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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 40.25 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation.
NANOS CME MISSION STATEMENT

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

To this end, the Society sponsors an annual scientific meeting which is its main CME (continuing medical education) activity. Recent advances in the structure and function of the nervous and visual systems as they pertain to neuro-ophthalmology, its pathology, new therapies, and new diagnostic and therapeutic technology comprise the major focus of the annual scientific meeting and its CME content. In addition, the Society supports joint sponsorship with other respected and recognized medical organizations that comply with the ACCME Essential Areas and their Elements.

Members of the Society, physicians, fellows, and resident physicians comprise the meeting participants and target audience for our CME program. They are predominantly neuro-ophthalmologists, Neurologists, and ophthalmologists but also include physicians and scientists from other disciplines and specialties.

The annual scientific meeting of NANOS includes the following types of activities: symposium topics of current interest, special lectures, reports of original research presented at both platform and poster sessions, and reports of special committees assigned to evaluate and report to the membership on specific problems and controversial issues.

The NANOS annual scientific meeting features advances and best practices in neuro-ophthalmology, so that as a result attendees can incorporate them into their medical practices. The scope of the meeting includes: enhancing our diagnostic skills by discussion of challenging cases, promoting evidence-based treatments and avoiding ineffective treatments, and using new diagnostic tools and techniques. Participants should learn the results of ongoing basic and clinical research in neuro-ophthalmology. NANOS uses member surveys, program evaluations (both during and after the meeting), meetings of its Scientific Program Committee, Education Committee, and Board of Directors, and other appropriate means to assess the effectiveness whether the program achieved these outcomes and discuss the knowledge gaps that exist in the field of neuro-ophthalmology that should be addressed in future educational activities.

The NANOS Board of Directors, Scientific Program Committee, Education Committee, and CME Committee review and assess the educational gaps and content and participant critiques of the annual NANOS CME program and general membership comments and suggestions to ensure that all educational objectives are achieved.

Adopted by the NANOS CME Subcommittee October 11, 2005

Adopted by the NANOS Board of Directors October 15, 2005

Reviewed and Approved by the NANOS Board of Directors February 10, 2007

Updated by the NANOS CME Subcommittee and NANOS Board of Directors October 21, 2011
This is the main meeting area. On this level, you will find the NANOS registration desk, exhibits, posters, general session and breakfast eating area. The opening reception will take place on the Ocean Terrace which is also on this level.

This is the second level of meeting space. On this level, you will find various rooms where committee meetings will take place.
NANOS would like to thank the following individuals for their generous donations:

**Silver $10,000 - $19,999**
- Preston C. Calvert, MD (In honor of Neil R. Miller, MD)
- Agnes Wong, MD, PhD, FRCS(C) (In memory of James A. Sharpe, MD, FRCPC)

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- Michael Salman, PhD, MRCP (In memory of James A. Sharpe, MD, FRCPC)

**Wirschafter Club $1,000 - $2,499**
- Thomas and Susan Carlow (In memory of James A. Sharpe, MD, FRCPC)
- Robert B. Daroff, MD (In honor of Bill Hoyt, MD, In Memory of Lawton Smith)
- Kathleen Digre, MD
- Amir Dolatabadi, MD (In memory of James A. Sharpe, MD, FRCPC)
- William Fletcher, MD (In memory of James A. Sharpe, MD, FRCPC)
- Deborah Friedman, MD, MPH (In memory of James A. Sharpe, MD, FRCPC)
- Leah Levi, MBBS (In honor of Thomas R. Hedges III, MD)
- Arun Sundaram, FRCPC (In memory of James A. Sharpe, MD, FRCPC)
- Martin ten Hove, MD, FRCS(C) (In memory of James A. Sharpe, MD, FRCPC)

**Averbuch-Heller Guild $500 - $999**
- Valerie Biosse, MD
- Edmond FitzGibbon, MD
- John Keltner, MD
- Andrew Lee, MD
- Nancy Newman, MD
- Peter Quiros, MD
- Owen White, MD, PhD (In memory of James A. Sharpe, MD, FRCPC)

**Hedges Club $250 - $499**
- Mohammad Fouladvand, MD (In memory of James A. Sharpe, MD, FRCPC)
- Larry Frohman, MD
- Lynn Gordon, MD, PhD
- Thomas R. Hedges III, MD (In memory of Thomas R. Hedges Jr.)
- Victoria Pelak, MD (In memory of William Pelak)
- Bradley Phillips, MD
- Prem Subramanian, MD
- Floyd Warren, MD

**Zaret Society $100 - $249**
- Anthony Arnold, MD
- David Bellows, MD, FACS
- Joseph Chacko, MD
- Kathleen Digre, MD (In memory of Harvey Birsner, MD)
- Kathleen Digre, MD (In memory of James A. Sharpe, MD, FRCPC)
- Scott Forman, MD
- Michael Lee, MD
- Simmons Lessell, MD
- Lawrence Metz, MD
- Mark Moster, MD
- John & Cecillia Reeder (In honor of Dr. Kathleen Digre)
- Richard Selbst, MD (In honor of Dr. Simmons Lessell)
- John Selhorst, MD (In memory of James A. Sharpe, MD, FRCPC)
- Harold E. Shaw Jr., MD
- Richard Sogg, MD (In memory of James A. Sharpe, MD, FRCPC)

*(as of February 5, 2014)*
NANOS would like to thank the following Supporters and Exhibitors for their financial support of these activities

2014 Supporters:

Merz Pharmaceuticals
Merz has contributed $10,000 (non-CME)

2014 Exhibitors:

Chadwick Optical
Eye Care and Cure
Heidelberg Engineering
i2eye Diagnostics Limited
Lippincott Williams & Wilkins
Merz Neurosciences
M&S Technologies Inc.
NeurOptics
Novartis Pharmaceuticals Corporation
Questcor Pharmaceuticals
Richmond Products, Inc.
Teva Neurosciences
Visionequip

(as of February 5, 2014)
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<th>Name</th>
<th>Commercial Interests</th>
<th>Nature / Role</th>
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<tbody>
<tr>
<td>Marie Acierno, MD</td>
<td>NONE</td>
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</tr>
<tr>
<td>Madhu Agarwal, MD</td>
<td>NONE</td>
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<tr>
<td>Geetha Athappilly, MD</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>Laura Balcer, MD, MSCE</td>
<td>Consulting and Clinical Trial Ad Board - Biogen Idec, Vaccinex, Questcor</td>
<td>Consultant</td>
</tr>
<tr>
<td>Rudrani Banik, MD</td>
<td>NIH/NEI 1 U10 EY017281-01A1, Quark Pharmaceuticals, Inc.</td>
<td>Site investigator for clinical trial</td>
</tr>
<tr>
<td>Valerie Biousse, MD</td>
<td>Santhera, Anabasis</td>
<td>Consultant</td>
</tr>
<tr>
<td>Ari Blitz, MD</td>
<td>Bayer Pharmaceuticals, Aesculab</td>
<td>Fees paid through university, Radiology coordination of hydrocephalus trial</td>
</tr>
<tr>
<td>Francois-Xavier Borrutat, MD</td>
<td>Novartis</td>
<td>Speaker</td>
</tr>
<tr>
<td>Swaraj Bose, MD</td>
<td>NONE</td>
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<tr>
<td>Beau Bruce, MD, MS</td>
<td>Kaiser Permanente</td>
<td>Consulting for CDC Vaccine Safety Datalink</td>
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<tr>
<td>Preston Calvert, MD</td>
<td>NONE</td>
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<tr>
<td>Jane Chan, MD</td>
<td>NONE</td>
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<tr>
<td>Robert Chang, MD</td>
<td>Iphone Adaptor</td>
<td>Inventor</td>
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<td>Pamela Chavis, MD</td>
<td>NONE</td>
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<td>Sophia Chung, MD</td>
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<td>Fiona Costello, MD, FRCP</td>
<td>Questcor, Allergan EMD Serono</td>
<td>Advisory Board Speaker Fees</td>
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<td>Robert Crow, MD</td>
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<td>Kathleen Digre, MD</td>
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<tr>
<td>Shlomo Dotan, MD</td>
<td>NONE</td>
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<tr>
<td>Ivy Dreizin, MD</td>
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<tr>
<td>Charles Eberhart, MD, PhD</td>
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<tr>
<td>Eric Eggenberger, DO, MSEpi</td>
<td>Genzyme, Acorda, Teva Biogen, Biogen-Idec Novartis Acorda</td>
<td>Speaker Speaker, consultant, research Research, consultant Consultant</td>
</tr>
<tr>
<td>Julie Falardeau, MD</td>
<td>NONE</td>
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<tr>
<td>Edmond FitzGibbon, MD</td>
<td>NONE</td>
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<tr>
<td>Clare Fraser, MD</td>
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<tr>
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<tbody>
<tr>
<td>Deborah Friedman, MD, MPH</td>
<td>Merck, Allergan, Inc, Zogenix, Neurology Reviews</td>
<td>Principal Investigator, Speaker's bureau, Advisory Board, Editorial Board</td>
</tr>
<tr>
<td>Benjamin Frishberg, MD</td>
<td>Speaker for Allergan</td>
<td>Speaker</td>
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<td>Larry Frohman, MD</td>
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<tr>
<td>Steven Galetta, MD</td>
<td>Biogen idec, Teva, Questcor</td>
<td>Consultant</td>
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<tr>
<td>Christopher Glisson, DO, MS</td>
<td>Biogen-Idec, Lundbeck, Inc Questcor</td>
<td>Speaker, Consultant, Consultant</td>
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<tr>
<td>Karl Golnik, MD, MEd</td>
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<tr>
<td>Lynn Gordon, MD, PhD</td>
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<td>Scott Haines, MD</td>
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<td>Thomas Hedges, MD</td>
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<tr>
<td>Gena Heidary, MD, PhD</td>
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<tr>
<td>William Hills, MD</td>
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<td>Thomas Hwang, MD, PhD</td>
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<tr>
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<tr>
<td>Randy Kardon, MD, PhD</td>
<td>Department of Defense (TATRC) Vision Research Program Grant, National Eye Institute, Department of Veterans Affairs, Novartis</td>
<td>Principal Investigator, Co-investigator, Principal Investigator</td>
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<tr>
<td>Jorge Kattah, MD</td>
<td>Questcor</td>
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<td>Bradley Katz, MD, PhD</td>
<td>Axon Optics, LLC</td>
<td>Management position</td>
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<td>Shalom Kelman, MD</td>
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<td>John Keltner, MD</td>
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<td>Bonnie Keung, MD</td>
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<tr>
<td>Shelley Klein, CO</td>
<td>NONE</td>
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<tr>
<td>Meliss Ko, MD</td>
<td>NONE</td>
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<tr>
<td>Greg Kosmorsky, DO</td>
<td>NONE</td>
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<tr>
<td>Howard R Krauss, MD</td>
<td>Glaxo Smith Kline, Quark Pharmaceuticals, River Vision</td>
<td>Sub-Investigator, Study Monitor</td>
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<td>Mark Kupersmith, MD</td>
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<tr>
<td>W. Curt LaFrance, Jr., MD, MPH</td>
<td>Gates and Rowan's Nonepileptic Seizures, Cambridge Univ Press</td>
<td>Editor</td>
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<tr>
<td>Byron Lam, MD</td>
<td>NONE</td>
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<tr>
<td>Cedric Lamirel, MD, PhD</td>
<td>Allergan France, MSD France</td>
<td>Speaker</td>
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<td>Klara Landau, MD</td>
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<td>Andrew Lee, MD</td>
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<tr>
<td>Michael Lee, MD</td>
<td>Neuro-ophthalmix, LLC, National Eye Institute, Eli Lilly, Pfizer</td>
<td>CFO, Founder, Site PI</td>
</tr>
<tr>
<td>Leah Levi, MBBS</td>
<td>NONE</td>
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<tr>
<td>Leonard Levin, MD, PhD</td>
<td>Allergan, Inotek, Merz, Quark</td>
<td>Attendance at advisory board, Laboratory testing of a drug, Consulting on drug development</td>
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<tr>
<td>Y. Joyce Liao, MD, PhD</td>
<td>NONE</td>
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<tr>
<td>Nancy Lombardo</td>
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<td>Katie Luneau, MD</td>
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<td>Neil Miller, MD, FACS</td>
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<td>Heather Moss, MD, PhD</td>
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<td>Mark Moster, MD</td>
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<td>Raghu Mudumbai, MD</td>
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<tr>
<td>David Myung, MD, PhD</td>
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<td>Nancy Newman, MD, MD</td>
<td>Santhera, Trius, Anabasis</td>
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<td>Steven Newman, MD</td>
<td>NONE</td>
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<td>Anil Patel, MD</td>
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<td>Vivek Patel, MD</td>
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<tr>
<td>Victoria Pelak, MD</td>
<td>Pfizer, American Academy of Neurology</td>
<td>Clinical trial, Speaking and teaching</td>
</tr>
<tr>
<td>Susan Pepin, MD</td>
<td>NONE</td>
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<tr>
<td>Paul Phillips, MD</td>
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<td>Howard Pomeranz, MD, PhD</td>
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<td>Agnes Wong, MD, PhD</td>
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<td>Patrick Yu-Wai-Man, BMedSci, MBBS, PhD, FRCOphth</td>
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North American Neuro-Ophthalmology Society
40th Annual Meeting

March 1–6, 2014
Wyndham Rio Mar Beach Resort • Rio Grande, Puerto Rico

Program Schedule

FRIDAY, FEBRUARY 28, 2014
4:00 p.m. – 8:00 p.m. Registration Rio Mar Foyer

SATURDAY, MARCH 1, 2014
9:00 a.m. – 4:00 p.m. Catamaran Sail and Snorkel Depart from El Yunque
7:00 a.m. – 8:00 p.m. Registration Rio Mar Foyer
7:00 a.m. – 9:00 p.m. Breakfast Rio Mar 6-10/Caribbean
7:00 a.m. – 4:00 p.m. Exhibits Rio Mar Foyer
8:00 a.m. – 4:30 p.m. When Neurosurgery & Neuro-Ophthalmology Collide [6.5 CME] Rio Mar 1-5
Organizers: Karl Golnik, MD, Neil Miller, MD & Steven Newman, MD
This one-day, pre-NANOS meeting session is for neurosurgeons and neuro-ophthalmologists. It will include 4 sessions: “Crucial Co-Management Conditions”, “Was it There Before Surgery?”, “When Things Go Wrong” and “Neuro-Ophthalmology to the Rescue.” Each of these sessions will be maximally interactive with case discussions and audience response system used in addition to lecture!
Upon completion of this session, attendees will be able to: 1) List the pros and cons of treatments for IIH; 2) Discuss relevant comanagement issues regarding pituitary tumors, orbital apex lesions and cavernous sinus fistula; 3) Describe the importance of identifying pre-existing neuro-ophthalmic deficits prior to surgery; 4) Outline the various neuro-ophthalmic complications of neurosurgery and how to recognize them; and 5) List treatment options for visual loss and diplopia.
12:00 p.m. – 5:00 p.m. NANOS Board Meeting Pelican
6:30 p.m. – 8:00 p.m. Opening Reception (all are welcome) Ocean Terrace
8:30 p.m. – 11:59 p.m. Bioluminescent Bay Kayak Tour–SOLD OUT Depart from El Yunque

SUNDAY, MARCH 2, 2014
6:00 a.m. – 6:45 a.m. Yoga Class Gazebo
6:30 a.m. – 5:30 p.m. Registration Rio Mar Foyer
6:30 a.m. – 7:45 a.m. Breakfast Rio Mar 6-10/Caribbean
6:30 a.m. – 3:30 p.m. Exhibits Rio Mar Foyer
This session is designed to present a wide variety of neuro-ophthalmic cases to an audience of physicians with varying neuroscience backgrounds who have a common intellectual interest in the broad range of conditions that impact the human visual pathways and ocular motor systems.

