice, “Doc, I am fine. I am good. I am ready to go”.⁷

Regarding Athletic Trainers

In my world they know far more than most neurologists about how to spot a concussed player coming off the field. This is because they spend all day during the week working with the student-athlete. Their job is to hunt down the injured. They are the first to notice cognitive or personality changes.¹⁻⁸ These changes are sometimes the only sign of a concussion despite a careful neurological and neuro-ophthalmologic examination until a formal computer assisted neuro-psychology examination is done.⁹⁻¹² I have gained tremendous respect for who athletic trainers are, their training and dedication. Well trained and veteran athletic trainers are difference makers on any team from my view of things.

Regarding Coaches

In my five years doing this at MSU, I have never had a coach question my judgment. Not once. I have had them thank me in many ways over and over. They have at times questioned my dress, my breath, my hair, but never my judgment. In observing coaches, I find them typically to be very good instructors especially regarding the transfer of manual skills. They are also superb motivators. Coaches are very focused on their players and their well being. Surprisingly so. They are, at the end of the day, almost uniformly terrific mentors and educators.

Regarding Emotion

It is difficult to be immune from the emotion of a player falling to their knees and crying because they have been disqualified from a game or from football for the year or longer based on an injury they just incurred. It remains essential that on the sideline you remain dispassionate regarding game outcome and focus only on player safety. That is a hard but an essential skill to acquire. It is also important to stay aloof to the pressure and excitement of the game and the environment no matter what the situation. That can also be surprisingly hard.

CONCLUSION

Although always interested in football and its pageantry, I never really imagined there was value added or significant purpose to a neurologist being on the sideline until I actually did this job the last five years at Michigan State University. I have observed and acted on enough practice and game time injuries involving the head and neck to now realize there is indeed an important role for neurologists.¹²⁻¹⁵ A team physician must be riveted on player safety.¹⁴ In a few instances, especially when diagnosing occult concussion or neck trauma a neurologist's presence can become very important.¹²⁻¹⁵ Accurately, but dispassionately, determining a player can continue to compete safely,¹⁴ even after absorbing what appeared to be a significant blow, can be a rewarding experience.

However, sideline Neurology/Neuro-Ophthalmology is not for everyone. Mistakes, even during highly contested, hard fought games in front of 100,000 people are not tolerable at any level. I have also realized football as a sport, despite its inherent dangers, is not going away. The key is to make it as safe as possible. Sideline Neurology and Neuro-Ophthalmology is assisting in this regard.

CME ANSWERS

1. b
2. a, b, c
3. b

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BRINGING TECHNOLOGY TO THE SIDELINE: NEW DATA FROM THE PUPIL AND OPTICAL COHERENCE TOMOGRAPHY (OCT)

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LEARNING OBJECTIVES

1. Describe what is the Neurological Pupil Index (NPI) and how it might be used to diagnose acute and chronic effects of traumatic brain injury (TBI)
2. Describe the OCT abnormalities that can occur after TBI
3. Describe the possible sites of damage in the visual system that can cause OCT abnormalities

CME QUESTIONS

1. Which of the following pupil parameters is *not* taken into consideration in the determination of the Neurological Pupil Index (NPI)?
 - a. Pupil resting, baseline size
 - b. Ambient lighting level
 - c. Pupil latency time
 - d. Pupil contraction velocity
 - e. Pupil dilation velocity
2. Which of the following OCT based features has *not* been found as a result of TBI:
 - a. Retinal nerve fiber layer thinning
 - b. Photoreceptor layer thinning
 - c. Homonymous retinal ganglion cell layer thinning
 - d. Retrograde thinning of the bipolar cell layer
3. True/False: There is evidence for chronic continual loss of retinal neurons over time following TBI greater than expected for aging.

KEY WORDS

1. Pupil Light Reflex
2. Optical Coherence Tomography
3. Neurological Pupil Index (NPI)
4. Retinal Ganglion Cell Layer
5. Traumatic Brain Injury (TBI)

ABSTRACT

Currently, it is not known if neuronal loss in the retina and brain after mTBI in either veterans or in the civilian population (especially in sports-related concussion) continues to progress over time. Closing this knowledge gap will be important for understanding and treating TBI-related visual symptoms and for establishing whether ocular biomarkers such as the pupil light reflex and optical coherence tomography (OCT) can be used to predict risk of CNS dysfunction and its progression over time.

BACKGROUND

Currently there is no information on the relationship between Traumatic Brain Injury (TBI), Chronic Traumatic Encephalopathy (CTE), and progression of visual deficits. CTE is now recognized as a devastating condition characterized by progressive dementia, impulsive behavior, and depression with a high rate of suicide.¹⁻⁶ A diagnosis of CTE is confirmed at autopsy, based on the characteristic pattern of neural degeneration in locations of the brain where physical forces are transmitted and focused during Traumatic Brain Injury (TBI), such as in the sulci and gyri of the cerebral cortex, for example^{2,7}. Most CTE patients have been found to have a history of repeated TBI, often from participation in contact sports such as football and boxing. However, CTE has also been documented in veterans with prior TBI.^{1,4,7} It is suspected that mild TBI initiates a process of progressive neural degeneration over time in susceptible individuals and that repeated incidents can manifest as CTE decades after the inciting injuries. Both single and repetitive injuries may predispose subjects to dementias including Alzheimer's disease and chronic traumatic encephalopathy. In an analysis of data from the National Alzheimer's Coordinating Center, 877 persons with dementia who had sustained a TBI were identified. Only those persons with TBI who had chronic deficits or dysfunction were associated with increased risk of dementia.⁸ This raises the important question of the long-term consequences of mild TBI in the absence of major deficits and dysfunction following the acute injury. To examine this issue, longitudinal studies examining cognition, function and neural status in mild TBI are needed. Recent research utilizing advanced neuroimaging with labeling for tau protein in human brain has shown

greater deposition with longer time intervals after TBI exposure both in autopsy specimens and in vivo with newer MRI labeling advances (Lee Goldstein MD PhD, and Ann McKee, Boston VA, personal communication).

Diffuse axonal injury (DAI) after TBI has been shown to disrupt axonal function and the communication among neurons. This can result in network dysfunction, which is amenable to assessment using magnetic resonance imaging techniques.⁹ MRI is a very flexible tool, which can provide quantitative information about brain anatomy (e.g. cortical thickness and volume), structural connectivity (e.g. measurement of white matter with diffusion MRI) and functional connectivity (e.g. resting functional MRI). Thus, MRI is an important tool for in vivo assessment of brain connectivity, especially in the visual pathways. There is now emerging evidence of brain abnormalities in studies of mild TBI. For example, in a study of examining cortical thickness in mild blast-induced TBI (n=12), Tate et al.¹⁰ found evidence of cortical thinning in the left superior temporal gyrus and left superior frontal gyrus. This thinning was associated with language and auditory functioning. Using resting state fMRI to examine functional connectivity, Han et al.¹¹ found reductions in the participation coefficient, a measure of between-module connectivity in service members who had suffered a concussive blast-related TBI. Using DTI, abnormal fractional anisotropy and mean diffusivity has been reported in mild TBI in some studies but not all. In our recent pilot studies using resting functional MRI (Kelvin Lim MD, Minneapolis VA), disconnections between visual cortex and medial frontal gyrus were found in veterans with mild TBI.

Very little is known about the chronic visual consequences of mild TBI, its progression, and its correlation with central nervous system (CNS) deficits.¹²⁻¹⁷ Glenn Cockerham MD and colleagues have reported that the quality of vision is significantly reduced in veterans after mild TBI (mTBI), using a questionnaire validated by the National Eye Institute (NEI). However, most of these veterans had a normal eye exam using standardized tests of vision, visual field, and examination of the retina and optic nerve. Unexpectedly, we found an almost 25% prevalence of significant loss of nerves in the inner layers of the retina of these veterans using in vivo retinal imaging by high-resolution optical coherence tomography (OCT) analyzed with an automated three dimensional segmentation of the retinal layers developed at the Iowa City VA. In pre-clinical studies on blast-induced mild TBI in mice, we have found evidence for a biphasic pattern of functional loss in the retina with progressive loss of retinal neurons over time.^{18,19} In humans, the visual system provides an ideal platform upon which connectivity in the brain and structural-functional associations can be prospectively studied after mild TBI owing to newer, sophisticated imaging and behavioral tests that define anatomical and functional connections.

I. THE PUPIL LIGHT REFLEX AS A BIOMARKER OF ACUTE CONCUSSION

A. WHY MONITOR THE PUPIL LIGHT REFLEX IN ACUTE CONCUSSION?

There is a critical need to identify a sensitive, rapid, easily obtainable biomarker to serve as an objective indicator of mild traumatic brain injury and as a predictor of outcome. Repeated concussive and even sub-clinical exposures to head trauma can produce a spectrum of chronic traumatic encephalopathy (CTE), resulting in stress points of damage in the brain, ranging in severity from mild cognitive impairment to severe dementia, disinhibited violent outbursts, motor dysfunction, reduced quality of life and even suicide.^{2,20} There is evidence that the pupil's reflex movement in response to a pulse of light reflects the status of the central nervous system following head trauma. The pupil light reflex (**Figure 1**) integrates a chain of neural events mediated by nerves passing through brain areas commonly affected by acute head trauma, and may also be affected chronically with repeated, mild head trauma which can be cumulative.^{18, 21-25} The pupil light reflex, unlike other measures of head trauma, is sensitive to acute, subclinical concussive forces. It may also have potential to be used to inventory cumulative effects of mild head trauma over time, which fulfills a critical need in evaluating people with repeated exposures of mild traumatic brain injury.

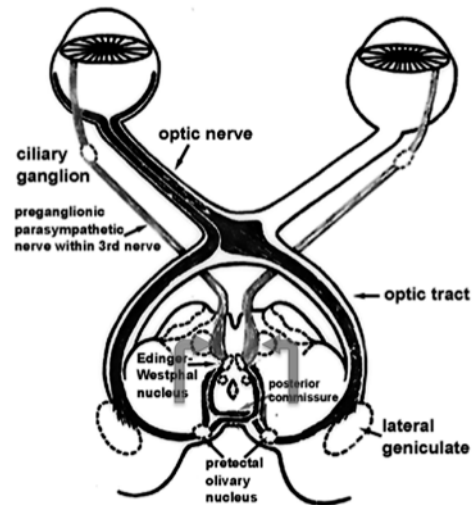


Figure 1: Schematic of the pupillary light reflex pathway, including the *afferent limb* (retina, including the melanopsin intrinsically photosensitive retinal ganglion cells, optic nerve, chiasm, optic tract and brachium of the superior colliculus), the *inter-neuron* consisting of nerves in the pretectal olivary nucleus in the midbrain which provide input via the posterior commissure to the *efferent limb* consisting of the pre-ganglionic parasympathetic neurons in the Edinger Westphal Nucleus and the axons traveling within the oculomotor nerve, synapsing in the ciliary ganglion to finally innervate the iris sphincter muscle. Supra-nuclear fibers from the reticular activating formation in the pons ascend into the midbrain (red arrows) to modulate the response of the preganglionic

parasympathetic neurons in the Edinger Westphal Nucleus during states of wakefulness and sleep. Sympathetic nerves innervating the iris dilator, also modulate pupil size and dilation. Concussion may theoretically affect the pupil light reflex throughout any portion of this pathway. However, the most likely location is within the midbrain pathways and connecting neurons that modulate the pupil motor center.

B. NEUROLOGICAL PUPIL INDEX (NPI) AND THE EFFECT OF CONCUSSION

The pupil light reflex can be easily recorded with a portable, hand-held computerized pupillometer that is commercially available from Neuroptics Inc. (Irvine, CA) as shown in **Figure 2**. The dynamics of pupil movement in response to a light pulse have been condensed into a single parameter of pupil reactivity, termed the Neurological Pupil Index (NPI) which has a value ranging from zero (non-reactive) to five (most reactive). The NPI incorporates a z-scale sum of pupil size, iris mechanics, contraction amplitude, latency, contraction velocity, and dilation velocity from the normal population.³ It has been determined from previous studies of intensive care patients with traumatic brain injury (TBI) compared to normal subjects that an NPI of greater > 3 is normal and ≤ 3 is associated with brain dysfunction and higher risk of morbidity.²¹⁻²³

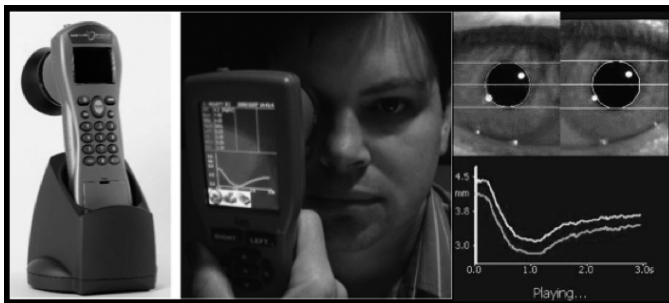


Figure 2: Hand held portable computerized pupillometer <http://www.neuroptics.com> is used to collect pupillary light reflexes in response to a 0.2 second duration light pulse given to the right and then left eye.⁶ The dynamics of pupil contraction, dilation and pupil size over 3 seconds (waveform on right lower panel) are used to compute a Neurological Pupil Index or NPI, independent of surrounding lighting conditions. The NPI predicts CNS status after head trauma.³ In our own recent study of 100 normal subjects age 18-30, the mean NPI was 4.2 ± 0.31 . Repeat testing by us on a subset of 10 normal subjects over the course of 5 days showed a standard deviation of only 0.135 (**Figure 3**).

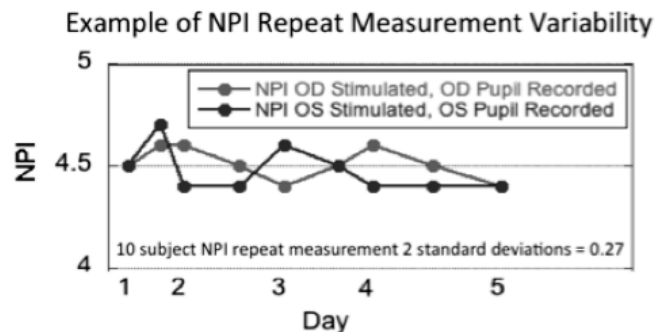
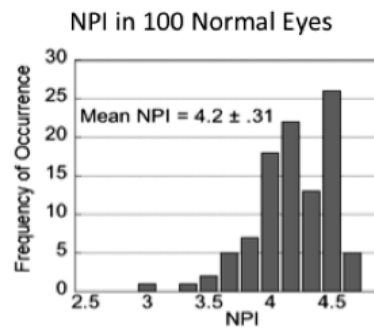


Figure 3: The neurological pupil index (NPI) is a scaled summated z-score measure of parameters of pupil reactivity, and was measured in 100 normal subjects age 18-30 (right eye NPI distribution shown in top bar graph). 10 of the subjects were retested during a 5-day period to define the repeat measurement variability (one such subject is shown in the line graph at the bottom). Two standard deviations encompassed an NPI changing by only 0.27 units in normal subjects, providing a highly reproducible repeat measurement and basis for defining significant change between test measurements in subjects being followed after mild TBI.