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

At the conclusion of this program, 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.

This course is designed to procure the following desirable physician attributes: medical knowledge; work in interdisciplinary teams.
Frank B. Walsh Session I
Moderators: Preston Calvert, MD & Valerie Touitou, MD, PhD

8:00 a.m. - 8:20 a.m.  An Ironclad Diagnosis 17
Marc J. Dinkin, MD

8:20 a.m. - 8:40 a.m.  Which One is The Real Zebra 19
Madhura A. Tamhankar, MD

8:40 a.m. - 9:00 a.m.  Renal Red Herring 21
John J. Chen, MD, PhD

9:00 a.m. - 9:20 a.m.  A candid look at a missed diagnosis 23
Edward Margolin, MD

9:20 a.m. - 9:40 a.m.  A Case of Cotton Wool Spots 25
Golnaz Moazami, MD

9:40 a.m. - 10:10 a.m.  Coffee Break

Frank B. Walsh Session II
Moderators: Vivian Rismondo, MD & Robert Shin, MD

10:10 a.m. - 10:30 a.m.  Blame it on the Pill 27
Sachin Kedar, MBBS, MD

10:30 a.m. - 10:50 a.m.  It’s not the tumor 29
Courtney E. Francis, MD

10:50 a.m. - 11:10 a.m.  Beware the Trojan Horse 31
Denize Atan, MD, PhD

11:10 a.m. - 11:30 a.m.  It’s déjà vu all over again 33
Aileen A. Antonio-Santos, MD

11:30 a.m. - 11:50 a.m.  Muscle Bound or Unbound? 35
Dane A. Breker, MD

11:50 a.m. - 1:10 p.m.  Lunch (Included)
Frank B. Walsh Session III
Moderators: Eric Eggenberger, DO & Rudrani Banik, MD

1:10 p.m. - 1:30 p.m.  Wear and tear vision
Kkonrad P. Weber, MD 37

1:30 p.m. - 1:50 p.m.  Is it a Crime to be Blind? I plead the 4th!
Jasmine Gopwani, MBBS, FRCS (Glasg) 39

1:50 p.m. - 2:10 p.m.  More Than a Cu-bit of Vision Loss
Philip M. Skidd, MD 41

2:10 p.m. - 2:30 p.m.  Almost Catastrophic
Danielle S. Rudich, MD 43

2:30 p.m. - 2:50 p.m.  Innocent until proven guilty
Heather E. Moss, MD, PhD 45

2:50 p.m. - 3:20 p.m.  Coffee Break

Frank B. Walsh Session IV
Moderators: Shalom Kelman, MD & Luis Mejico, MD

3:20 p.m. - 3:40 p.m.  Ataxia at the Masquerade Ball
Krista I. Kinard, MD 47

3:40 p.m. - 4:00 p.m.  Burned by Diplopia
Bonnie M. Keung, MD 49

4:00 p.m. - 4:20 p.m.  I can’t stand the double vision
Iris Ben Bassat Mizrachi, MD 51

4:20 p.m. - 4:40 p.m.  Much-Ado About Acute Vision Loss
Mahsa A. Sohrab, MD 53

4:40 p.m. - 5:00 p.m.  A TAAD Bit Unusual
Nisreen K. Mesiwala, MD 55
An Ironclad Diagnosis

Marc J Dinkin¹,², George Parlitsis¹, Sarju Patel¹, Alex Merkler², Audrey Schuetz³, Cristiano Oliveira¹

¹Weill Cornell Medical College, Department of Ophthalmology New York, NY, USA, ²Weill Cornell Medical College, Department of Neurology New York, NY, USA, ³Weill Cornell Medical College, Department of Pathology New York, NY, USA

History & Exam

A 43-year-old man with AIDS and a CD4 count of 4, non-compliant with HAART, presented with four days of headache, photophobia and vision loss in his left eye. There was a history of treated syphilis and CMV retinopathy. On neuro-ophthalmological examination, visual acuities were 20/40 OD (formerly 20/25) and count fingers OS (formerly 20/20). He could see 12/12 color plates OD and 0/12 OS and there was a relative afferent pupillary defect OS. The left eye was slightly injected with anterior chamber inflammation. Funduscropy demonstrated a raised focal area of chorioretinitis with a few satellite lesions and adjacent retinal hemorrhages. Humphrey visual field testing revealed a temporal hemianopsia OD and severe diffuse field loss OS. Optical coherence tomography (OCT) demonstrated extension of the retinal lesion from the outer retinal layer inward, suggestive of spread from the choroid. MRI brain with contrast revealed a 9 x 16 x 12 mm enhancing, T2 hyperintense mass centered in and expanding the optic chiasm, suggestive of an optic pathway glioma versus lymphoma per neuroradiology. There was T2 extension into the left optic tract.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
An Ironclad Diagnosis
Answer
Final Diagnosis
Inflammatory demyelination of optic chiasm and tract due to infection by Mycobacterium haemophilum.
Summary of Case
Inpatient evaluation revealed a positive FTA and reactive RPR (1:8). ACE was elevated at 83U/L (reference 9-67 U/L).
Bacterial and fungal cultures, cryptococcal antigen and toxoplasma IgG/ IgM antibodies were negative. Quantiferon TB
gold was indeterminate. The patient was treated empirically with valgancyclovir, vancomycin, cefazolin, dapsone,
azithromycin, fluconazole and, to cover neurosyphilis, IV penicillin. Lumbar puncture revealed a mild pleocytosis of 9
WBCs, protein of 40 and glucose of 47. Gram stain, culture, KOH prep, cryptococcal antigen and HSV, CMV, VZV, EBV,
JC virus and toxoplasmosis PCR were negative. VDRL and treponema pallidum DNA PCR were negative. Beta-2
microglobulin was elevated at 2.7 (reference 0-2.4mg/L) but cytology and flow cytometry were negative, revealing only an
increased number of benign lymphocytic and monoctyoid cells. CSF ACE was normal at 1.4 U/L, there were no
oligoclonal bands, AFB culture showed no growth and MTB amplification was negative. The patient refused a second
lumbar puncture, but a vitreous biopsy revealed negative gram stain, culture, KOH prep and treponema pallidum assay.
There was an improvement on empiric antibiotics and IV methylprednisolone from CF to 20/80 OS, but this reversed with
cessation of steroids. As vision continued to worsen, a biopsy of a small portion of the optic chiasm was performed and
revealed lymphocytic infiltrates in a perivascular and parenchymal distribution, with massive demyelination and axonal
preservation. Biopsy was negative for spirochetes. However, acid fast stain revealed innumerable bacilli which PCR
revealed to be Mycobacterium haemophilum. The patient stabilized on a regimen of azithromycin, rifabutin, moxifloxacin
and prednisone. However, seven months later, in the setting of partial non-compliance with the antibiotic regimen, he
developed new left optic nerve enhancement, even as the chiasmal disease improved. One month later, with further noncompliance, there was new extension into the hypothalamus.
Struggle/Dilemma of the Clinical Presentation Description
This case underscores the challenges in diagnosing chiasmopathies in immunocompromised patients. Syphilis was
suggested by the history, but alternative infections and CNS lymphoma remained possibilities. Our dilemma was whether
to risk vision loss from chiasmal biopsy in exchange for the potential benefits of making an expedited diagnosis, allowing
directed therapy in a patient with precipitous visual loss. Finally, the lack of prior descriptions of this entity causing a
chiasmopathy added to the diagnostic challenge.
Keywords: Mycobacterium haemophilum, Optic chiasm, Demyelination, Chorioretinal lesion, HIV
References
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Phowthongkum, Puengchitprapai, Udomsantisook, Tumwasorn, Suankratay, Spindle cell pseudotumor of the
brain associated with Mycobacterium haemophilum and Mycobacterium simiae mixed infection in a patient
Sharma, Pradhan, Varma, Rathi, Irreversible blindness due to multiple tuberculomas in the suprasellar cistern,
Garg, Paliwal, Malhotra, Tuberculous optochiasmatic arachnoiditis: a devastating form of tuberculous
Lindeboom, Bruijnesteijn van Coppenraet, van Soolingen, Prins, Kuijper, Clinical manifestations, diagnosis,

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History & Exam
A 15-year-old male complained of headaches and nausea, two months after appendectomy. He also noted symptoms of nocturia and excessive thirst for two years. An MRI of the brain revealed an avidly enhancing suprasellar mass abutting the optic chiasm and extending into the hypothalamus. An oncologic evaluation included a negative PET/CT, normal serum and CSF markers (alpha fetoprotein and beta-human chorionic gonadotropin), negative CSF cytology, normal skeletal survey, and negative bone scan. On ophthalmologic examination vision was 20/20 vision in each eye with normal color, no APD and bilateral mild visual field defects. Optic nerve pallor was noted in both eyes. A transphenoidal biopsy revealed a dense inflammatory infiltrate composed of lymphocytes (CD4+ T cells and CD20+ B cells). There was no evidence of granulomas or malignancy noted in the specimen and the diagnosis of lymphocytic hypophysitis (LYH) was made. The patient was started on steroids and showed improvement in his visual fields to near normal. Five weeks later while on prednisone taper (15mg/day), the patient presented with visual decline in the left eye to 20/70 and worsening visual fields. An MRI showed no appreciable interval change of the nodular thickening and enhancement of the pituitary stalk, with enhancement and enlargement of the left more than right optic chiasm. Given the temporal relationship to tapering of the steroids, this was believed to be a persistent more aggressive inflammation that was involving the optic chiasm that is rarely reported in patients with LYH1. Given the rapidity of vision loss, the patient was treated with pulsed intravenous steroids that led to rapid visual recovery by two weeks. The vision after initial stabilization deteriorated while he was on prednisone 40 mg/day. From an endocrinological standpoint the patient remained stable. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
Which One is The Real Zebra

Answer

Final Diagnosis
Suprasellar germinoma with optic chiasm involvement.

Summary of Case
A repeat MRI showed an interval decreased thickening and enhancement of the infundibulum and sellar contents. Due to steroid related side effects, a rheumatologic consultation was obtained for consideration of steroid sparing agents and a re-review of the pathology was requested. Additional H&E stain recuts and immunohistochemical stains were performed for CD1a, 3, 4, 5, 8,10,20,68, 79a, 138, BCL1&6 and Ki67. Pathology showed an atypical lymphoid aggregate composed of CD20, CD 79a+ B cells with focally high Ki67 index, negative kappa and gamma staining. A very small focus of cells on the biopsy was seen which looked atypical although given the rarity of diagnosis, it was difficult to determine whether they were part of the inflammatory process or whether they represented a small focus of neoplastic cells. Given the lack of radiographic progression seen on MRI and modest response to steroids it was felt that this was an aggressive form of LYH. The patient was started on steroid sparing agents. Over the next 8 weeks he received mycophenolate, plasmapheresis, rituximab, and cyclophosphamide. After initial stability the vision progressively declined to 20/150 in the left eye with presence of bilateral visual field defects. An MRI scan continued to show stable enlargement of the pituitary stalk and the optic chiasm. The slides were sent to the National Cancer Institute for another opinion. CD-117 (c-kit) immunostaining was performed on the destained H&E section. The large atypical cells were strongly positive for CD 117 consistent with a CNS germinoma. A repeat metastatic work up was negative including negative lumbar puncture for cytology and tumor markers and a negative brain and spine MRI. The patient underwent proton radiation therapy and vision stabilized at 20/20 in the right eye and 20/80 in the left eye at last follow up visit.

Struggle/Dilemma of the Clinical Presentation Description
Optic neuritis has been rarely reported as a complication of LYH and can be steroid refractory (1). Lack of significant disease progression on imaging and the negative pathological markers did not support a malignant etiology despite attempts to rule out a neoplasm. LYH in children can mask an occult germinoma and rarely may be steroid responsive (2-5). This case reaffirms the need to maintain a high index of suspicion despite the initial response observed with steroid therapy.