C. EVIDENCE FOR THE NPI BEING AFFECTED BY HEAD TRAUMA AND PRECEDING CHANGES IN INTRACRANIAL PRESSURE

In the 2011 study by Chen et al,²¹ the NPI correlated with the maximally recorded intracranial pressure and duration of raised pressure in ICU patients with head trauma. In a number of patients, a drop in the NPI preceded the rise in intracranial pressure. The portable hand-held pupillometer device provides a 100 footcandle bright white, LED flash (group of four light emitting diodes for stimulating each eye) for 0.2 seconds and records the resulting pupil movements over the next 3 second time window. It has been previously shown that the NPI is not dependent upon the background lighting condition. The pupil light reflex integrates a chain of neuronal processes mediated by brain areas and neuronal tracts commonly affected by acute head trauma and disruption at any step will result in abnormal reflex functionality.^{18, 21-25}

D. EVIDENCE FOR THE PUPIL LIGHT REFLEX AND NPI BEING AFFECTED BY HEAD TRAUMA AND TBI

The use of the pupil light reflex (PLR) to assess mTBI has recently garnered attention as a potential biomarker for head trauma sustained by military personnel due to advancements in automated PLR recording capabilities (Capo-Aponte et al., 2013). Notably, this study used a military population as test subjects to test pupil light reflex variability between healthy service members (n=20) and those who have experienced a blast-induced mTBI (n=20), and recorded the dynamics of the pupil light reflex using a portable, computerized pupillometer device. Between-eye comparisons (right eye vs. left eye) showed no statistically significant differences within groups, therefore single eye data was combined for each participant before comparing group results. Eight parameters were measured, four of which were statistically different between control and injured groups (constriction latency, 75% recovery time, average constriction velocity, and dilation velocity). The statistical significance was reported to be robust for these four parameters (Student's t-test, p values ranging from 0.003-less than 0.001). The Capo-Aponte et al. study is a well-designed effort that provides strong evidence of efficacy for the PLR.

Another study investigating the PLR in mTBI patients²⁷ reported significant differences between groups for several parameters (peak velocity of constriction, average velocity of dilation, maximum pupil diameter, and amplitude of constriction) and statistical significance of differences for these measures was also strong (Student's t-test, p values <0.001). The Thiagarajan and Ciuffreda study,²⁷ however, reported some contradictory results to the Capo-Aponte et al. study;²⁶ parameters statistically different in one study were not different in the other and vice versa. We note the two studies used the same pupillometer device, but one study used acutely-injured patients and the other (Thiagarajan and Ciuffreda) used chronically-injured patients (more than 1 year post-injury). Only two parameters were different between groups in *both* studies: average constriction velocity and average dilation velocity. Additional experimentation is recommended to verify these differential results, as added value may be found for military medicine by developing a test capable of differentiating acute and chronic injury.

An important innovation was realized from the results of a recent pilot study led by our Iowa clinical research team, which validated the usefulness of the NPi as an acute biomarker of TBI predicting neurological outcome. The NPi was recorded in 128 patients being evaluated for acute TBI in the University of Iowa Emergency Treatment Center. An abnormal NPi at intake was found to be highly predictive of outcome and seriousness of acute traumatic brain injury in an emergency room setting. Specifically, patients with an NPi ≤ 3 (compared to patients with NPi > 3) were found to have a significant likelihood of:

- 1) Worse Glasgow Coma Scale,
- 2) Head CT scan abnormalities
- 3) Need for neurosurgical intervention
- 4) Longer length of hospitalization
- 5) Need for skilled care after discharge from the hospital

E. THE POTENTIAL OF THE NEUROLOGICAL PUPIL INDEX AS AN INDICATOR FOR RETURN TO PLAY AFTER CONCUSSION ON THE FOOTBALL FIELD

The use of the NPi to evaluate acute military and sports related head trauma might be very sensitive to acute concussion, since a baseline NPi or pregame NPi can be compared to measurements during and after combat or sports play. For example, after sustaining a significant head impact event during military operations or during a sports game, the absolute value of the NPi may still be in the normal range, but the change from baseline may be greater than expected by chance (**see Figure 4**), indicating a severe enough injury to warrant observation or further evaluation.

If the reduction in NPi reflects the severity of brain insult, then acute changes in the NPi and the duration of such changes may provide a viable biomarker for an in-field assessment of head trauma and influence decisions on safe return to duty. If changes of NPi are sustained, then there may also be a use for the NPi in monitoring cumulative effects of injury and relating these to assessments of cognitive function and structural changes in the brain.



Figure 4: Effect of acute concussion on the Neurological Pupil Index (NPI) in 3 college football players. Players being evaluated for acute concussion were tested at the time and on subsequent days and their pupil response was compared to their baseline, pre-season NPI measurement. Measurements of NPI are shown for the right and left eye stimulation at baseline (0 time) and at subsequent days. Note the acute decrease in NPI at Day 1 and the return of NPI at the time the players were deemed ready to return to play.

F. SUMMARY OF PUPIL LIGHT REFLEX AS AN INDICATOR OF CONCUSSION AND TBI

These results showed that the Neurological Pupil Index (NPI) has potential to be a significant biomarker of acute brain trauma that is predictive of outcome and as a biomarker that predicts the need for further evaluation. Ongoing prospective, confirmatory studies are currently being conducted in Emergency Treatment Centers and in sports related head trauma. These results are relevant to assessment of traumatic brain injury from a variety of causes, including blunt trauma from falls and motor vehicle accidents, blast and concussion related TBI, and in sports-related head trauma.

The attractiveness of the pupil light reflex is that it is probably the easiest measurement to accurately obtain in a TBI setting, it is based on an objective, involuntary reflex that does not require subject cooperation, it can be obtained with a commercially available portable hand-held battery powered instrument that can be used in the field, it can be obtained under room lighting conditions and does not require a dark environment. In addition, the results can be automatically analyzed and instantaneously displayed at the time of measurement. It has the potential of being used as an absolute measurement and also as a measurement over time to look for small changes that might be clinically significant. At this time there are very few studies, but the results and ease of attaining measurement, as well as low cost, make it an attractive candidate for diagnosis and monitoring of acute TBI that warrants further investigation.

II. OPTICAL COHERENCE TOMOGRAPHY (OCT) OF THE RETINAL NERVE FIBER LAYER AND RETINAL GANGLION CELL LAYER AS A CHRONIC BIOMARKER OF CONCUSSION AND TRAUMATIC BRAIN INJURY (TBI)

In collaboration with Glenn Cockerham MD, National Program Director, VA Ophthalmology and Palo Alto VA and Kelvin Lim MD, Minneapolis VA Trauma Center, we have extensively analyzed spectral domain OCT of the retina of veterans at both sites with a history of mild TBI compared to an age-matched cohort without TBI. Subjects received extensive ophthalmologic exams, including high and low contrast vision, and visual field testing. The scans were analyzed at the Iowa City VA with our team of image analysis experts (Mona Garvin PhD) using the Iowa Reference Algorithm, which is an automated software segmentation of the retinal layers using a three dimensional, graph-based approach (**Figure 5**) that was developed by Iowa co-investigators.²⁸⁻³⁰

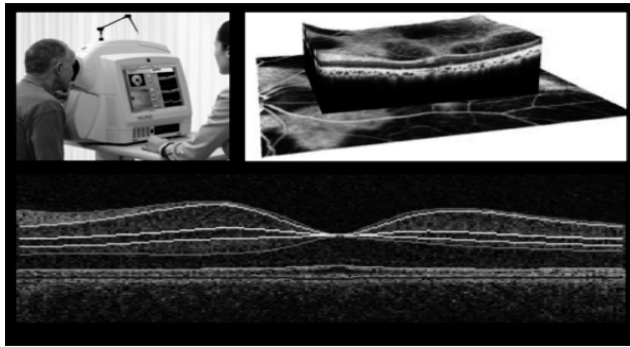


Figure 5: Fourier domain optical coherence tomography (OCT) through an undilated pupil showing the retinal layers, segmented by a custom Iowa algorithm based on a 3D graph approach. The images are collected within seconds in each eye and the segmentation software algorithm automatically finds the different retinal layers and computes thickness of each layer. The inner layers of the retina containing the retinal ganglion cells and their axons making up the retinal nerve fiber layer (RNFL) were shown to become significantly thinned in 21-23% of eyes as a result of TBI (see Figure 6) and will be used as a structural outcome measure in this study.

3D analysis of optical coherence tomography of the retinal layers (28-30) in this group of veterans (Figure 6) revealed significant thinning of the retinal ganglion cell layer in 21% of patients and thinning of the retinal nerve fiber layer in 23% in spite of normal or near normal visual field and contrast sensitivity. The results shown in Figure 6 are for the average thickness of the retinal ganglion cell layer encompassing 7 degrees of the macula in the central retina. The results for the retinal nerve fiber layer were also analyzed for the overall average thickness in the peripapillary circumferential retinal location. For both the segmented retinal ganglion cell layer and the retinal nerve fiber layer, there were many cases of regional loss on the probability plots (Figures 7 and 8). In many eyes of TBI veterans, the average layer thickness was still within the normal range, but regional probability plots showed significant regional thinning. We expect to identify even a higher percentage of TBI veterans showing abnormal thinning based on regional statistical analysis of the OCT scan.

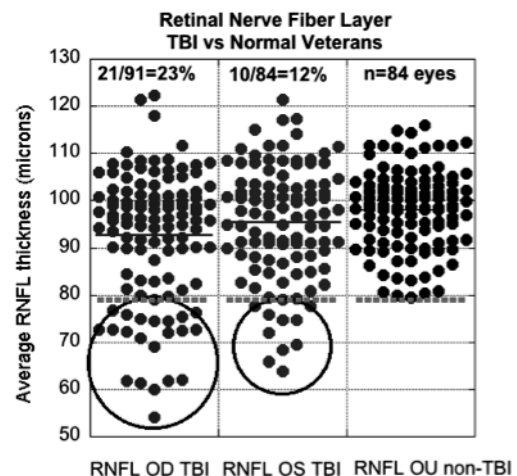
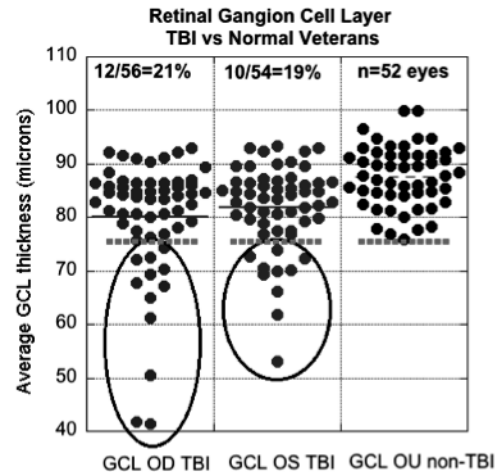


Figure 6. The top graph shows the distributions (dot plots) of the OCT derived average thickness of the retinal ganglion cell-inner plexiform layer complex (GCL) in the macula of the right and left eyes for veterans with a history of mild TBI compared to age matched normal veterans. Note that there is a 21% prevalence of thinning of the GCL in the right eyes (red) below the lower limit of the normal eyes (black) for the overall average thickness of the GCL. The bottom graph shows a similar distribution for the retinal nerve fiber layer (RNFL; axons of the retinal ganglion cells) surrounding the optic nerve in the same cohorts (but in a greater number of veterans imaged with the RNFL scan). Analysis of regional loss of neurons and their axons show an even higher percent of veterans with TBI having significant thinning.

The detailed spatial maps showing regional loss of retinal neurons in the macula and surrounding the optic nerve head is shown in an example of a veteran who had mild TBI the year before (Figure 7).

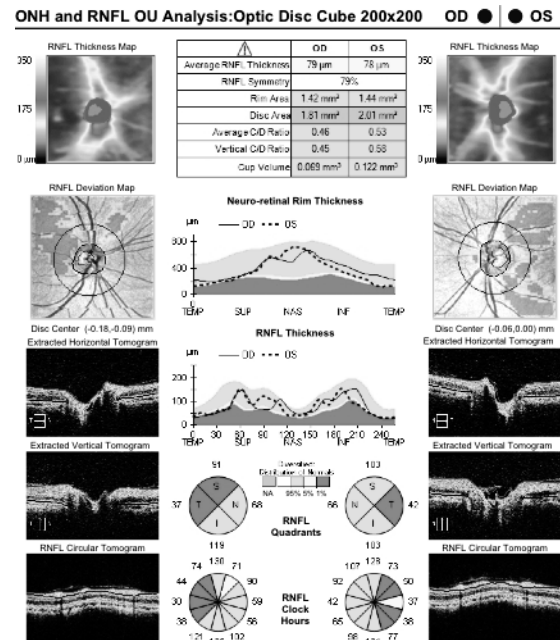
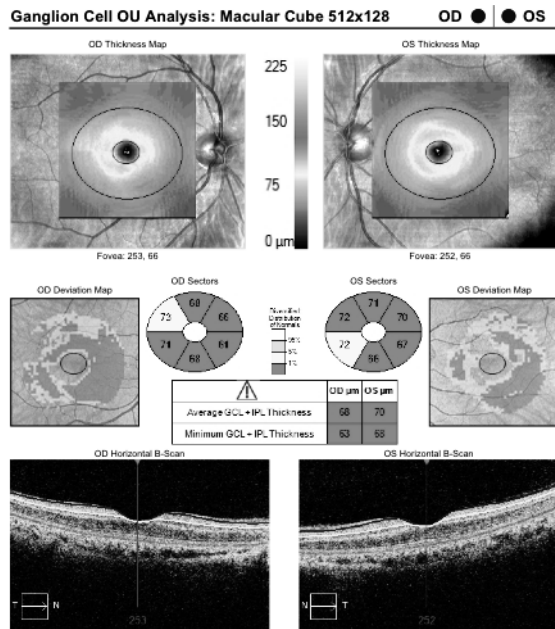


Figure 7: OCT imaging reports showing results of analyzed OCT scans of the right and left eye centered on the macula (left panel) and optic nerve head (right panel). Top of each panel shows the color-coded thickness map of the retinal ganglion cell layer (left panel) or retinal nerve fiber layer (right panel). Middle panel shows areas of significant thinning as either red pixels (less than 1st percentile of normal) or yellow pixels (less than 5th percentile of normal). Bottom of each panel shows representative B scans in which the different retinal layers are seen. In this example of a veteran with previous TBI, there is significant thinning of the retinal ganglion cell layer and the retinal nerve fiber layer in each eye, without any other ocular abnormalities detected.

The same patient example in **Figure 7** is shown in **Figure 8** (left panel) with repeat testing 3 years in a row to show the reproducibility of the OCT imaging and quantification of retinal ganglion cell layer thickness. Note the similarity in

the probability plots for each test year. An OCT example of another veteran with mild TBI is shown in the right panel of **Figure 8**. This veteran demonstrated a homonymous visual field defect from damage to the central, post-geniculate visual pathways seen on MRI scans, demonstrating transynaptic retrograde degeneration of the retinal ganglion cell layer in a homonymous matching pattern in each eye. We have recently reported a well-documented case with an abscess of the occipital cortex that also showed evidence of transynaptic retrograde degeneration of the retinal ganglion cells by OCT.³¹ In the near future, we will attempt to determine whether structural loss in the retina after mild TBI is primary or secondary to transynaptic retrograde degeneration. This will be accomplished based on analysis of the congruence of retinal thinning in homonymous locations, MRI findings, and also whether the pupillary light reflex (a pregeniculate neural reflex) shows any evidence of deficit.