Keywords: Optic neuropathy, Lymphocytic Hypophysitis, Germinoma

References

Renal Red Herring

John J. Chen¹, John J. Brinkley¹, Namrata Singh², Amanda C. Maltry¹, Bruno A. Policeni³, Richard C. Allen¹⁴, Reid A. Longmuir¹, Matthew J. Thurtell¹

¹University of Iowa Department of Ophthalmology and Visual Sciences Iowa City, IA, USA, ²University of Iowa Department of Internal Medicine Iowa City, IA, USA, ³University of Iowa Department of Radiology Iowa City, IA, USA, ⁴University of Iowa Department of Otolaryngology Iowa City, IA, USA

History & Exam
A 71 year-old Caucasian male with a history of Wegener’s granulomatosis presented with vision loss OU and horizontal binocular diplopia. His past medical history was significant for Wegener’s granulomatosis, which was diagnosed in 2000 on the basis of a renal biopsy. He was previously treated with various combinations of cyclophosphamide, azathioprine, and prednisone. His recent treatment regimen had included oral prednisone (7.5mg daily) and azathioprine (150mg daily). However, against medical advice, he had stopped taking his immunosuppressants for six months prior to his presentation in June 2013. His past history was also remarkable for Graves’ disease, atrial fibrillation, hypertension, diabetes, and subdural hematoma in 2008 requiring surgical evacuation. At presentation, he reported a several week history of binocular horizontal diplopia on leftward gaze and concurrent progressive vision loss OS>OD. He also reported mild eye pain OS and occasional epistaxis. On examination, best-corrected visual acuity was 20/50 OD and 20/200 OS. Pupil examination demonstrated a 1.5 log unit RAPD OS without anisocoria. Intraocular pressures were normal. There was 3 mm of relative proptosis OS with a moderate abduction deficit OS. Anterior segment examination revealed cataract OS. Dilated funduscopic examination showed trace temporal optic disc pallor OS. Goldmann visual fields revealed central depression OD and a dense cecocentral scotoma OS. The RNFL thickness was within normal limits OU on optical coherence tomography. B-scan ultrasonography of the orbits revealed a highly-reflective mass superotemporally in the posterior orbit OS. MRI showed a well-circumscribed extraconal lateral orbital mass. CT demonstrated a soft tissue mass in the left orbital apex extending into the superior orbital fissure with associated erosion of the greater wing of the sphenoid, but without associated calcification. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
Renal Red Herring

*Answer*

**Final Diagnosis**
Renal cell carcinoma metastasis to the orbit.

**Summary of Case**
Workup revealed a positive P-ANCA of 1:2560 and myeloperoxidase antibodies (MPO) of >8.0. Proteinase 3 antibodies were negative. While the high P-ANCA titer was suggestive of a possible relapse of Wegener’s granulomatosis, imaging of the lesion demonstrated heterogeneous signal on FLAIR with adjacent bony erosion, minimal inflammatory changes, and no sinus disease, which were all atypical of Wegener’s granulomatosis. Because there was a compressive optic neuropathy OS and the imaging findings were atypical for orbital involvement from Wegener’s granulomatosis, a lateral orbitotomy with biopsy of the orbital mass and lateral decompression of the orbit was performed, for diagnostic and therapeutic purposes. Histologically, the lesion consisted of lobules of clear cells separated by a fine capillary network. The cells had round to oval-shaped nuclei and clear cytoplasm, some with foamy cytoplasmic vacuoles. The nuclei ranged from bland to moderately pleomorphic, with nuclear vacuoles and prominent nucleoli. Immunohistochemical stains were positive for pancytokeratin, AE1/AE3, vimentin, and PAX 8 with weak focal positivity of the RCC marker. Staining was negative for cytokeratin 7. These pathologic findings were consistent with metastatic renal cell carcinoma to the orbit. The patient did not have a prior history of renal cancer. Subsequent CT scan of the chest, abdomen, and pelvis revealed a 11 x 15 x 11 cm right renal mass compatible with renal cell carcinoma. The CT also showed multiple pulmonary nodules and a lytic lesion in the right proximal femur, suspicious for metastases. Cytoreductive nephrectomy was considered, but was not recommended because of the distant metastases and co-morbidities. In addition, he was not a candidate for immunotherapy or for an autologous vaccine trial due to his immunosuppression for underlying Wegener’s granulomatosis. He is scheduled to start radiation therapy to the femoral lesion and will undergo pazopanib chemotherapy.

**Struggle/Dilemma of the Clinical Presentation Description**
The patient’s symptoms began while off immunosuppression for his Wegener’s granulomatosis and were initially thought to represent a relapse of Wegener’s granulomatosis. Secondly, despite Wegener’s granulomatosis commonly affecting the kidneys, associated renal cell carcinoma has been reported rarely. To our knowledge, this is the first report of renal cell metastasis to the orbit as the presenting sign of an underlying primary renal cell carcinoma in a patient with Wegener’s granulomatosis.

**Keywords:** Wegener's Granulomatosis, Renal Cell Carcinoma, Diplopia, Optic Neuropathy, Metastasis
A candid look at a missed diagnosis.

Edward Margolin\(^1\), Jasmine Gopwani\(^1\), Robert Willinsky\(^1\)

\(^1\)University of Toronto, Department of Ophthalmology and Vision Sciences and Dept of Medicine, Division of Neurology
Toronto, ON, Canada, \(^2\)University of Toronto, Department of Medical Imaging Toronto, ON, Canada

**History & Exam**

A 37 year old woman with a history of migraine noticed an increased frequency and severity of headaches for the past year. She had visited multiple emergency rooms and consulted her family physician on many occasions. She was diagnosed with migraine, stress, and “drug seeking” presumed from a history of past (intravenous?) heroin use. Eventually she presented to the emergency department of our hospital complaining of worsening headache severity and a new onset of blurred vision in both eyes. Visual acuity was 20/200 OU, and both optic nerves were severely swollen with multiple hemorrhages. Humphrey Visual Fields (24-2) demonstrated severe constriction. Her BMI was 18.5. She admitted to intravenous drug use in the past but insisted that she had not used illegal drugs for the past 1.5 years and had been actively participating in Narcotics Anonymous meetings. The urine drug screen was negative for all commonly tested illicit drugs. After MRI of the brain and orbits was interpreted as normal, lumbar puncture revealed an opening pressure of 53 cm of water. CSF analysis demonstrated a protein of 2.71g/L, glucose of 0.6mmol/L and WBC count of 583. CSF cultures as well as testing for syphilis, viruses, fungi, acid fast bacilli, Lyme disease, inflammatory markers, sarcoidosis, and lymphoma were all negative on repeated testing. Headache persisted despite a transient decrease in symptoms after the lumbar puncture, lumbar drain insertion, and treatment with high doses of oral acetazolamide and oral steroids. Eight subsequent lumbar punctures disclosed negative grain stains and cultures, smears, flow cytometry and cytology testing. A diagnostic procedure was performed.

**Financial Disclosures:** The authors had no disclosures.

**Grant Support:** None
Final Diagnosis
Candidal meningitis causing bilateral disc edema and increased intracranial pressure in an immunocompetent patient.

Summary of Case
Tenth lumbar puncture was performed. It returned a positive culture of *Candida albicans*. Smears however were still negative. Treatment with liposomal amphotericin B was initiated and led to resolution of headaches and improvement of the bilateral disc edema. The patient was discharged home after 2 weeks. Unfortunately, she was readmitted 3 weeks later with the recurrence of all original symptoms. High protein and low glucose in CSF usually betoken infectious meningitis, with neoplastic and sarcoid-associated meningitis as less likely causes. In this case bacterial and viral meningitis were unlikely given that symptoms were present for a long time, and the patient was relatively well. The remaining most likely cause was fungal meningitis. Repeated testing for cryptococcal antigen, histoplasmosis, blastomyces and coccidium (most common causes of fungal meningitis) was negative. The patient was considered immunocompetent (repeated testing for HIV was negative) although the past history of intravenous drug abuse was likely a risk factor for fungal meningitis. After a prolonged course of intravenous and oral antifungal therapy and several readmissions, visual acuity improved to 20/40 bilaterally, optic nerve head edema resolved, and visual fields improved. The patient was left with residual bilateral optic neuropathy. When initial MRI was re-examined, subtle enhancement of meninges was noticed which was previously overlooked.

Struggle/Dilemma of the Clinical Presentation Description
*Candida albicans* meningitis is very rare in immunocompetent individuals. We found no reported cases of it causing persistently elevated intracranial pressure with papilledema. This case is a reminder that multiple CSF cultures and smears might be required for a positive yield when fungal meningitis is suspected. Fungal meningitis should be considered in cases with persistently elevated intracranial pressure and papilledema. Subtle enhancement of meninges should be looked for on MRI when CSF formula is suggestive of meningitis.

Keywords: Candida Meningitis, Papilledema, Increased intracranial pressure

References
**A Case of Cotton Wool Spots**

*Golnaz Moazami, Hermann Schubert, Sampson Jacinda, Riley Claire*

*Columbia University New York, NY, USA*

**History & Exam**

A 31 year old Caucasian male was admitted to a local ER after being found unresponsive on a couch at home, incontinent of urine, and having vomited with tongue bruising. He was arousable in the ER but febrile to 102 F with WBC= 19,000. He was loaded with dilantin, and emergency CT showed a left posterior temporal lesion with surrounding edema. He was given IV dexamethasone, empirically started on vancomycin, ceftriaxone, and acyclovir. No LP was performed. He was transferred to our NICU for further work-up. An MRI with contrast was performed which showed multiple T2/FLAIR hyperintense foci within the subcortical and deep white matter. A rim-enhancing lesion was noted in the left posterior temporal lobe measuring 18 X 21 X 11 mm. MR spectroscopy demonstrated slightly increased choline ratio and a lipid peak. His past history was notable for bilateral hip replacement secondary to avascular necrosis, “migraines” for the past three years, and “scotoma” in the right eye of unknown etiology with a reported negative MRI, MRA, and LP six months prior. Repeat imaging 3 days later showed no improvement on MRI, and a procedure was performed. The patient developed tingling of his lower extremities, uncontrolled hypertension, heptosplenomegaly, and proteinuria, at which point MRI of T and C-spine was performed and ophthalmology and nephrology consult requested. On exam, visual acuity was 20/20 OD and 20/50 OS. Slit lamp exam was negative. Color plates were 4/6 OU. He had no RAPD. A diagnostic procedure was performed.

**Financial Disclosures:** The authors had no disclosures.

**Grant Support:** None.
A Case of Cotton Wool Spots

Answer

Final Diagnosis
Herns syndrome= hereditary endotheliopathy with retinopathy, nephropathy, and stroke.

Summary of Case
31 year old male with family history of father dead from brain tumor at age 57, past history of avascular necrosis requiring bilateral hip replacement , three year history of migraines, and visual scotoma who presented with seizures secondary to a brain mass which was biopsied and resected. The brain biopsy showed extensive coagulative necrosis of parenchyma with many macrophages, organizing hematoma, no granulomas, and no neoplasm. He was found to have retinal vascular disease, and acute renal failure. Renal biopsy was performed and showed extensive duplication of glomerular basement membrane with ischemic and segmental sclerosing features suggestive of chronic endothelial injury.

Struggle/Dilemma of the Clinical Presentation Description
The patient was initially thought to have a brain tumor; later work-up initiated for demyelinating disease was unfruitful. The clinical eye findings were pointing to vasculitis with ischemia. The endotheliopathy from the kidney biopsy along with the patient's family history led to genetic testing which finally led to the diagnosis.

Keywords: Hereditary, Retinopathy, Cerebrovascular, Endotheliopathy, Nephropathy

References

Blame it on the Pill

Sachin Kedar1,2, Padmaja Sudhakar1, Stuart Tobin3, William O Connor4, Fernando Decastro5

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History & Exam
A 62 year old white male developed headache, blurred vision, redness and watering in both eyes a week after starting a male enhancement pill, ExtenZe®. Three months earlier, he had been evaluated for malaise and weight loss and found to have lymphopenia, elevated TSH (20.3) and anti-thyroid peroxidase antibody (2874) with normal T3, ESR, B12 and folate. Ophthalmic exam revealed bilateral optic disc edema and normal visual acuity with enlarged blindspot and inferonasal field defect in the right eye. Contrast enhanced MRI of the brain and orbits was normal. Lumbar puncture on two occasions revealed opening pressures of 36 cm and 42 cm of H2O respectively with normal CSF contents. He was treated with acetazolamide for presumed pseudotumor cerebri. Shortly thereafter, he developed a rash on his legs that was attributed to “poison ivy” from “mowing his lawn”. When it spread to his abdomen and arms, it was attributed to drug allergy either from acetazolamide or ExtenZe® and both were discontinued. He was seen by a dermatologist and a skin biopsy was “non-diagnostic”. Neuro-ophthalmic exam (2 months from onset of papilledema) revealed visual acuity of 20/30 OD and 20/20 OS. He had an irregular pupil with posterior synchiae OD but no afferent pupillary defect in either eye. He had anterior vitreous cells OD, and keratic precipitates, AC flare and optic disc edema in both eyes. Humphrey visual fields were unchanged. Fluorescein angiogram showed disc leakage in both eyes. A pustular eruption with necrosis and scab crusting on a pink red inflammatory base distributed in a serpiginous fashion was seen across the chest and extremities. A procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Blame it on the Pill

Answer

Final Diagnosis

Summary of Case
A second skin biopsy at our institute revealed mixed dermatitis pattern with features of granuloma annulare and neutrophilic dermatosis consistent with Sweet’s syndrome. Work-up for systemic malignancy was negative. The rash improved with a course of prednisone but led to steroid induced diabetes. He developed hoarseness of voice and dyspnea. Laryngoscopy revealed laryngitis and an ulcer on the epiglottis. He had an elevated ESR (114), CRP (8), ANA (1:320), and myeloperoxidase antibody (MPO)(21). High-resolution chest CT showed interstitial lung disease. Pulmonary function testing revealed FVC of 85% and FEV1/FVC of 92%. Right lobe wedge biopsy of the lung revealed obliterative fibrosis and smooth muscle metaplasia in areas of prior bronchioles, typical for chronic obliterative bronchiolitis usually associated with collagen vascular disease. The constellation of findings of positive ANA, lymphopenia (at presentation), neutrophilic dermatosis, interstitial lung disease (BOOP- bronchiolitis obliterans with organizing pneumonia) and positive MPO was highly suggestive of systemic lupus erythematosus (SLE). He was started on azathioprine and prednisone was tapered. This resulted in resolution of disc edema in the right eye and improvement in the left. A follow up contrast enhanced MRI of brain and orbits was normal. A follow up lumbar puncture (for headache) showed normal opening pressure (11 cm H2O), and normal CSF contents. Sweet’s syndrome (SS) is an acute neutrophilic dermatosis characterized by erythematous plaques and papules that presents with fever and leukocytosis, usually seen in association with autoimmune disease, malignancy or medication use. Neuro-sweet is believed to be a distinct entity with meningoencephalitis as the cause of raised CSF pressure leading to papilledema.

Struggle/Dilemma of the Clinical Presentation Description
Initial presentation with papilledema, normal brain MRI, elevated CSF opening pressure and normal CSF led to a presumed diagnosis of “pseudotumor cerebri”. Lack of high grade fever, leukocytosis and inflammatory markers made diagnosis of SS and SLE difficult. Skin rash was erroneously attributed to allergic reactions that delayed correct diagnosis. Subsequent development of skin rash, epiglottis ulcer, respiratory complaints and arthralgia prompted immunological studies and biopsies that confirmed diagnosis.

Keywords: disc edema, Lupus, Sweet syndrome, Headache, increased intracranial pressure

References
**History & Exam**

A 58 year old woman with a history of metastatic parotid adenocarcinoma presented with bilateral vision loss over 2 months. She had undergone surgical resection of the tumor followed by fractionated external beam radiation with a total of 66.6 Gy 18 months prior to presentation. She was recently found to have metastatic disease involving V3 and Meckel’s cave on the left. On initial exam, her vision was 20/125 right eye, 20/50 left eye, without APD. She had reduced color vision in both eyes (2.5/14 right eye, 3/14 left eye). She had a left facial droop secondary to her parotid resection with resulting mild exposure keratopathy in the left eye. Posterior segment exam was unremarkable. Perimetry was normal in the left eye and showed superior/central depression in the right eye. The day following initial evaluation she underwent stereotactic radiosurgery to her left middle cranial fossa lesion, with a total dose of 2.12 Gy to the left optic nerve. Her vision loss progressed to counting fingers in the right eye and 20/200 in the left eye over the following month and at last follow-up was 8/200 right eye and 4/200 left eye.