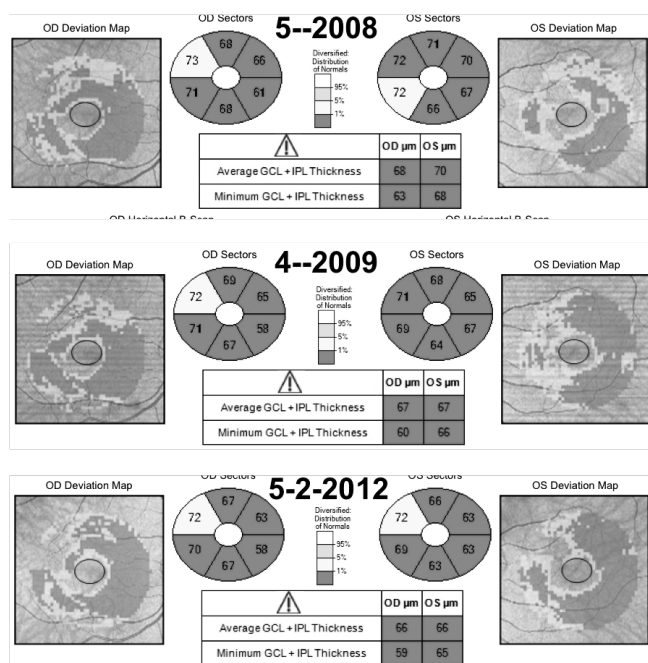
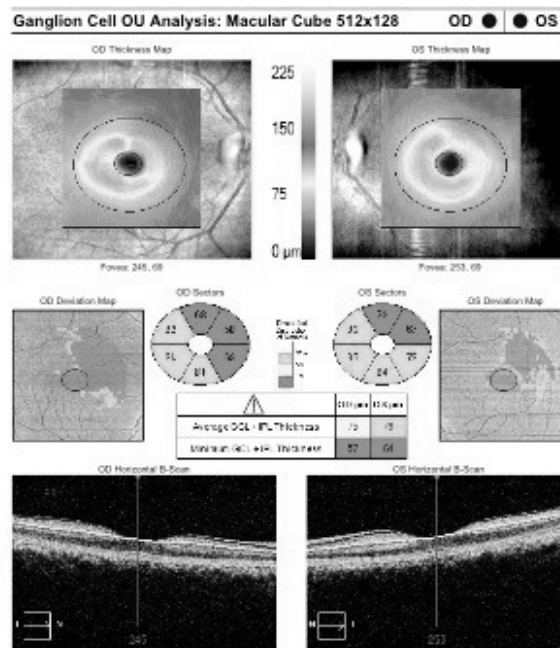


Figure 8: OCT Report (**left panel**) showing thinning of the retinal ganglion cell layer-inner plexiform layer in the right and left eyes of the TBI veteran shown in Figure 7, left panel, repeated over time. The red colored areas are the retinal locations with thinning less than the 1% level of normal eyes. The same patient was scanned in 2008, 2009, and 2012, which shows remarkable repeatability of the regional pattern of thinning. **Right panel** shows a veteran with a homonymous visual field defect that had damage to the central visual pathways demonstrating retrograde degeneration of the inner retinal layer in a homonymous pattern (see red areas in center row), matching in each eye. The top row is the thickness map of the retinal ganglion cell layer showing loss in the upper right homonymous quadrant. This indicates that the OCT analysis can also detect secondary retinal thinning due to the visual pathway being affected in the central nervous system from TBI.

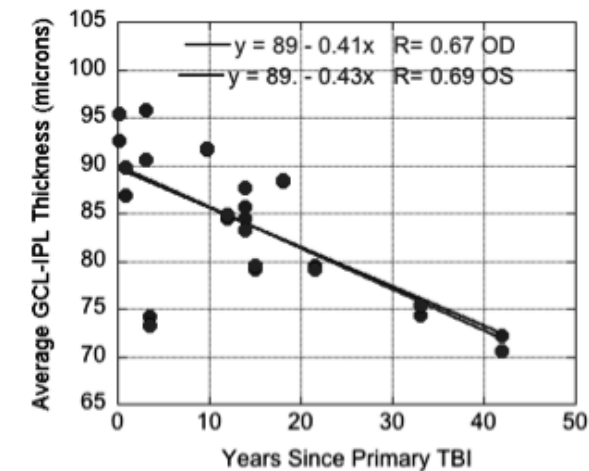
We also have prospectively studied OCT of the retina in the University of Iowa Football team to determine the reproducibility of OCT results and any long-term progressive changes in retinal structure due to sports-related concussion. In August 2013 we tested each eye of 103 players during pre-season training camp and then again at the end of the season in December 2013, as well as a control cohort 25 athletes on the University of Iowa varsity track team. We found that the OCT analysis was extremely repeatable using automatic retina tracking and using the first, baseline scan as the reference scan in order to ensure scanning of the same location of the retina on subsequent



test dates. The standard deviation of the repeat test 4 months later was only one micron for the average thickness of the retinal ganglion cell layer and 2.5 microns for the average retinal nerve fiber layer thickness (similar for both the football and track team cohorts). This indicates that OCT could be a very sensitive tool for detecting progression over time due to the low repeat measurement variability. This study is now in its third year on the returning players and will complement the longitudinal study proposed here in veterans who are no longer exposed to repeated TBI.

To date, the Minneapolis VA has enrolled 19 veterans with TBI and 22 age-matched veterans without TBI. Our 3D graph-based software segmentation algorithm was used to analyze the retinal ganglion cell layer thickness and retinal nerve fiber layer thickness. A cross-sectional analysis of ganglion cell layer thickness vs. years after mild TBI showed a significant negative slope of approximately 0.42 microns/year for the right and left eyes and no significant slope less than 0 for the normal eyes in this age group (**Figure 9**; top). An example of one eye retested during the year showed a loss of 1.6 microns/year (**Figure 9**; bottom graph). Ongoing prospective studies will characterize how much neural degeneration occurs over longer time periods, funded by the Chronic Effects of Neurotrauma Consortium (CENC). In a mouse model of overpressure blast injury, effects of blast were seen on retinal ganglion cell function, followed by retraction of dendrites and eventual loss of retinal neurons by OCT and by histological analysis.¹⁹

Average Ganglion Cell-IPL Layer Thickness vs Time Since TBI



Retinal Ganglion Cell Layer Thinning Over Time
Veteran with TBI Tested 3 Times

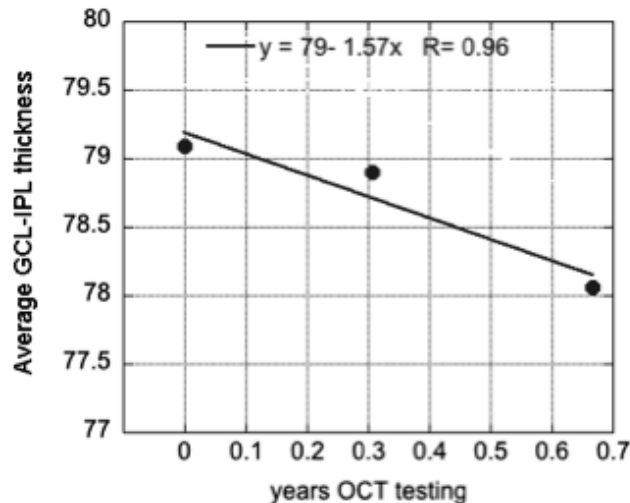


Figure 9: Top graph shows a cross sectional analysis of retinal ganglion cell layer thickness of the right and left eyes of 19 veterans vs. number of years after their mild TBI, revealing a negative slope. An example of one veteran tested 3 times in the last year is shown in the right graph, demonstrating a negative slope of 1.6 microns/year of thinning of the average thickness of the retinal ganglion cell layer.