**Financial Disclosures:** The author had no disclosures.

**Grant Support:** Unrestricted departmental grant from Research to Prevent Blindness
Final Diagnosis
Leber hereditary optic neuropathy (11778 mutation).

Summary of Case
She was initially prescribed lubricating eye drops by an outside ophthalmologist. After initial neuro-ophthalmologic evaluation, she underwent MRI brain and orbits to evaluate for optic nerve enhancement due to concern for radiation optic neuropathy. The MRI showed no optic nerve enhancement or compression. Fluorescein angiography revealed no macular disease. Full field ERG was normal. VEP showed marked prolongation of the P100 bilaterally. High volume lumbar puncture including cytology was unremarkable. Paraneoplastic panel was negative. MTDNA testing was positive for 11778 mutation.

Struggle/Dilemma of the Clinical Presentation Description
The patient developed bilateral sequential vision loss in the setting of metastatic adenocarcinoma and prior radiation. She was not of the typical age at onset, did not have the typical optic nerve findings, and denied any family history of LHON. LHON has commonly been described to have an inciting stressor (alcohol, tobacco, medications). There are no reports of vision loss occurring in the setting of treatment of malignancy or in association with radiation therapy.

Keywords: Vision loss, Leber hereditary optic neuropathy, Radiation therapy

References

History & Exam
A 57 year-old Afro-Caribbean woman presented to the Emergency Department with a complete left sided ptosis, left internal and external ophthalmoplegia and no perception of light vision of the left eye. Her symptoms had progressed over the preceding 2 weeks associated with anorexia, fevers and weight loss. Her inflammatory markers were elevated with CRP=92mg/L and ESR=127mm/hr. She had a past ocular history of insulin-requiring type 2 diabetes mellitus causing proliferative diabetic retinopathy, which had been treated successfully with pan-retinal photocoagulation 2 years previously. Her last documented Snellen visual acuities were 6/9 in each eye. HbA1c on admission was 109mmol/mol (normal range 20-42mmol/mol). In addition, she had a medical history of systemic hypertension, hypercholesterolemia, and cerebrovascular disease treated with an antiplatelet drug, thiazide diuretic, ACE inhibitor and statin. Head and orbit MRI combined with CT demonstrated widening of the left superior orbital fissure and orbital apex with erosion of the bone of its medial wall. There was an ill-defined soft tissue mass extending into the left infratemporal fossa and mucosal thickening of the sphenoid sinus and fat of the left petrous temporal bone. Trans-sphenoidal surgery demonstrated a chronic inflammatory infiltrate of the respiratory epithelial mucosa without granulomata or evidence of malignancy. There was no evidence of fungal hyphae on periodic acid-Schiff and Grocott stains. No organisms were observed on Gram staining of the samples. However, subsequent enrichment cultures grew Staphlococcus epidermidis, Pseudomonas aeruginosa, and Propionibacterium acnes. The patient was treated empirically with intravenous anti-fungal and broad spectrum antibiotics but nevertheless developed left peripapillary flame and blot haemorrhages and cotton wool spots, indicating progressive retinal and optic nerve ischemia. Moreover, her renal function started to deteriorate. Consequently, she underwent further neuroimaging and a definitive procedure.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Final Diagnosis
This diabetic patient had a left orbitopathy, multiple cranial neuropathies, pachymeningitis and skull base osteomyelitis caused by *Pseudomonas aeruginosa*. The original source of the organism was an otitis externa that had remained clinically silent for 6 months.

Summary of Case
The patient had further contrasted MRI imaging of the head and orbit, showing persistent soft tissue swelling of the left orbital apex with intracranial extension along the meninges in the left temporal fossa and left cavernous sinus, and focal skull base osteomyelitis. She underwent a second trans-sphenoidal endoscopic biopsy and debridement of the left orbit. Gram stain of the biopsy showed pus cells but no organisms, and calcofluor stain did not demonstrate fungi. Nevertheless, enrichment cultures grew *Pseudomonas aeruginosa* sensitive to tazobactam. Importantly, histology of the second biopsy showed an acute on chronic sino-sinusitis with pyogenic response consistent with a bacterial not fungal infection. The patient was maintained on oral ciprofloxacin monotherapy and began to demonstrate clinical improvement with normalization of her renal function. Retrospectively, we found she had a 6-month history of chronic left otalgia following an episode of otitis externa that was treated with a short course of oral ciprofloxacin. Ear swabs at that time grew skin flora and *Pseudomonas* species that were thought to represent colonization by these organisms only. Though she did not complain of otorrhea or otalgia at the onset of her orbital signs, the ear canal was the most likely source of infection. Diabetics are particularly susceptible to malignant otitis externa (MOE) complicated by skull base osteomyelitis and multiple cranial neuropathies, which has a mortality of up to 50%1. Prompt diagnosis by tissue biopsy combined with debridement of necrotic tissue is required to maximize outcome4. Although most cases are caused by *Pseudomonas aeruginosa*, fungi and other organisms are also implicated2,3. The facial nerve or lower cranial nerves are most commonly involved in MOE, whereas involvement of the optic nerve is rare5,7. Nevertheless, an otological history ought to be sought from diabetic patients with suspected orbital infection.

Struggle/Dilemma of the Clinical Presentation Description
We initially made a presumptive diagnosis of fungal orbital infection, based on the patient’s history of poorly controlled diabetes. Our dilemma was whether we should continue her nephrotoxic intravenous antifungal medication when her renal function was deteriorating, knowing that we had not yet demonstrated fungal hyphae in her biopsy specimens and that this was very difficult to do. Subsequently, we based our management on definitive histological and microbial culture evidence with a good outcome.

Keywords: Diabetes mellitus, *Pseudomonas aeruginosa*, Malignant otitis externa, Skull base osteomyelitis, Multiple cranial neuropathies

References
It's déjà vu all over again

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History & Exam
A 51-year-old male with a history of amblyopia OD presented in February 1999 with hyperemia, swelling and periorbital pain of the left eye. Visual acuity (VA) was 20/80 OD and 20/25 OS; color vision was 10/11 Ishihara plates OU, and Goldmann perimetry showed an inferior quadrantanopia OS. There was an RAPD OS, a comitant 15-prism diopter esotropia, and a 5-mm proptosis OS. Brain and orbits CT and MRI showed enhancing retrobulbar masses. CBC, CMP, ANA were normal. ESR was 53. Further diagnostic work-up was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
It's déjà vu all over again

**Final Diagnosis**
Erdheim-Chester disease and glioblastoma multiforme

**Summary of Case**
X-rays of the femur showed sclerosis. CT showed peri-aortic soft-tissue thickening. A left orbital biopsy revealed diffuse xanthogranulomatous inflammation, fibrosis, and lymphoplasmacytosis, consistent with Erdheim-Chester Disease (ECD). The patient underwent 6 cycles of doxorubicin, cyclophosphamide, and vincristine, with subsequent azathioprine for 14 years. In December 2012, he developed a left middle cerebral artery (L MCA) stroke with residual right homonymous hemianopia (R HH). Immunosuppression was discontinued. Bone pain recurred. In April 2013, VA was 20/60 OD, 20/25 OS; Ishihara color vision was 10/11 OU. There was no RAPD. Automated perimetry showed R HH. Head CT revealed a new ring-enhancing right frontal lobe lesion, enhancing orbital lesions, and L MCA encephalomalacia. CT showed new perirenal infiltration and fascial thickening. Despite great debate regarding the etiology of his brain lesion, the patient declined further evaluation. He died 5 months later. Aside from orbital ECD, autopsy revealed pericardial (CD68+/CD1a-) and perirenal foamy histiocytic infiltrates with myxoid changes alternating with hyalinized fibrosis. There were other hypercellular intracerebral lesions aside from the right frontal mass on autopsy, with pleomorphic cells, mitoses, and necrosis, diagnostic of glioblastoma multiforme (GBM). There are no reported ECD cases with GBM. GBM may have developed secondary to chance mutation. Our other potential theories regarding GBM development in this long-standing case of ECD are: 1. BRF proto-oncogene mutations are seen in many ECD patients, gliomas, and GBM’s. This patient may have the genetic architecture to develop both ECD and GBM. 2. Chronic azathioprine use may increase neoplasm risk. In this case, azathioprine induced ECD remission, but possibly led to GBM development. Some azathioprine-treated patients have developed BRF-mutation-associated tumors. Since 1999, interferon-alpha has significantly improved survival for ECD patients. Vemurafenib, an BRF-mutant inhibitor, has been used with promising results.

**Struggle/Dilemma of the Clinical Presentation Description**
The patient had long-bone sclerosis and biopsy-proven Erdheim-Chester Disease (ECD), a rare non-Langerhans histiocytosis. He was treated with azathioprine, but was lost to follow-up. He discontinued azathioprine 14 years later. A new intracerebral lesion developed. Although intracranial ECD has been reported, these are mostly meningeal or involve the hypothalamic-pituitary axis. Autopsy revealed a right frontal lobe glioblastoma multiforme (GBM). It is unclear whether chronic immunosuppression or an ECD-associated oncogene mutation contributed to GBM development.

**Keywords:** Erdheim-Chester disease, glioblastoma multiforme, immunosuppression, second malignancy

**References**

Muscle Bound or Unbound?

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History & Exam
A 52 year old former Olympic athlete developed myalgias, cramping, and stiffness in the upper arms, chest, thigh, and calves in 2009 after a blood transfusion for hematochezia attributed to antiplatelet treatment following coronary stenting. Symptoms were worst in the morning, when he could not walk. Simvastatin was stopped without improvement. There was no history of fever, night sweats, or skin lesions and no pertinent family history. Neurologic examination was normal except for increased gastrocnemius muscle bulk and percussion-induced waves of muscle contraction in the calves and thighs. EMG showed infrequent gastrocnemius fasciculations but no evidence of neuropathy, myopathy, or myositis. Percussion-induced muscle contraction was not electrically silent. Paraneoplastic panel demonstrated elevated striated muscle and acetylcholine receptor antibody titers, but single-fiber EMG did not demonstrate increased jitter or blocking. There was a high CPK (500), slight elevation in liver enzymes, and low 25-hydroxy vitamin D. CBC, vasculitis panel, myositis antibody profile, ESR, CRP, hepatitis screening, HIV, SPEP/UPEP, B12, and thyroid studies, CT of chest, abdomen, and pelvis and caveolin-3 (CAV3) genetic testing were normal. A 7-day trial of prednisone 20mg/day did not improve CPK elevation or cramping. Four months later, the patient developed diplopia and was sent for neuro-ophthalmologic examination.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
Muscle Bound or Unbound?

Final Diagnosis
Autoimmune rippling muscle disease and myasthenia gravis.

Summary of Case
Neuro-ophthalmic examination disclosed left upper lid ptosis that worsened with prolonged upgaze. Ocular ductions were brisk, full, and smooth without nystagmus. There was a left hypertropia that varied with gaze position. Our diagnosis is rippling muscle disease (RMD) and myasthenia gravis (MG). First described in 1975, RMD is characterized by muscle stiffness, cramping, and percussion-induced muscle contractions that are electrically silent in the genetic form with mutations in caveolin-3 (CAV3). Our patient’s features suggested acquired RMD, an autoimmune disorder with antibodies against titin, a sarcomere support protein. MG also has anti-titin antibodies and shares some overlapping immunoreactive sequences with RMD, but was not associated with RMD until 1996. In 1995, Kosmorsky et al reported (at this meeting and in the JNO) a patient who had muscle rippling and intermittent esotropia attributed to muscle cramping because the EMG did not show a decremental response. Muscle biopsy showed findings consistent with RMD. Because MG was not suspected, neither acetylcholine receptor antibody (ARAB) testing nor single-fiber EMG was done. Three years later, that patient was examined elsewhere by Ansevin et al, who reported florid ocular and systemic myasthenic signs and only mild muscle rippling, a positive ARAB, EMG electrodecrement, and clinical improvement following edrophonium chloride testing. Repeat muscle biopsy showed the findings described by Kosmorsky and later by Schoser et al. Review of those reports led our pathologist to consider the findings distinct from either MG or genetic RMD. Thirteen cases of coexisting RMD and MG have since been reported, but only one has had RMD symptoms preceding MG, and none has had elevated ARAB in the absence of MG symptoms, as our patient had. Treatment of our patient with pyridostigmine 240mg/day worsened the rippling and cramping, a previously reported phenomenon. Prednisone 20 mg/day rapidly improved all manifestations.

Struggle/Dilemma of the Clinical Presentation Description
The diagnosis of RMD was a challenge because the more common form of RMD is usually genetic, yet family history was absent, genetic testing was negative, and rippling was non-silent. The diagnosis of MG was not suspected initially despite the very elevated acetylcholine receptor antibody level because he had neither clinical manifestations nor EMG evidence of that condition. This "pre-clinical" form of MG is rare.

Keywords: Rippling muscle disease, Myasthenia, Anti-titin antibody, Autoimmune diseases

References
Wear and tear vision

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History & Exam
A 66-year-old woman presented with a four-month history of insidious bilateral visual loss. Ophthalmologic examination revealed visual acuity reduced to finger counting in both eyes. On fundus examination, maculae and optic discs appeared normal. Visual fields showed bilateral central scotoma with mainly nasal defects. Past medical history was extensive including type 2 diabetes and coronary artery disease with myocardial hypertrophy. Surgical history included bilateral hip replacements with revision on the left. Review of systems was notable for recurrent depression, fatigue and decreased appetite with weight loss. She also complained of paresthesias in her hands and feet, imbalance, and bilateral hearing loss. Electroretinography (ERG) revealed severe cone dysfunction. Based on the clinical and ERG findings, cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR) or autoimmune retinopathy (AIR) was suspected. An extensive tumor screening including brain MRI, FDG-PET-CT and anti-CNS antibodies (including anti-recoverin for CAR) did not reveal any small-cell lung carcinoma, gynecologic tumor, melanoma or other malignancy. Autoimmune screening was negative. Two years after first presentation, the patient consulted an orthopedic surgeon because of chronic left hip pain and muscle tenderness after hip replacement surgery. A diagnostic test was performed.

Financial Disclosures: K.P. Weber received funding for travel and acts as an unpaid consultant to GN Otometrics.

Grant Support: None
**Wear and tear vision**

*Answer*

**Final Diagnosis**
Cobalt neurotoxicity from hip prosthesis abrasion.

**Summary of Case**
Radiography of the hip was suggestive of periarticular wear debris around the prosthesis. As the patient underwent hip prosthesis revision, the surgical site revealed a worn-down CoCrMo metal head with high quantities of metallic debris around the prosthesis. The blood test revealed extremely elevated cobalt levels (6975 nmol/l, normal <17) confirming the diagnosis of cobalt neurotoxicity. Endogenous cobalt poisoning may induce toxic effects in both retinal ganglion cells and optic nerve fibers (1, 2). Previously reported cases described improvement of sight after metal ion concentrations decreased. Although cobalt concentrations decreased rapidly during the months after hip revision, the patient’s vision did not improve. Our patient’s course suggests that the neurotoxic effects may be irreversible when cobalt poisoning persists for too long at very high levels. In hindsight, the deterioration of the patient’s general condition including many of her varied symptoms could be attributed to cobalt toxicity (3). The patient did not only suffer from vision loss, but also from hearing impairment and imbalance. Accordingly, video head impulse testing demonstrated bilateral vestibular loss. Although the patient has not been formally tested, the acral paresthesias could be indicative of a cobalt-induced polyneuropathy. In addition, the patient suffered from cardiomyopathy, as confirmed by heart muscle biopsy showing cardiomyocytic degeneration, vacuolation and atrophy, as well as mild fibrosis. The circumstances leading to the toxic metallosis in the hip could be explained by the sequence of implants used (4). Initially, the hip prosthesis had to be revised because of a fracture of the ceramic femoral head (5). The ceramic head was then replaced by a metal head paired with a polyethylene inlay. Presumably, fine ceramic particles left behind from the broken head subsequently adhered to the polyethylene inlay grinding down the new metal head like a grindstone.

**Struggle/Dilemma of the Clinical Presentation Description**
The patient suffered from insidious visual loss accompanied by a gradual decline of her general condition. She was turned upside down to find a presumed malignant cause – without success. At that stage, the neuro-ophthalmologists were clueless. The mystery was only solved by the presence of mind of the orthopedic surgeons, who initiated investigations for cobalt poisoning, when they saw the x-rays demonstrating destruction of the femoral head.

**Keywords:** Visual loss, Cobalt toxicity, Hip prosthesis, Retinopathy, Optic neuropathy

**References**

History & Exam

A 30 year old previously healthy man from Sudan presented to a community hospital with a seizure. MRI revealed a "right frontal lobe tumor". Brain biopsy was performed but the pathology findings were inconclusive. Initial interpretation was “brain tissue with increased cellularity consistent with gliosis but no evidence of malignancy”, however second opinion was of “gliomatosis cerebri with the growth pattern of exceptionally extensive infiltration”. Yet another pathologist read it as “mild lymphocytic meningitis with no definite neoplasia”. CSF analysis demonstrated mild lymphocytosis but normal cytology and flow cytometry. The patient was treated conservatively until nine months later when he was admitted for a psychotic episode with hallucinations after attempting to stab the floor nurse with a knife. Neuro-imaging revealed new a left frontal lobe lesion. Second brain biopsy was suggestive of chronic encephalitis and meningitis. Extensive infectious work-up was negative. Neuroimaging was unchanged. Six months later vision on the right deteriorated over two weeks to no light perception, vision on the left was 20/20. The right optic nerve was very pale. MRI, in addition to previous surgical changes, showed enhancement of the right optic nerve. A course of high dose intravenous steroids was given; however, the vision remained unchanged on the right, and two months later vision in the left eye started to deteriorate and measured 20/70. Another course of high dose intravenous steroids was administered. Extensive work up including CT chest/abdomen/pelvis, repeated CSF analysis, neuroimaging, and multiple serologies was non-contributory. One month later vision in the right eye improved to light perception and dramatically declined on the left to no light perception. Another course of high dose steroids was administered. MRI demonstrated leptomeningeal enhancement and involvement of the cavernous sinus. A gold quantiferon test returned positive and presumptive diagnosis of tuberculous meningoencephalitis was made. Triple anti-tuberculous therapy was initiated. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
Final Diagnosis
Immunoglobulin G4-related hypertrophic pachymeningitis involving cerebral parenchyma and causing severe bilateral optic neuropathy.

Summary of Case
Patient was transferred to quaternary center 1.5 years after initial presentation for repeat brain and dural biopsy. Repeat MRI revealed bilateral worsening of pachymeningeal thickening and enhancement especially along left cavernous sinus and anterior and middle cranial fossae extending to the superior orbital fissure. The diagnosis of tuberculous meningitis was at this point rejected because of negative cultures/PCR performed on the biopsy specimen, long survival, and high pre-test probability of a positive gold quantiferon test given patient’s background. The third brain biopsy demonstrated dura with large collections of mixed inflammatory cells consisting of lymphocytes, plasma cells and macrophages and multiple vague non-caseating granulomas. No abnormal mitotic figures, atypia or necrosis were seen. Immunohistochemical stains revealed mixed population of CD3+ and CD20+ lymphocytes, CD138+ plasma cells, CD68+ macrophages. Various IgG stains were all positive including IgG, IgA, IgG4, IgM and IgD. This was consistent with diagnosis of hypertrophic pachymeningitis. Hypertrophic pachymeningitis (HP) is an inflammatory condition in which the dura mater of the cranium or spine becomes thickened, leading to symptoms that result from mass effect, nerve compression, or vascular compromise. The differential diagnosis of hypertrophic pachymeningitis includes immune-mediated conditions such as rheumatoid arthritis, vasculitis, malignancies and infections. Because in this case staining for IgG-4 was positive and patient presented initially with a brain mass, it was concluded that this case represents IgG-4-related disease as a cause of HP. IgG-4 related disease is a recently described entity which can cause tumefactive lesions at multiple locations and has been proposed as a common etiology of non-infections HP.

Struggle/Dilemma of the Clinical Presentation Description
This case is unique in its presentation of hypertrophic pachymeningitis with frontal lobe lesions and severe bilateral optic neuropathy, no response to several courses of steroids, and brain biopsies with dramatically different interpretations. Final diagnosis was eventually reached after the third brain biopsy and staining for IgG-4. Familiarity with this disease which produces tumefactive lesions and dural thickening could have led to much earlier diagnosis, initiation of sustained immunosuppression, and possibly a better outcome.

Keywords: Pachimeningitis, IgG-4

References
History & Exam
A 45 year-old, right-handed, man, presented after awakening with no vision in his left eye. Two days earlier he had experienced a brief episode of binocular horizontal, and then oblique, diplopia. One week prior, he developed left facial numbness and “sinus pain” on the same side; a five day course of azithromycin did not improve his symptoms. The patient’s medical history included only a migratory arthritis previously labeled ankylosing spondylitis. He had been treated with steroids, hydroxychloroquine, and sulfasalazine, but was off all medications at the time of the vision loss. Review of systems was positive for unexplained 20 pound weight loss over three months, night sweats, and chills. He also had developed a raised nodule on each elbow, one from which he expressed “pus,” several weeks prior to his vision loss. He had a 20 pack-year history of cigarette use and occasionally used alcohol and marijuana. The family history and remainder of the social history were non-contributory. Neuro-ophthalmic examination showed the external appearance of the eyes and face to be normal. The vision was 20/20 with full color OD; no light perception OS. There was a relative afferent pupillary defect on the left; with no anisocoria or ptosis. There were full ductions OD; limited adduction (-4), elevation (-3) and infraduction (-1), with slow abduction OS. The anterior segments were normal. The right optic nerve was normal; on the left the nerve was slightly full with attenuated vessels. There was anesthesia of the face in the distribution of V2 on the left. Initial laboratory studies showed thrombocytosis (605), ESR of 38 and CRP of 5.4 (<0.7 normal). MRI was obtained. Lumbar puncture returned normal opening pressure and CSF composition. Further laboratory tests and a procedure were performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
More Than a Cu-bit of Vision Loss

Answer

Final Diagnosis
Polyangiitis with granulomatosis meningitis

Summary of Case
The patient was treated with five days of high dose intravenous steroids without improvement in his vision or strabismus. ANCA (160; <20 dils) returned elevated, with positive anti-proteinase 3 (PR3) antibodies (>8; <0.4). While the dural biopsy showed nonspecific vascular injury, and the elbow lesion biopsy suggested granulomatous inflammation, the clinical presentation of multiple cranial neuropathies with acute onset of symptoms, particularly the optic neuropathy, suggested an ischemic insult. This was supported by the lack of response to steroids and the MRI imaging. With support from the skin biopsy, a diagnosis of ANCA positive vasculitis, most consistent with polyangiitis with granulomatosis was given. He was transitioned from steroids to cyclophosphamide without progression (at two months when last seen). Repeat MRI at two weeks showed a significant decrease in the dural enhancement, with an increase in the abnormal T2 signal in the apical portion of the left optic nerve; there was still no enhancement of the nerve. He is followed by rheumatology with a plan for long-term immunosuppression. Additionally, the patient is followed by nephrology and pulmonology, despite no evidence at present for lung or renal disease. Polyangiitis with granulomatosis is an uncommon autoimmune disease that often affects the head and neck; neurologic manifestations are uncommon, and meningitis has only rarely been described in the past. In a large review, about a third of patients with ANCA-positive vasculitis presented with ophthalmic manifestations; only a small percent of these (<1%) present with oculomotor nerve palsy and/or optic neuropathy. Data are sparse, however there is some literature that suggests a poorer prognosis when anti-PR3 positive patients are compared with ANCA positive patients with positive anti-myeloperoxidase antibodies, and thus it is important to follow these patients closely and treat their disease aggressively.

Struggle/Dilemma of the Clinical Presentation Description
The patient had been worked up in the past for symptoms labeled “migratory arthritis.” Prior to the acute presentation with vision loss no definitive diagnosis had been made; there had not been prior justification for long-term therapy or monitoring for systemic involvement. MRI of his head showed diffuse meningeal enhancement, however, a biopsy of the dura was non-specific. It was the biopsy of a skin nodule which helped confirm the diagnosis, and guide treatment.

Keywords: Polyangiitis with granulomatosis, ANCA positive vasculitis, Posterior ischemic optic neuropathy, Meningitis, Anti-proteinase 3 antibodies

References

Almost Catastrophic

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History & Exam
A 36 year-old Caucasian male presented to his ophthalmologist with one month of headache, blurry vision, and intermittent diplopia. The patient denied transient visual obscurations, tinnitus, prior medical problems or use of steroids/Vitamin A/antibiotics. He was 235 pounds and 5’9”. Because examination showed bilateral optic disc edema he was referred to an ER where MRI/MRV/MRA showed a partially empty sella turcica and no cerebral venous sinus thrombosis (CVST). LP opening pressure was 40mmHg with normal CSF profile. Idiopathic intracranial hypertension (IIH) was diagnosed. Acetazolamide 500mg bid was started. He was discharged with recommended follow up with a neurologist in several weeks. He returned to his ophthalmologist who then referred him to neuro-ophthalmology. Blood pressure was 123/79. Visual acuity was OD 20/40+2, OS 20/30. Diplopia had resolved. There was no RAPD and he was orthophoric. Color vision (Ishihara) was 13/15 OU. Humphrey visual fields showed enlargement of the blind spot OU with inferonasal field loss OS>OD. Grade IV-V disc edema with hemorrhages and exudates extending into the macula was present OU. Given the dramatic papilledema and field loss, acetazolamide was increased to 500mg qid and optic nerve sheath decompression was scheduled. Prednisone was prescribed until surgery could be arranged. Pre-operative testing revealed microcytic anemia and thrombocytopenia (hemoglobin 7.1, hematocrit 23.4, platelets 45,000, MCV 48, PTT 31.4). Surgery was postponed and the patient was referred to a hematologist who felt that the patient had idiopathic thrombocytopenia and iron deficiency anemia. The patient then developed nephrolithiasis treated with a renal stent. Diamox was discontinued and prednisone was decreased. Several days later, he was found to have a rapidly rising BUN (53mg/dL) and creatinine (2.4 mg/dL). Urinalysis showed 2+ protein with many RBC and WBC. Additional testing was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
Almost Catastrophic

**Final Diagnosis**
Pseudo idiopathic intracranial hypertension with almost catastrophic antiphospholipid antibody syndrome with renal, ocular and hematological involvement.

**Summary of Case**
Further testing showed that the patient was positive for antiphospholipid antibody (APL), anticardiolipin antibody and lupus anticoagulant. Beta 2-glycoprotein 1 IgG was 4099GPL (normal <10GPL). Because of the rising BUN/creatinine, a kidney biopsy was performed which showed glomerular microthrombi, establishing the diagnosis of almost catastrophic antiphospholipid syndrome (CAPS) with renal, ocular and hematological involvement. Review of the first MRV and subsequent auto-triggered elliptic-centric-ordered (ATECO) MRV was negative for CVST. Review of old records showed prior thrombocytopenia and positive APL 2 years prior even though he was not aware of it. APS is characterized by thromboembolic events, including deep venous thrombosis, cerebral venous thrombosis, and glomerular microthrombi. It has been reported to cause elevated intracranial pressure, but usually, there is documented cerebral venous thrombosis. There are few reports of intracranial hypertension associated with APS in the absence of cerebral venous sinus thrombosis. The exact mechanism is unknown, but it has been hypothesized that intracranial hypertension may result from direct damage to the endothelial cells and arachnoid villi capillaries from the antiphospholipid antibodies, which impairs CSF flow. Pendse et al. reported a patient who initially presented as IIH with no evidence of CVST on MRV. The patient developed CVST a year later with fulminant catastrophic antiphospholipid syndrome (CAPS). Patients with APL who develop venous and arterial thrombosis in 3 or more organs in one week are diagnosed with CAPS. Their hypothesis for the initial presentation of IIH without thrombosis consisted of three possible mechanisms: 1. Chronic progressive evolution of CVST that was missed in multiple initial MRV. 2. Diagnostic procedure, i.e. Lumbar puncture, precipitating thrombosis, 3. Diuretics, i.e. acetazolamide, producing hyperviscosity, leading to thrombosis. Our patient was treated with IVIG, plasmapheresis, steroids and anticoagulation. He experienced improvement in his symptoms and visual fields and has had no other systemic complications.

**Struggle/Dilemma of the Clinical Presentation Description**
Determining the etiology of the papilledema was challenging. He presented with signs and symptoms of idiopathic intracranial hypertension, but also had thrombocytopenia and anemia without evidence of cerebral venous sinus thrombosis on MRV. As we followed the patient, he developed thrombotic glomerular microangiopathy and was found to have antiphospholipid syndrome, leading to the diagnosis of pseudo IIH secondary to antiphospholipid antibody with almost catastrophic antiphospholipid syndrome picture.