SUMMARY OF OCT AS A CHRONIC OCULAR BIOMARKER IN TRAUMATIC BRAIN INJURY (TBI)

The take home point is that there is preliminary evidence both in a cross-sectional analysis and in some of the individual TBI patients that progressive thinning of the retina appears to be occurring after mild TBI and may represent a spectrum of chronic traumatic encephalopathy (CTE). Interestingly, in spite of retinal thinning due to neuron loss, many of the patients still maintain normal visual field sensitivity, implying that there is some degree of compensation, at least in relation to the standard

visual field sensitivity paradigm used clinically. This is an important result and indicates that structural analysis in the setting of mild TBI may be a sensitive indicator of neuron loss occurring before loss in visual function can be detected with standard clinical tests of visual sensitivity.

CME ANSWERS

1. b
2. d
3. True

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EMERGING ISSUES IN CONCUSSION

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LEARNING OBJECTIVES

1. Describe the emerging issues in concussion
2. Determine why vision testing is important in sideline assessment
3. Characterize the debate surrounding chronic traumatic encephalopathy (CTE) and its potential causal factors
4. Describe who is at high risk for concussion

KEYWORDS

1. Concussion
2. Chronic Traumatic Encephalopathy (CTE)
3. Energy States
4. Rapid Number Naming
5. King-Devick Test

CME QUESTIONS

1. Which of the following characteristics would render an individual least likely to have prolonged post-concussive symptoms?
 - a. Premorbid anxiety
 - b. History of attention deficit disorder (ADD)
 - c. Premorbid depression
 - d. Symptom checklist total score > 13
 - e. Isolated double vision
2. Which of the following is false?
 - a. Following a concussion, you are three times more likely to have another one
 - b. The risk of recurrent concussion is greatest in the first 10 days after a concussion
 - c. Concussion is always a functional disorder rather than a structural one
 - d. Undetected concussion is more common than detected concussion
3. Which of the following sideline tests have been demonstrated to be the most effective in distinguishing concussed vs. non-concussed athletes?
 - a. Rapid number naming
 - b. Convergence insufficiency testing
 - c. Nystagmus evaluation
 - d. Saccade testing

INTRODUCTION

Concussion is defined as a complex pathophysiological process affecting the brain from an impulsive force transmitted to the head or from a direct blow to the head, face, neck or elsewhere on the body that results in a new neurological sign or symptom.¹ Increasing public awareness of the incidence of sports concussion, estimated at 4 million per year, and the possible long-term consequences on brain function are becoming a growing concern for participants in contact and collision sports.² Additionally, an increasing number of military personnel are returning from recent conflicts with blast-induced concussion and traumatic brain injury (TBI).³⁻⁵

During concussion, linear and rotational accelerations of the brain occur relative to the skull producing pressure and shear forces throughout the brain tissue.⁶ This may lead to tissue damage and diffuse axonal stretching. This may, in turn, lead to diffuse axonal injury (DAI), which can cause disruption of cortical and subcortical pathways producing neurobehavioral dysfunction.^{6,7} Exposure to repetitive concussion or sub-concussive impacts is now recognized as having possible long-term neurological consequences, including neurodegenerative disease.^{2,8-10} The general lack of radiological signs after concussion on conventional MRI and CT have often left medical professionals to rely primarily upon clinical signs and symptoms to diagnose concussion.¹¹⁻¹⁶ In the acute or sideline setting, there is a need for testing that can be quickly administered to help confirm the diagnosis of concussion—or more importantly, given the simple clinical definition, to force critical thinking regarding a potentially meaningful neurologic event. In this talk, we examine some emerging issues in concussion.

IDENTIFYING THOSE AT RISK

One of the key measures to enhance concussion prevention is to better identify the group of individuals that are most at risk. Age—there is no consistent data, but youth athletes may be more vulnerable. Sex—women appear to be more vulnerable when playing similar sports like soccer, possibly due to weaker neck muscles.¹⁷⁻²¹ Sport—all sports have risk, but wrestling, field hockey, football, rugby, soccer, hockey, lacrosse are the ones with relatively high rates of concussion.¹⁷⁻²¹ There may be some athletes that are vulnerable to prolonged post-concussive effects including those with premorbid anxiety, depression, cognitive impairment and high symptom scores right after their injury.²²⁻²³ Those patients with the earliest exposure to contact football may be the most vulnerable to cognitive impairment later in life.²⁴ Following a concussion, you are 3 times more likely to have another one and most of that risk is early (first 10 days).²⁰ In addition, multiple concussions are associated with prolonged recovery and multiple symptoms. For some, there may be long term cognitive and behavioral disturbances. For this reason we need sideline diagnostic tools for unclear situations and to add structure to the concussion evaluation. It can be a problem for both the athlete and the coach to make a determination if a meaningful neurological event has occurred. Furthermore, the problem of undetected concussions far exceeds that of detected concussions.²⁵ Finally, for some athletes, the injury will not only be functional, but structural (see below neuro-imaging section).

See comment in PubMed Commons below. The development of a range of sideline screening tests has occurred in response to the concussion epidemic. Sideline tools such as the Sports Concussion Assessment Tool, 3rd Edition (SCAT3) include a Symptom Checklist and the Standardized Assessment of Concussion (SAC). The SAC is a cognitive component of SCAT3 that has also been incorporated into the Military Acute Concussion Evaluation (MACE). To test balance, the SCAT3 includes a modified version of the Balance Error Scoring System (BESS),¹ while the Child-SCAT3 relies upon the more recently developed timed tandem gait test. While both balance and neuro-psychological testing have been shown to be effective in the assessment of concussion, there remain opportunities for improving the ability to consistently capture all concussive events quickly.²⁵⁻²⁹ Balance function can be affected by fatigue³⁰⁻³² and previous injury.^{26,33} The SAC has largely been validated using earlier concussion definitions, which required alteration of mental status, loss of consciousness, or post-traumatic amnesia.^{33,34} As such, the reported sensitivities of these measures may have been greater than those that could result when applied using more broad definitions of concussion. Furthermore, since concussive symptoms often go unreported at the high school or collegiate levels, there is a need for sensitive and quantitative concussion tests that can be used to support clinical or lay-witness suspicion of an event.^{35,36} Recent work has demonstrated that the addition of a rapid,

simple vision-based performance test to cognitive and balance-based sideline tests enhances the ability to detect concussions at youth and collegiate levels of play.^{37,38} The efferent visual pathways are particularly vulnerable to injury in the acute setting of concussion³⁹⁻⁴³ and may be assessed through visual performance measures such as rapid number naming tasks. The K-D test is a 2-minute rapid number naming assessment in which an individual reads numbers aloud quickly from test cards or a computer-based application. The K-D test requires eye movements (saccades, convergence and accommodation), attention and language function. These tasks involve the integration of functions of the brainstem, cerebellum, and cerebral cortex. Eye movement tests can detect dysfunction not detected by cognitive tests and balance tests and at the same time require sensory and cognitive integration.

HEAD IMPACT TELEMETRY SYSTEM (HITS)

The HITS system provides information about the number, magnitude, and location of head impacts via a series of accelerometers that are incorporated into the padding of football helmets.⁴⁴ Broglio and colleagues found that factors such as a rotational acceleration greater than 5500 rad/s, linear acceleration greater than approximately 96 g, and location of impact might predict concussion.⁴⁴ HITS allows even impacts without a clinical manifestation to be tallied, and there is growing evidence that these sub-concussive repetitive impacts may lead to structural compromise as seen with diffusion tensor imaging.⁴⁵⁻⁴⁷ Further research is necessary to determine whether impact evaluations through HITS can improve our prediction of short- and long-term sequelae of concussion. Most disturbing is that cognitive impairment may occur without evidence of concussion.⁴⁸ In one study of 11 high school football players followed serially with helmet telemetry, ImPACT, and functional MRI, four athletes without concussion had impaired cognition.⁴⁸ These athletes had the greatest number of head collisions, particularly over the dorsolateral prefrontal cortex. We need to learn much more about the significance of subconcussive blows and whether these changes are short term or long lasting.