**Keywords:** Papilledema, Visual field loss, Cerebral venous sinuses

**References**

History & Exam
A 31 year-old male experienced right eye blurring and pain. He was diagnosed with optic neuritis and treated with IV steroids. Nine days later he developed headache, worsening vision, speech trouble and right-sided weakness. Two days later he developed low-grade fever and trouble walking. He had NLP vision in the right eye and saw 20/20 with a nasal field deficit with the left eye. There was bilateral disc elevation. He had receptive aphasia, right arm weakness, flaccid paraplegia, and a T4 sensory level. MRIs showed extensive enlargement and enhancement of the right optic nerve, a left temporo-parietal lesion with patchy enhancement, focal diffusion restriction, mass effect and hemorrhage, and non-enhancing, longitudinally extensive, spinal cord lesions. Extensive inflammatory (including NMO Ig), vascular and infectious evaluations were unrevealing. He was treated with IV methylprednisolone and plasma exchange followed by a steroid taper. Visual acuity improved to count fingers with the right eye. Two months after presentation he lost vision in the left eye. MRIs showed new diffuse enhancement of the left optic nerve and new enhancement of the spinal cord lesion. CSF had elevated IgG index/synthesis rate, but no oligoclonal bands. He had an IgG kappa monoclonal protein. Further testing for malignancy was unrevealing. Spinal cord biopsy showed a macrophage rich lesion. He was treated with IV methylprednisolone, plasma exchange and cyclophosphamide with recovery of left eye vision to 20/800. 7 months after presentation vision declined to light perception with the right eye and hand motion with the left eye. He received rituximab with improvement in left eye vision to 20/400. Eleven months after initial symptoms, while being treated for bacteremia he became unresponsive. MRI showed an extensive lesion of the brainstem and cerebellum with mass effect, patchy enhancement, focal diffusion restriction, and hemorrhage. Within 4 hours he lost brainstem reflexes and did not recover.

Financial Disclosures: The authors had no disclosures.

Grant Support: NIH K12EY021475
Final Diagnosis
Neuro-myelitis optica

Summary of Case
Post-mortem histopathologic examination of the brain stem/cerebellar lesion revealed extensive, focally necrotizing inflammation, primarily composed of neutrophils but with a significant number of CD68-positive macrophages and a smaller number of CD3-positive T-cells. CD20-positive B-cells were rarely detected. There was vascular and perivascular deposition of eosinophilic material. GFAP staining highlighted extensive fragmentation of astrocytic processes in perivascular areas. There was perivascular loss of aquaporin 4 immunoreactivity. Luxol fast blue-PAS special staining and neurofilament immunostaining indicated no selective loss of myelin. Immunofluorescence demonstrated perivascular reactivity for C3/C4, and IgG without reactivity for IgM, C1q, Kappa and Lambda. Lower spinal cord and left parietal lesion sections demonstrated atrophy and extensive multifocal cavitation associated with macrophagic infiltrates. There was significant myelin loss, axon loss and extensive gliosis. Eye and optic nerve sections demonstrated multifocal predominantly chronic but focally acute inflammatory infiltrates in the subarachnoid space around atrophic optic nerves. There was marked loss of retinal ganglion cells in the retina bilaterally. Special stains, immunostains, electron microscopy and postmortem cultures did not show evidence for infectious organisms. The clinical, radiographic and pathologic distinction of diseases on the demyelinating spectrum is challenging and evolving. At presentation, a diagnosis of acute hemorrhagic leukoencephalitis was favored. NMO was diagnosed based on disease progression and relapse. The pathologic findings of perivascular deposition of IgG, complement, neutrophilic infiltrates, loss of AQP4 and destruction of perivascular astrocytes support this. The mechanism of tissue injury in NMO including the relative timing of astrocytic injury versus demyelination due to secondary oligodendrocyte injury remains incompletely understood. It has been proposed that in a subset of NMO cases oligodendrocyte apoptosis and selective loss of minor myelin proteins occurs simultaneously with astrocyte pathology. Our case demonstrates extensive astrocytic pathology without significant selective demyelination and provides support for reports indicating that astrocyte injury predates demyelination in NMO.

Struggle/Dilemma of the Clinical Presentation Description
Though a disease on the demyelinating spectrum was the favored diagnosis from the outset, the hemorrhagic lesion and relapsing nature made categorization challenging. In the absence of proof, extensive testing was pursued to exclude other etiologies such as infectious, neoplastic, paraneoplastic and ischemic. Interpretation of serologic testing was tempered by concern that it was affected by immunomodulating therapy.

Keywords: Optic neuritis, Demyelinating disease, Autopsy

References
Ataxia at the Masquerade Ball

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History & Exam
A 52-year-old right-handed salesman presented in July 2007 with a 5-year history of slowly progressive imbalance. In 2002 he developed difficulty using his eyes together and then imbalance resulting in frequent backward falls. He reported oscillopsia and episodic vertigo. He later developed fatigue, dysarthria, memory and concentration complaints, weight loss, numbness of his right foot, easy bruising, and neurasthenia. He had a brother with trouble walking. After an extensive evaluation, he was diagnosed with spinocerebellar ataxia. On presentation in 2007 he had normal vision, saccadic pursuit, slow saccades, gaze-evoked rotatory and downbeat nystagmus, abnormal VOR suppression, esotropia with trace bilateral abduction deficits, and intermittent square-wave jerks. His neurologic exam showed dysarthria, a wide-based ataxic gait, unsteady tandem walk, absent ankle reflexes, and decreased peripheral sensation. Past medical history included hypertension, mononucleosis, hepatitis, pericarditis, and squamous cell cancer. Treatment with acetazolamide and memantine were not helpful. Symptoms worsened despite physical and occupational therapy. He became disabled and wheelchair bound. Brainstem evoked responses were abnormal. Nerve conduction studies, swallow evaluation, and neuropsychological testing were normal. Repeat MRI was read as normal except for microvascular disease. In 2014 Annual Meeting Syllabus | 47
Ataxia at the Masquerade Ball

Answer

Final Diagnosis
Primary CNS Vasculitis

Summary of Case
MRI from 2007 and 2012 were re-reviewed and multiple punctate hyperintense foci were identified that had not been previously appreciated. These foci had increased in number on repeat imaging in 2013. Brain biopsy May 2013 revealed multifocal perivascular and intramural chronic inflammatory cells, with focal astrogliosis and neither granulomas nor giant cells. Leptomeningeal biopsy showed fibrotic leptomeninges with hyperplastic meningotheial cells and psammoma body deposition. Immunohistochemistry was negative for CMV, VZV, congo red, and thioflavin. Immunohistochemical staining also showed predominantly CD3-positive T-cells. Cerebral angiogram showed irregularity of right and left internal carotid arteries and right vertebral artery suggestive of vasculitis. He was treated with steroids with complete resolution of the enhancing lesions on repeat brain MRI. His clinical picture has improved slightly on chronic immunosuppression. Primary CNS vasculitis is rare, with non-specific signs and symptoms of CNS dysfunction. It is regarded as a diagnosis of exclusion. Three histopathologic presentations are recognized: granulomatous, lymphocytic, and necrotizing. There are no validated diagnostic criteria for primary CNS vasculitis and although angiography is helpful, it has limited sensitivity. Brain biopsy has strong negative and positive predictive values. A Mayo Series followed 101 patients for an average of 13 months and found that 81% responded favorably to prednisone. Of these patients, there was increased mortality despite treatment and approximately one quarter had relapse of their illness. Pizzanelli et al. reported a series of 8 patients. Patients classified as having moderate disease were treated with steroids. Patients with severe disease were treated with steroids plus immunosuppression. Patients were followed for 7-62 months with only one patient suffering a relapse. They concluded that brain biopsy and angiography are helpful for diagnosis and that treatment should be tailored to the patient’s clinical picture until diagnostic and therapeutic guidelines are developed.

Struggle/Dilemma of the Clinical Presentation Description
The diagnosis of vasculitis was obscured by the patient’s predominant signs and symptoms, which mimicked spinocerebellar ataxia, with similar neurologic abnormalities in the family. His rate of decline was faster than is typically seen in SCA. This patient’s six-year clinical course was atypically indolent, as most primary CNS vasculitides are rapidly progressive.

Keywords: CNS vasculitis, CNS angiitis, Spinocerebellar ataxia, Brain biopsy, Angiography

References
Burned by Diplopia

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History & Exam
A 46 year-old Vietnamese man was seen in neuro-ophthalmology clinic for diplopia. In March 2012 he sustained a concussion and forehead laceration from a motor vehicle accident. In August 2012, he developed painless, binocular, vertical diplopia, which limited him from painting art. In November 2012, his examination showed -2 limitation of up-gaze OD. He had 18 prism diopters of right hypotropia at primary gaze; this increased to 30 prism diopters with upgaze. An MRI of the orbit showed an enlarged homogenously enhancing right superior rectus muscle. His thyroid studies, ACE and ANA levels were normal. Computed tomography (CT) of the chest was unremarkable. He received one month of oral prednisone taper and had complete resolution diplopia. Subsequently, he developed fatigable upper extremity weakness, which was initially presumed secondary to steroid myopathy. In January 2013, he was hospitalized for acute respiratory distress and dysphagia. In addition, he also presented with bilateral ptosis and generalized weakness. The acetylcholine binding antibody was elevated at 36.8 nmol/L (Ref <0.02). His total CPK was elevated at 798 ng/ml (ref<170) with evidence of cardiac myositis (CPK-MB 112 ng/ml ref <2.4 and troponin 0.078 ref <0.035). A muscle biopsy showed polymyositis. He also presented with pancytopenia with profound neutropenia (WBC 1500/ul) requiring treatment with filgastrin (Neupogen). He received IVIG and PLEX with good response, and was subsequently discharged on oral prednisone and filgastrim. He returned to the hospital on February 2012 with a Stevens Johnson–like rash. The dermatology service attributed this rash to filgastrin, therefore this medication was discontinued. However, despite termination of filgastrim, his rash worsened. A CT of the abdomen showed a mesenteric mass. A CT-guided biopsy of the mesenteric mass was inconclusive. An open biopsy was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
Burned by Diplopia

Answer

Final Diagnosis
The final diagnosis was follicular dendritic cell sarcoma with associated Castleman’s disease and paraneoplastic syndrome.

Summary of Case
His rash progressed with extensive perioral and skin desquamation involving 70% of the skin surface requiring transfer to a burn unit. The skin biopsy showed desquamation and lichenoid inflammation consistent with paraneoplastic pemphigus. Within a week, he succumbed to cardiopulmonary arrest. His constellation of symptoms is unified by a paraneoplastic process from follicular dendritic cell sarcoma (FDCS) causing: paraneoplastic pemphigus (PP), polymyositis, myasthenia gravis and autoimmune neutropenia. His serum paraneoplastic panel was positive for Acetylcholine Receptor Binding Antibody (36.8 nmol/L, ref <0.02), Acetylcholine Receptor Modulating Antibody (96% ref 0-20%) and Striational Antibody (1:2457 ref <1:60). Paraneoplastic pemphigus is a rare, life-threatening autoimmune bullous disease characterized by severe, intractable mucositis and polymorphous skin eruption, often times difficult to differentiate from Stevens-Johnson syndrome (SJS). Approximately 75% of SJS are caused by medications, 25% by infections and rarely malignancy (<1%). Our patient received filgastrim to treat neutropenia, and this drug was initially thought to be the cause of the extensive skin rash. Differentiating PP from SJS by skin biopsy is extremely important because PP is commonly associated with neoplasm while SJS is not. In addition, the use of IVIG is beneficial in PP and potentially harmful in SJS. In two thirds of cases, PP occurs in patients with a known neoplasm, while one third of patients develop the mucocutaneous disease before the neoplasm is detected. In one case report, PP was the first manifestation of FDCS (Kwei-lan et al). Castleman’s disease (CD) represents a non-neoplastic lymphoproliferative disorder with various clinical and morphological features that have been associated with FCDS. Despite this known association between CD and FDCS, there have only been few reported cases of FDCS with pre-existing CD, especially in abdominal lesions.

Struggle/Dilemma of the Clinical Presentation Description
Despite the involvement of multiple specialists, a unifying diagnosis was not made until late in his course. Different neuro-ophthalmologic diagnoses were considered as the cause of his diplopia including orbital pseudotumor, myopathy, and myasthenia gravis. One unanswered question is whether or not an orbit muscle biopsy early in presentation would have changed the outcome. Since his ophthalmoplegia resolved with steroids, this muscle enlargement may have represented autoimmune orbital myositis rather than metastasis.

Keywords: Paraneoplastic Pemphigus, Castleman's Disease, Follicular dendritic cell sarcoma , Myasthenia, Polymyositis

References
I can’t stand the double vision

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History & Exam
A 37 year-old woman was referred to our clinic due to bilateral ptosis and vertical binocular diplopia. She denied diurnal variations, muscle weakness or bulbar symptoms. In the past year she had been suffering from bouts of abdominal pain, diarrhea, and severe weight loss (>40 pounds), and she presented a few times with bowel obstructions. She underwent partial resection of the ileum and was treated with total parenteral nutrition and later on with percutaneous endoscopic gastrotomy (PEG). Her past medical history was significant for uncontrolled hypothyroidism. Familial history was positive for Crohn’s disease in her brother and myasthenia gravis in her father. On presentation to our clinic she was cachectic and very weak with difficulty standing. Visual acuity was 20/20 in both eyes, color vision and visual fields were normal in both eyes. She had 2 mm ptosis of her left upper eye lid without fatigue nor a change in eyelid position after 45 min rest. Pupils were 3 and 4 mm with sluggish reaction and light-near dissociation with no APD. Extraocular movements were full with right hypertropia, not consistent with a pattern of trochlear nerve palsy and no change after rest test. Fundoscopy was normal. Slit lamp examination demonstrated iris streaming and tear film insufficiency which was confirmed by Schirmer test.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
I can't stand the double vision

Answer

Final Diagnosis
Autonomic autoimmune gangliopathy in conjunction with myasthenia gravis

Summary of Case
MRI of the brain and orbit with contrast demonstrated a parietal lesion with enhancement and edema, brain stem was normal. Paraneoplastic panel, collagenogram, lactate, pyruvate, thymidine phosphorilase, southern blot for mitochondrial DNA, acetylcholinesterase antibodies including MuSK antibodies were all normal. Tension test was negative. Total body CT and PET CT ruled out malignancy. Colon pathology demonstrated enteric ganglionitis with degenerative neuropathy. The working diagnosis was autonomic failure and a complete autonomic evaluation was performed and demonstrated minimal RR variability, pathologic blood pressure reaction to Valsalva maneuver, abnormally low dihydroxyphenylglycol (DHPG), dihydroxyphenylacetic acid (DOPAC) and dihydroxyphenylalanine (DOPA). MIBG scintigraphy was compatible with sympathetic post ganglionic denervation. Due to the family history for autoimmunity, the diagnosis of autoimmune autonomic dysfunction was considered. Serum sample was positive for Ganglionic AchR antibodies, and the patient was diagnosed with autoimmune autonomic ganglionopathy (AAG). She was treated with IV methylprednisolone with minimal improvement and therefore was started on plasma exchange, mycophenolate mofetil and pyridostigmine. Two months into treatment ptosis and diplopia gradually improved, pupils did not change. She reports significant improvement in her bowel function and abdominal pain; she gained 20 pounds and eats a soft diet. Autonomic functions improved and she can currently function almost normally with elastic stockings. Her main concern is severe dry eye; Schirmer test at her last visit measured less than 1 mm after 5 minutes. Autonomic autoimmune gangliopathy is an immune mediated disease characterized by prominent involvement of autonomic nerves and ganglia that leads to severe diffuse autonomic failure. In 50% of patients with AAG, acetylcholine receptor autoantibodies against α3 subunit are detected in the serum. Patients usually present with signs and symptoms of widespread autonomic dysfunction evolving over days to month including orthostatic hypotension, gastrointestinal dysmotility, anhidrosis, sicca syndrome, and impairment of the pupillary light reflex. In the majority of patients the disease is idiopathic but it can be paraneoplastic in 15% of patients. Diplopia is not a reported complaint in patients with AAG; we therefore believe that she had a combination of AAG and an atypical pattern of myasthenia gravis, which was not confirmed by AchR antibodies, sfEMG or edrophonium testing.

Struggle/Dilemma of the Clinical Presentation Description
Myasthenia gravis is an autoimmune chanellopathy mediated by antibodies that target the α1 subunit of nAChRs at the neuromuscular junction, which differs from the α3 subunit attacked in AAG. Reports of patients having both AAG and MG are very rare; most cases are due to malignant thymoma or paraneoplastic syndrome. The resolution of the ptosis and diplopia with immunosuppressive treatment and plasmapheresis supports the diagnosis of MG. Normal paraneoplastic work-up and CT excluded malignancy.

Keywords: Myasthenia, Addies pupil, Autonomic Dysfunction, Autoimmune

References
Much-Ado About Acute Vision Loss

Mahsa A. Sohrab¹, Andrea Birnbaum¹, Michael Sidiropoulos², Lois Polatnick³, Nicholas J. Volpe¹

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History & Exam
A previously healthy myopic 35-year-old Caucasian man without any significant medical or surgical history developed acute bilateral vision loss. Six weeks prior to admission, he had progressive fatigue and right face, arm, and leg pain. He was diagnosed with sinusitis at an Urgent Care clinic and given amoxicillin, despite a documented penicillin allergy. He was subsequently admitted to the hospital with persistent symptoms including cough and shortness of breath, and underwent treatment for serology-proven Chlamydia pneumonia with levofloxacin and doxycycline. During his admission, he had acute renal failure with renal biopsy showing acute tubular necrosis that resolved with hydration, and received prednisone, valacyclovir for oral ulcers, and fluconazole for thrush. An initial MR study showed a focal left frontal white matter lesion consistent with developmental venous anomaly. He was discharged home in stable condition, returning one week later with blurred vision and a diffuse, non-pruritic rash involving his palms, soles, buttocks, genitals, and face. Given his persistent fevers, pancytopenia, and vision loss with negative thrombotic and vasculitic work-up, he was transferred for further evaluation. On examination, he had bilateral arm, leg, palm, sole, penile shaft and buttock skin scattered bullae and purpuric papules with hemorrhagic and necrotic centers. His visual acuity was count fingers at 6 feet in the right eye and no light perception in the left eye, with a superotemporal visual field defect by confrontation in the right eye. He had a right afferent pupillary defect. His intraocular pressures were normal and motility was full. His anterior segment examination was normal. Posterior segment examination revealed mild disc edema with scattered dot-blot hemorrhages and arteriolar attenuation in the right eye and florid disc edema with small vitreous hemorrhage and arteriolar attenuation with scattered dot-blot hemorrhages in the left eye.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
Much-Ado About Acute Vision Loss

Answer

Final Diagnosis
Bilateral Ischemic Optic Neuropathy secondary to Pityriasis Lichenoides Et Varioliformis Acuta (PLEVA) or Ulceronecrotic Mucha-Habermann Disease

Summary of Case
He was initially diagnosed with ischemic optic neuropathy and left eye vascular occlusions. However, fluorescein angiography (FA) revealed normal filling and transit times, inconsistent with retinal or choroidal vascular occlusions. Given these results, the disc edema was deemed secondary to an infiltrative neuropathy causing secondary ischemia with resultant multi-layered hemorrhages. Laboratory work-up revealed pancytopenia with negative HIV testing, hepatitis panel, Mycoplasma titer, Treponema antibody, cANCA, pANCA, CCP and dsDNA. The initial differential diagnosis included post-infectious or drug-induced hypersensitivity and hemophagocytic lymphohistiocytosis (HLH). Hematology ruled out HLH based on diagnostic criteria and review of peripheral blood smears.1-5 Repeat MRI brain revealed multiple hyper-intense cortical and subcortical white matter lesions concerning for emboli or meningoencephalitis, but lumbar puncture had normal opening pressure and was negative for infection. A diagnostic skin biopsy was then performed, revealing interface dermatitis with superficial and perivascular lymphocytic infiltrate without evidence of vasculitis, viral cytopathic changes, or tumor, consistent with pityriasis lichenoides et varioliformis acuta (PLEVA) or ulceronecrotic Mucha-Habermann disease versus erythema multiforme. A rare acquired dermatitis also thought to be a post-infectious immune system derangement, PLEV A is characterized by erythematous scaly papules with hemorrhagic, papulonecrotic lesions, CNS changes, high fevers, interstitial pneumonitis, pancytopenia, and diffuse intravascular coagulation.6-8 The patient improved on a one-week course of intravenous methylprednisolone, and was discharged home on oral prednisone, currently transitioning to methotrexate maintenance therapy. His right eye vision improved to 20/40 and final MRI revealed interval resolution of all hyper-intense lesions.

Struggle/Dilemma of the Clinical Presentation Description
Vision loss has not been reported in either erythema multiforme or PLEV A, but both could lead to immune complex-mediated infiltration causing bilateral ischemic optic neuropathy. While vasculitis would have been the simplest unifying diagnosis, biopsies did not support the diagnosis. Dermatopathologists disagreed between PLEV A versus post-infectious erythema multiforme. Given the rarity of CNS findings in PLEV A, a hypersensitivity drug-reaction from treatment with amoxicillin versus a post-infectious hypersensitivity from Chlamydia pneumonia also were suspected.

References
History & Exam
A 12 year-old previously healthy boy presented to the emergency room with a five-day history of progressive frontal headaches and acute onset of horizontal, binocular diplopia on left gaze. He had no significant medical history and his only significant ocular history was mild myopia and X-linked color-blindness. On ophthalmic exam, his vision was 20/20 OU, he identified 1/11 color plates OU, and had a normal pupillary exam with no relative afferent pupillary defect. His extraocular movements were full OD, with a mild deficit on abduction OS, and visual fields were full to finger counting. His anterior segment exam and fundus exam were unremarkable. He was diagnosed with a partial left CN VI palsy, and an MRI showed a 4cm mass abutting the pituitary gland on the left. CTA confirmed the mass as an aneurysm arising from the cavernous portion of the left internal carotid artery measuring 3.8x3.7cm. Four days after admission, he developed right-sided hemiparesis and left pupil dilation. An angiogram indicated acute thrombosis of his left internal carotid artery and no filling of the aneurysm. MRI showed a left middle cerebral artery stroke with multiple embolic strokes distal to the aneurysm. On reexamination, his visual acuity was 20/40 OS with 8mm fixed, dilated left pupil, with no relative afferent pupillary defect by reverse and complete ophthalmoplegia OS with 4mm of ptosis, 2 mm of levator function OS, no intorsion, decreased facial sensation V1-V3 on the left, full confrontation visual fields OU and otherwise unremarkable anterior and fundus exams. About 2 weeks after admission, CTA showed a stable, thrombosed left ICA and he was discharged with improvement in his hemiparesis and no changes to his ophthalmic exam.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
Final Diagnosis
Thoracic Abdominal Aneurysms and Dissection (TAAD) Spectrum with MYH11 mutation

Summary of Case
Two months after his initial presentation, a repeat CTA showed recanalization of the left ICA to the ophthalmic segment, so he underwent sacrifice of the left ICA one month later. About 5 months after initial presentation, his ophthalmic exam still showed visual acuity of 20/70 OS with fixed, dilated pupil but no RAPD, EOM OS with -4 supraduction -3 adduction -2 abduction -3 infraduction and some segmental, vermiform pupillary movements on adduction and downgaze, and lid retraction on downgaze. His visual fields remained full to FC, and he had severely decreased corneal sensation OS. His cornea was irregular and showed an area of paracentral thinning. The remainder of his exam is unchanged. Medical Genetics evaluated the patient given his aneurysm and to rule out a connective tissue disorder. His physical exam was significant for mild pectus excavatum of lower sternum, mild scoliosis, height in the 95-97th percentile, significant arm span to height ratio, high-arched palate, crowding of his teeth, hand to height ratio significant for arachnodactyly with hyperconvex nails and mild syndactyly of toes. He underwent DNA testing for a panel of twelve genes for connective tissue disorders and was found to have a heterozygous, missense mutation in the MYH11 gene consistent with Thoracic Abdominal Aneurysms and Dissection (TAAD) spectrum (1). His mother and sister also tested positive for the same mutation. MYH11 mutations are known to cause aortic valve abnormalities and patent ductus arteriosus in TAAD (2). Recent studies, however, indicate that TAAD and cerebral aneurysms may actually be a novel phenotype inherited as a single gene disorder (3), which may explain the cerebral aneurysm as the presenting feature for TAAD in our patient.

Struggle/Dilemma of the Clinical Presentation Description
1. Expansion of the mass caused the progressive cranial nerve palsies that remain the patient's greatest disability. Would surgical intervention have ameliorated this in any way? 2. What further testing is indicated for his mother and sister? 3. How/when should his ptosis be repaired? 4. Can he ever wear contact lenses?

Keywords: Aneurysm, Cranial Nerve Palsies, Internal Carotid Artery, Diplopia, Ptosis

References
Monday, March 3, 2014

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Moderators: Madhu Agarwal, MD & Janet Rucker, MD

Provision of evidence-based medicine is the ultimate goal of high quality medical care and this goal emphasizes the importance of familiarity with pertinent clinical trials and published literature. The symposium is designed to assist the practicing Neuroophthalmologist in review of recent important medical literature published on four neuro-ophthalmologic topics: transient ischemia and stroke prediction; myasthenia gravis, traumatic brain injury; and abnormal spontaneous eye movements. Each expert presenter will provide a critical review of recent clinical research studies, practitioner take home points, and ample time for audience interaction, questions, and discussion.

Upon completion of this session, attendees will be able to: 1) Utilize evidence-based medicine to direct the expedited evaluation and predict stroke risk of patients with transient monocular vision loss; 2) Apply an evidence-based approach to the diagnosis and management of myasthenia gravis; 3) Understand the importance of ocular motor testing in the field of traumatic brain injury; and 4) Prescribe medical treatments for various types of nystagmus, with an understanding of the underlying suggested pathomechanisms of treatment efficacy.

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

7:30 – 7:50 a.m. Journal Club: Update: Transient Ischemic Attack and Stroke Prediction

Valérie Biousse, MD

7:50 – 8:00 a.m. Q&A

8:00 – 8:20 a.m. Journal Club Update: Myasthenia Gravis

Judith Warner, MD

8:20 – 8:30 a.m. Q&A

Schedule continued on next page
In medical school we were taught “when you hear hoof beats, think horses not zebras”. However neuro-ophthalmology is the land of zebras. We tend to do a great job of thinking of them, but effective evaluations and treatment are less clear. The focus of this symposium is the rarer neuro-ophthalmic conditions, that we all consider in the differential diagnosis list, but for which there is often little evidence and fewer guidelines. During this session four speakers will distill a breadth of knowledge in the areas of paraneoplastic syndromes, toxic/nutritional optic neuropathies, IgG4 disease and hereditary optic neuropathies into clinically relevant pearls.

At the conclusion of this program, participants should be able to: 1) Approach diagnosis and treatment of possible paraneoplastic syndromes in an effective and efficient manner; 2) Apply Koch’s postulates to determine toxic optic neuropathy causality; 3) Understand how IgG4 disease fits within the framework of orbital, brain and systemic pseudotumors; and 4) Outline alternative and experimental treatment strategies for inherited optic neuropathies.

This course is designed to procure the following desirable physician attributes: medical knowledge; employ evidence-based practice; critically appraise the current evidence...
The use of Visual Electrophysiology in neuro-ophthalmology practices is increasing. These techniques provide functional information about the visual system that can complement or enhance the clinical examination as well as structural information provided by optical imaging modalities. There is increasing use of these techniques both for clinical purposes, but also as a method to study neurologic disease in general. It is critical for the neuro-ophthalmologist to understand the role of these tests, limitations of their use, and the role they play in localizing functional deficits in the visual system. This session will review basic techniques, their role in clinic and in clinical research, and discuss how neuro-ophthalmologists can incorporate these tests into daily practice. There will also be a live, hands on demonstration of these techniques.

At the conclusion of this program, participants should be able to: 1) Understand the role of visual electrophysiology in a neuroophthalmology practice and clinical research; 2) Better understand how to match each test to a specific clinical question; and 3) Develop a better understanding of test interpretation and common artifacts.

Neuro-ophthalmologists are in the unique situation of utilizing a variety of examination techniques that overlap between neurology and ophthalmology. Many Neurology trained neuro-ophthalmologists have only one year of training to learn ophthalmic skills, while Ophthalmology trained neuro-ophthalmologists only three months in advanced strabismus and minimal exposure to the general neurologic examination. A panel of experts in neuro-ophthalmology including an orthoptist will discuss these techniques and then divide into small groups to demonstrate and have the participant improve their skills hands-on. Key topics will include: Retinoscopy (use of retinoscopy/lens racks), Binocular vision examination (Worth 4 dot, prism cover test measurement, Maddox Rod and Double Maddox Rod), Color vision testing, Gradient acuity testing, Contrast acuity testing, Lancaster red/green and neurologic examination pearls.