EMERGING ISSUES: OTHER EQUIPMENT

There is no conclusive evidence that mouth guards, head bands or caps reduce the occurrence of concussion. Of course, there have been plenty of testimonials. Even state of the art helmets have marginal benefit in reducing concussion. The absolute effect is quite small in the 2 to 3 percent range.^{49, 50}

EMERGING ISSUES: EDUCATION

We need to have educational programs for all of those involved with sport including the athletes, coaches, parents and other stakeholders. It makes sense to reduce the number of head hits and our youth sports leagues need to implement those changes that are occurring at the professional and collegiate levels. For instance, contact practices have been dramatically reduced in both the NFL and in the Ivy League. When examining the total concussions occurring during a season it is widely recognized that most occur during practice. We need to educate our athletes on the best techniques and the importance of not leading with your head. One proposal that seems to make sense is to start contact later at the high school level and higher. For instance, youth athletes should play flag football until they enter high school. Education programs should be community based because the reality is that most youth leagues are not going to be able to have a trained professional on the sidelines to make concussion assessments.

EMERGING ISSUES: NEUROIMAGING

CONVENTIONAL MAGNETIC RESONANCE IMAGING (MRI)

Routine MRI is often normal with concussions,^{51,52} though susceptibility-weighted imaging (SWI) sequences can show micro-hemorrhages with sub-concussive or concussive injury.⁵³ One prospective study of patients with mTBI found brain atrophy in 4/19 patients 3-7 months post-injury, however further work is necessary to extend this to those exclusively with concussive injuries.⁵⁴ One report found that college football players had decreased hippocampal volumes compared with controls, that there was an inverse relationship between left hippocampal volume and years of football played, and that those with a history of concussion had the smallest hippocampi.⁵⁵ Another study found that in college and preparatory school ice hockey players, self-reported cognitive symptoms such as difficulty concentrating, difficulty remembering, and mental “fog” were associated with decreased cortical thickness in frontal, parietal and temporal regions regardless of concussion history.⁵⁶ This was interpreted as suggesting that the structural changes and symptoms reflected repetitive sub-concussive blows rather than concussions in this cohort, though direct HITS monitoring was not done and there were no controls, so it is possible that the cognitive symptoms described and the changes in cortical thickness were not related to head injury at all. Future studies are necessary to determine whether the volumetric structural changes observed in these young athletes correlate with long-term sequelae.

DIFFUSION TENSOR IMAGING (DTI)

Diffusion tensor imaging (DTI) detects the diffusion of molecules that are mostly water.⁵⁷ Fractional anisotropy is a measurement of the fraction of diffusion magnitude,⁵⁸

and has been shown to reflect the integrity of the white matter.^{51,59} Concussed athletes in comparison to controls have been found to have increases in fractional anisotropy and decreased trace and radial diffusivity in the right corona radiata, right posterior limb of the internal capsule, right superior temporal white matter,⁶⁰ and optic radiations.⁶¹ A correlation between the severity of post-concussive symptoms and changes in mean diffusivity and fractional anisotropy was identified in one study,⁶² suggesting perhaps that symptom severity may be related to degree of diffuse axonal injury.

Maruta and colleagues correlated DTI measures with abnormalities on their test of eye movements in which subjects tracked a target in a circular trajectory in chronic TBI patients.⁶³ They found that variability in gaze error correlated with DTI changes in areas frequently compromised in TBI, including in the right anterior corona radiata, the left superior cerebellar peduncle, and the genu of the corpus callosum.⁶³

DTI also has been investigated in individuals with subconcussive impacts with small cohorts suggesting that there can be white matter changes that correlate with HIT measurement data.⁶⁴⁻⁶⁶ The clinical significance of the changes demonstrated on DTI, whether from concussive or subconcussive impacts, awaits further study. Nonetheless the DTI findings in combination with HITS provide promising tools to detect quantifiable, objective metrics of injury which may have only a very subtle clinical manifestation if any, but could potentially have prognostic value. Nonetheless, DTI studies have had conflicting results with some studies not demonstrating significant findings in concussed athletes.

FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)

Blood oxygen level dependent (BOLD) fMRI detects changes in hemoglobin oxygenation and can provide a readout of oxygen consumption associated with neuronal activation.⁵⁹ Post-concussive changes in fMRI have been detected acutely and chronically,⁶⁷⁻⁷² though there are some conflicting reports in the literature. One recent pilot study of 8 concussed collegiate football players found increased connectivity with fMRI with the brain “at rest” 1 day after a concussion, but then decreased connectivity by day 7 and partial restoration of connectivity by day 30.⁷³ Another study of resting state connectivity found increases in areas involved in executive function in individuals who sustained a concussion in the prior 6 months compared to controls, though the two groups performed similarly on tests of executive function, suggesting the concussed individuals compensate to achieve similar results.⁷⁴

Patients with chronic post-concussive syndrome who were performing a visual working memory task were found to have decreased BOLD signal intensities in the right mid-DLPFC corresponding to their symptom severity.⁷⁵ Johnson and colleagues performed fMRI while concussed

subjects performed a variety of tasks of saccades and pursuit and found increased activation in regions such as the cerebellum, frontal lobes, and visual cortices.⁷⁶ One limitation of these fMRI studies is that it can often be difficult to interpret the significance of changes in BOLD signal given the complexity of neuronal circuitry.⁷⁷

MAGNETIC RESONANCE SPECTROSCOPY (MRS)

Magnetic Resonance Spectroscopy (MRS) detects the concentration of molecules and can be used to assess brain metabolism.⁵⁹ The most consistent finding is that concussion leads to lowered concentrations of N-acetylaspartate (NAA) as well as lower NAA to creatine (Cr) and NAA to choline (Cho) ratios in the white matter⁷⁸⁻⁸¹ as well as gray matter.⁸² In addition, studies have found that abnormalities in metabolites take longer to resolve than post-concussive symptoms,^{78,81} and can even be detected 1 year after injury when symptoms have persisted.⁸³ The exact time course of return of the NAA level to baseline is unclear. In one cohort whose symptoms took 3 days to recover, it took 30 days for the NAA/Cho ratio to return to baseline but in another cohort whose symptoms took about 15 days to recover, 45 days were required.^{78,84} Another study found decreases in NAA/Cr in DLPFC and motor cortex when they looked 6 months after the concussion even though symptoms resolved in most cases within a week, and also found a decreased myo-inositol to Cr ratio in the motor cortex chronically but not acutely, though the authors state that the prolonged changes may be due to ongoing subconcussive injury because most of the athletes had returned to practice within 1 week of injury.⁸² MRS has not extensively been studied in repetitive subconcussive injury, but one study found that over one season of a contact sport, female athletes (but not male) had a decrease in NAA/Cr ratio;⁸⁵ much more study, preferably in combination with HITS, is necessary. Thus MRS can detect changes in brain metabolism in the absence of symptomatic manifestation of the brain injury, after recovery from post-concussive symptoms.

CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

CTE received a lot of media attention as a result of the potential long-term deleterious effects of repeated concussive events, such as depression, altered cognition, and neurodegenerative diseases (e.g. CTE and Alzheimer's disease). The story really started to take hold a decade ago when the pro-football player for the Steelers, Mike Webster, who suffered from profound behavioral changes was found to have pathological findings consistent with CTE.⁸⁶ From there, Dr. Ann McKee and colleagues began to describe many cases in former football players and other collision sport athletes including those playing soccer, hockey and rugby.^{87,88} There has been considerable debate as to whether CTE is a distinct entity from other neurodegenerative conditions that result in abnormal tau deposition. Iverson and colleagues argue that tau deposition may be evident earlier in life and that a small

amount even in the 20's may be evident.⁸⁷ They also argue that there have only been a small number of cases (less than 10) noted in high school athletes despite the millions that have played the sport. Nonetheless, there appears to be a signature pathological lesion in CTE that includes tau deposition in the superficial cortex, the perivascular areas and frontal and temporal lobes. It is true that we need better controls to be definitive, but the absence of proof is not the proof of absence and we should be careful if we have no better explanation for these pathological changes. There are many unanswered questions about CTE including the role that drugs, alcohol and other substances may play in this condition. Finally, we need to understand whether it is concussion, sub-concussive blows or both that lead the predisposed individual to develop CTE. There is a strong suggestion that the number of concussions is important, but we don't know if the duration of exposure is also important. There is no diagnostic tool to predict these long term complications and CTE, although PET imaging that detects tau may be play a role.⁹⁰

EMERGING ISSUES: SERUM BIOMARKERS

The reliability of multiple biomarkers, including s100b, tau, Apolipoprotein E, and neurofilament light chain to support the diagnosis of concussion or predict long-term outcomes is under investigation. S100b has been found to be elevated with concussion,^{91,92} and is possibly associated with worsened outcome though there are conflicting studies.⁹³ Plasma total tau and serum SNTF remain elevated for several days after concussion and have been used to prognosticate those who develop PCS lasting longer than 6 days.⁹⁴

There is some recent evidence that subconcussive injuries can lead to changes in biomarkers as well. Neselius and colleagues looked at 30 boxers versus controls and found that 80% of boxers had elevated cerebrospinal fluid neurofilament light chain 1-6 days post bout, and those with persistent elevation after 14 days had significantly poorer performance on Trail Making A and Simple Reaction Time tests.⁹⁵ CSF samples are better than serum, but only low amounts are obtained and are hard to get. As we all know, LP's are no fun for patients. Furthermore, CTE is a protein aggregate disorder and it therefore may be hard to get free tau and other meaningful biomarkers in the CSF. Saliva may be a better body fluid to sample since it does not require a blood draw.

EMERGING ISSUES: MANAGEMENT

The management of concussion should be individualized with a graduated return to play. Some patients may require a team of professionals including neurologists, therapists and neuropsychologists. The mainstay to treatment is cognitive rest to a degree with those returning to full activity right away experiencing delayed

recovery. This must be balanced against excessive rest,⁹⁶ which may produce excessive rumination. The next phase of management is going to be therapeutic trials of medications, transcranial magnetic stimulations and other modalities. Hyperbaric oxygen therapy advocated in certain circles has failed in recent trials.

EMERGING ISSUES: THE FUTURE

We are going to need multi-center clinical, educational and research efforts to validate testing. A visual performance like rapid number naming is going to need to be added to the testing battery. Neuro-ophthalmology should play a role in which test(s) makes the most sense. We are going to need predictive neuro-imaging and serum biomarkers to correlate clinically. A big question is whether we should routinely test our collision sport athletes after the competition. Studies would suggest that the answer should be yes. Telemedicine might bring professionals closer to the sidelines where they are needed most in our high school and youth populations.

CME ANSWERS

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North American Neuro-Ophthalmology Society

42nd Annual Meeting

February 27 – March 3, 2016
JW Starr Pass Marriott • Tucson, Arizona

NANOS ON-SITE REGISTRATION/HELP DESK HOURS:

Location:	Arizona Foyer
Saturday:	2:00 pm - 8:00 pm
Sunday - Wednesday:	6:30 am - 5:30 pm
Thursday	6:30 am - 12:30 pm

SATURDAY, FEBRUARY 27

Opening Reception

6:00 pm - 7:30 pm

Ania Terrace

Please join us for the Opening Reception on the Ania Terrace at the JW Starr Pass Marriott. All are welcome to attend the opening reception, which features complimentary cocktails and several food stations.

SUNDAY, FEBRUARY 28

Members-in-Training Program and Reception

5:30 pm - 6:30 pm

San Luis

New to Neuro-Ophthalmology? All students, residents and fellows-in-training are encouraged to attend!

MONDAY, FEBRUARY 29

WIN Luncheon

12:15 pm - 1:30 pm

Starr Circle Terrace

Join your colleagues for the Women in Neuro-Ophthalmology (WIN) Luncheon & Meeting. Lunch tickets are available for purchase. However, all are welcome to attend even without the purchase of a lunch.

TUESDAY, MARCH 1

Afternoon Excursions

The Kartchner Caverns, Arizona Sonora Desert Museum, and Desert Horseback Trail Ride excursions all include admission, transportation, and a boxed lunch. All excursions will depart from the Starr Circle Terrace.

Kartchner Caverns - \$95/person

12:15 pm - 5:00 pm

Kept secret since its discovery in 1974, Kartchner Caverns, 12 miles south of Benson, Arizona, was announced to the world in 1988. Still virtually pristine, this massive limestone cave has 13,000 feet of passages and two rooms as long as football fields. Finally opened as a state park November 12, 1999, this underground wilderness will remain protected while offering visitors a rare tour through multi-colored cave formations. The temperature inside the caverns averages 72°F year round, with the humidity at 99%.

Notes: Comfortable clothing, flat shoes, and a light jacket are recommended for this underground walking tour.

Arizona Sonora Desert Museum - \$75/person

12:30 pm - 5:30 pm

Recognized as a world-renowned zoo, natural history museum and botanical garden. Trip Advisor states that it is one of the Top 10 Museums in the World. This “living museum” houses over 1200 kinds of plants and 300 species of animals that live in enclosures designed to replicate their niche in the wild. The Desert Museum is Southern Arizona’s most popular visitor attraction. Nestled in Tucson Mountain Park, the Desert Museum exhibits the living, outdoor world of nature found in the Sonoran Desert region.

Notes: It is suggested that guests wear comfortable shoes and bring hats, sunglasses, sunscreen and cameras.

Desert Horseback Trail Ride - \$125/person

12:30 pm - 4:30 pm

Feel the west come alive as you join knowledgeable wranglers on a 90 minute ride through the panoramic vistas of Arizona’s most famous desert. As you venture along the desert trails, winding through towering Saguaro Cactus, mesquite groves and other desert plant life, your guide will tell of the abundant plant and animal life.

Notes: It is suggested that guests wear casual long pants and closed toe shoes and bring sunscreen and sunglasses.

NANOS Golf Tournament - \$135/person

1:00 pm - 6:00 pm

Spend an afternoon golfing in the NANOS tournament at the Starr Pass Marriott Golf Course, which is one of Arizona’s premier desert courses. Price includes driving range balls and golf cart (Lunch is not included). Club rentals will be available at the hotel for \$69/set (plus tax) which includes 2 sleeves of golf balls.

NANOS Bike Group:

Jason Barton and Michael Wall have organized a ride on road bikes on the Rillito River route. All interested parties can contact Jason Barton at jasonbarton@shaw.ca for more details and bike rental information.

WEDNESDAY, MARCH 2

Annual NANOS Banquet and Reception

Old Tucson

5:30 pm - 10:00 pm

Join us for the NANOS Annual Banquet and Reception at Old Tucson, *Where the Spirit of the Old West Comes Alive*.

Re-live the Wild West in a real 1800s old west town and experience high-flying stunts, a gun fight, Old-Time Photos, live music and dancing, a classic BBQ Dinner, and much more! All attendees are encouraged to dress in their best ‘Country Wild West’ attire. Please be sure to wear comfortable shoes that are equipped for walking on gravel paths. Buses will depart from the Starr Circle Terrace at the JW Starr Pass Marriott at 5:30 pm. Buses will bring guests back to the hotel as they fill throughout the evening. The last bus will depart Old Tucson at 10:00 pm.

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