At the conclusion of this program, participants should be able to: 1) Learn the nuances of advanced examination skills and equipment used in neuro-ophthalmology; 2) Gain hands on experience with the equipment needed for these techniques; and 3) Learn how to integrate these examination skills into neuro-ophthalmic practice and patient care.

While all our welcome to attend, this forum is specifically designed for residents, fellows and neuro-ophthalmologists in the early years of their career. We have incorporated last year’s positive, constructive feedback and present a re-vamped format. The revised forum will have multiple rotating roundtable discussions in small groups facilitate by YONOs, who have just walked in your footsteps, to mid-career folks, who can shed light on the next steps ahead.
Topics include: How to negotiate your first contract (academic and private practice), Demystifying academic promotion: from assistant to associate professor, a hands-on CV workshop: how to put your best foot forward on paper (bring your CV), and neuroophthalmology 2014: how to blend your neuro-ophthalmic career with pediatrics, oculoplastics, clinical research and more! Because you asked, we will also work to provide additional networking opportunities with fellowship directors and prospective employers during the latter half of the forum!

5:00 p.m. – 7:00 p.m. SCIENTIFIC PLATFORM PRESENTATIONS: SESSION I [2 CME] Rio Mar 1-5
8:30 p.m. – 11:59 p.m. Bioluminescent Bay Kayak Tour–SOLD OUT Depart from El Younque Foyer
LEARNING OBJECTIVES

1. To understand the basis for the new definition of TIA and its consequences for TIA diagnosis and management
2. To recognize the need for developing strategies for immediate evaluation and treatment of patients with transient visual loss presumably related to transient ischemia or the eye or brain
3. To be able to predict the risk of stroke in patients with transient visual loss and adequately triage patients with transient visual loss based on risk stratification

CME QUESTIONS

1. Regarding patients presenting with transient visual loss, choose the correct answer:
   a. Retinal TIA patients should be managed as outpatients because the risk of stroke is small and the prognosis usually good.
   b. Retinal TIA patients do not need to have brain imaging.
   c. Recent AHA guidelines recommend that patients with transient visual loss be evaluated emergently similar to patients with cerebral TIAs.
   d. The risk of cardiovascular death is lower in retinal TIA patients than in cerebral TIA patients.

2. Diagnostic recommendations after a TIA include the following (choose one correct answer):
   a. Neuroimaging evaluation within 24 hours of symptom onset, preferably with magnetic resonance imaging, including diffusion sequences (DWI-MRI).
   b. Noninvasive imaging of the cervical vessels.
   c. Electrocardiography as soon as possible after TIA; prolonged cardiac monitoring and echocardiography in patients in whom the vascular etiology is not yet identified.
   d. Hospitalization of patients with TIA if they present within 72 hours and have an ABCD2 score ≥ 4, indicating high risk of early recurrence, or if the DWI-MRI is abnormal, or if the evaluation cannot be rapidly completed on an outpatient basis.
   e. All of the above.

3. Regarding the risk of stroke after a TIA (choose one correct answer):
   a. Approximately 10 to 15% of patients have a disabling stroke within 3 months after a TIA, with half occurring within 48 hours after resolution of the TIA symptoms.
   b. Hemispheric TIA from severe internal carotid artery stenosis is associated with the highest risk of stroke (20% at 3 months) compared with other causes.
   c. The risk of stroke after a TIA is much higher when the DWI-MRI is abnormal, reinforcing the need to admit all TIA patients who have an abnormal DWI-MRI.
   d. One of every 4 patients with acute retinal ischemia has acute brain infarction on brain DWI-MRI. 18% of patients with retinal TIA have positive brain DWI-MRI.
   e. All of the above.

KEYWORDS

1. Transient visual loss
2. Retinal transient ischemic attack
3. Transient ischemic attack
4. Stroke
5. Risk stratification

INTRODUCTION

Transient ischemic attacks (TIAs) are common and portend a high-short term risk of stroke. Recent guidelines from the American Heart Association and National Stroke Association suggest that all TIA patients should be evaluated emergently in a specialized unit, either as an inpatient or outpatient, based on local availability. The risk of stroke and vascular death is high after a retinal TIA, and patients with presumed vascular transient visual loss should be evaluated and treated similarly to those with transient cerebral ischemia or minor stroke. Neuro-ophthalmologists need to establish standardized protocols to assure rapid and complete evaluation and treatment for patients with TIA, with particular attention to urgency and close observation in patients at high risk of stroke.
PART I: TRANSIENT ISCHEMIC ATTACKS (TIA): THE FACTS

INCIDENCE AND PREVALENCE OF TIA / BURDEN OF STROKE

- The estimated incidence of TIA in United States is around 200,000 to 500,000 per year with a population prevalence of 2.3% (translates into about five million individuals) [1,2,3].
- TIAs account for approximately 0.3% of ER visits [4].
- Precise estimates of the incidence and prevalence of TIAs are difficult to determine due to the varying criteria used in epidemiological studies to identify TIA.
- Lack of recognition of the transitory symptoms likely leads to gross underestimates.
- Approximately 15% of strokes are heralded by a TIA [3].
- The short-term risk of stroke after TIA is ~3% to 10% at 2 days and 9% to 17% at 90 days [3].
- Individuals who have had a TIA and survive the initial high-risk period have a 10-year stroke risk of approximately 19% and a combined 10-year stroke, myocardial infarction, or vascular death risk of 43% (4% per year) [3].
- Within 1 year of TIA, ~12% of patients will die [3].
- Stroke mortality has declined in recent years, but stroke remains the primary cause of disability in the US, and its resulting economic and social burden is enormous [3].

LACK OF PUBLIC AWARENESS OF TIA

- Most health professionals and the public consider TIAs benign but regard strokes as serious. These views are incorrect. Stroke and TIA are on a spectrum of serious conditions involving brain and eye ischemia, just as angina and acute myocardial infarction are part of the continuum of acute coronary syndromes [5,6].
- Both TIA and stroke are markers of reduced cerebral and ocular blood flow and an increased risk of disability and death. However, TIAs offer an opportunity to initiate treatment that can forestall the onset of permanent disability.
- A nationwide survey in the US found that only 8% of laypersons were able to correctly define or identify one common manifestation of TIA [2].
- More than one third of patients with a diagnosis of TIA do not seek medical attention within 24 hours of the event, resulting in delayed management [5,6].
- Physician compliance with current guidelines is poor, and more educational efforts to increase healthcare providers’ awareness of the danger of TIA are needed.

THERE IS A NEW DEFINITION OF TIA

The American Heart Association revised the most recent definition of TIA, describing it as “a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction” [8].

- The new definition of TIA includes the absence of acute brain infarction on diffusion-weighted imaging (DWI).
- This newly proposed definition of TIA by the American Heart Association implies that a brain MRI with DWI be performed immediately on all patients with suspected TIA (including those with retinal TIAs).

URGENCY IN THE MANAGEMENT OF PATIENTS WITH TIA

- Large cohort and population-based studies reported in the last 10 years have demonstrated a higher risk of early stroke after TIA than generally suspected.
- 10 to 15% of patients have a stroke within 3 months, with half occurring within 48 hours after resolution of the TIA symptoms [7,8,9].
- Acute treatments for TIA have also evolved, with new data supporting early (within 2 weeks, and ideally within 2 days of the TIA) rather than delayed carotid endarterectomy for TIA patients with carotid stenosis [10].
- The risk of cardiac events is also elevated after TIA [7,8,9,10].

Any patient with suspected TIA should be evaluated urgently in order to identify those at high risk of immediate stroke and cardiac ischemia.

This includes all patients with transient visual loss whether due to occipital TIA or retinal TIA.

NEW CLASS I AND CLASS II EVIDENCE HAVE LED TO RECOMMENDATIONS FOR THE RISK STRATIFICATION AND MANAGEMENT OF ALL PATIENTS WITH SUSPECTED TIA.

- Patients with TIAs are at high risk of early stroke, and their risk may be stratified by clinical scale, vessel imaging, and magnetic resonance imaging, including diffusion sequences (DWI-MRI) [7-17].
- Diagnostic recommendations include [7-11]:
  - TIA patients should undergo neuromaging evaluation within 24 hours of symptom onset, preferably with DWI-MRI.
  - Noninvasive imaging of the cervical vessels should be performed and noninvasive imaging of intracranial vessels is reasonable.
  - Electrocardiography should occur as soon as possible after TIA and prolonged cardiac monitoring and echocardiography are reasonable in patients in whom the vascular etiology is not yet identified.
  - Routine blood tests are reasonable (see below).
It is reasonable to hospitalize patients with TIA if they present within 72 hours and have an ABCD2 score ≥ 4, indicating high risk of early recurrence, or if the DWI-MRI is abnormal (when DWI-MRI shows acute cerebral ischemia in any part of the brain), or if the evaluation cannot be rapidly completed on an outpatient basis.

**RETINAL TIAS ARE AS BAD AS CEREBRAL TIAS**

- Most health professionals and the public consider retinal TIAs benign with a low risk of subsequent stroke. This is incorrect.
- The risk of stroke, cardiac events and death after a true retinal TIA is likely as high as for patients with a cerebral TIA [18].
- One of every 4 patients with acute retinal ischemia has acute brain infarction (anywhere) on brain DWI-MRI [19].
- 18% of patients with retinal TIA have positive brain DWI-MRI [19].

**PART II: JOURNAL CLUB - MAJOR RECENT ARTICLES ON TIA**

**REVIEWS ON MOST CURRENT MANAGEMENT OF TIA:**


**HEART DISEASE AND STROKE STATISTICS:**


**NATIONAL GUIDELINES (CAN BE DOWNLOADED FROM RESPECTIVE WEBSITES):**

**NATIONAL STROKE ASSOCIATION:**


**NICE (UK):**


**AMERICAN HEART ASSOCIATION:**


STROKE RISK STRATIFICATION AFTER TIA:


TIA MANAGEMENT AND COST:


RETINAL ISCHEMIA:


PART III: CEREBRAL TRANSIENT ISCHEMIC ATTACK (TIA)

CLINICAL VIGNETTE 1:

A 65-year-old man calls his physician immediately after recovering from a 10 minute episode of difficulty speaking and weakness of the right side of his face and right arm. His medical history is unremarkable. How should he be treated?

Recent scientific studies have revised our understanding of 3 key aspects of TIA:

1. How it is best defined.
2. What the early risk of stroke and other vascular outcomes is.
3. How it is best evaluated.
4. Definition of TIA

DEFINITION OF TIA

According to the World Health Organization criteria proposed in 1988, TIA is defined as rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting less than 24 hours, with no apparent nonvascular cause [12].

The past decade has seen a shift in emphasis from the time-based (<24 hours) to the tissue-based definition of TIA, which includes symptom duration < 1 hour and the absence of acute infarction on diffusion-weighted imaging MRI (DWI-MRI) [13,14,15]. This has resulted in DWI-MRI being used to fulfill a key role in the diagnostic evaluation of patients with TIA. Indeed, numerous studies have shown that between 30 and 50% of patients with traditionally defined TIA have evidence of infarction somewhere in the brain on MRI [14,15,16]. It is important to emphasize that these acute infarctions seen on DWI-MRI are often small and multiple and can be found anywhere in the brain, not necessarily corresponding to the clinical symptoms (for example, a patient with a retinal TIA may have an abnormal brain DWI-MRI, with acute infarcts obviously not corresponding to the clinical symptoms).

The American Heart Association recently revised the newly proposed definition of TIA, describing it as “a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction” [8,16]. The typical symptom duration is less than 1 or 2 hours; however, prolonged episodes do occasionally occur. Evidence of acute infarction detected by DWI-MRI (and ocular funduscopic examination) among patients with TIA distinguishes between TIA and ischemic stroke and portends higher risk of stroke after TIA.
DIFFICULTIES IN DIAGNOSING TIA:

Because neurologic and visual symptoms are by definition transient, the clinical examination is classically normal, and therefore the diagnosis relies exclusively on the clinical history alone, and specifically on the recollections of the patient who was neurologically or visually impaired during the event. This makes the diagnosis of TIA difficult for the non-specialist and the rate of falsely positive diagnosis of TIA is relatively high, particularly in the ED. Episodes misdiagnosed as TIAs are heterogeneous and include those due to migraine, seizure, vasovagal syncope, arrhythmia, hypoglycemia, anxiety, and conversion disorder [8,17,18,19]. However, specific symptoms are more reliable than others to make a presumed diagnosis of TIA.

Hemispheric TIA (carotid artery TIA): relatively easy
Any acute hemiparesis, hemisensory loss, aphasia, dysarthria, hemianopia (often described as non-specific acute visual loss)

Retinal TIA (carotid artery and ophthalmic artery TIA): more difficult
Acute, monocular visual loss; partial (altitudinal) or complete, but most often blackout of vision (not “blurry”, or “difficulty focusing”)

Posterior circulation TIA (brainstem and occipital lobes): difficult
– false positive diagnosis of TIA common
Acute vertigo, dizziness, gait instability, confusion, dysarthria, visual disturbances (including diplopia and binocular visual loss), particularly if more than one symptom at the same time

TWO CASE SCENARIOS WITH THE SAME CLINICAL HISTORY, BUT DIFFERENT OUTCOMES:

Acute binocular visual loss lasting 15 minutes and resolving completely.
- Normal examination and normal visual fields
- Normal DWI-MRI of the brain

TIA evaluation and management per local stroke neurology protocol

STROKE
Admission to stroke unit for immediate evaluation and treatment

Acute binocular visual loss lasting 15 minutes and resolving completely.
- Normal examination and normal visual fields
- Abnormal DWI-MRI of the brain (acute infarction in the left hemisphere)
Overall, stroke is preceded by a TIA in approximately 15% of patients, and a quarter of these will occur shortly after the TIA [3,20,21].

For decades, it was clear that the long-term (3-5 years) outcome of ischemic stroke following TIA was as high as 30 to 40%. However, in 2000, new data suggested that much of this risk is front-loaded in the first hours to days after the TIA [22]. Numerous studies confirmed this subsequently. The risk of stroke is highest within the first 24 hours and decreases thereafter [23,24,25,26].

Approximately 10 to 15% of patients have a disabling stroke within 3 months after a TIA, with half occurring within 48 hours after resolution of the TIA symptoms.

RISK OF STROKE AFTER A TIA

The risk of stroke is also high after a TIA. In one large study of 1327 patients [27], 2.6% of TIA patients were hospitalized for major cardiovascular events (myocardial infarction, unstable angina, or ventricular arrhythmia) within 3 months.

Individuals who have had a TIA and survive the initial high-risk period have a 10-year stroke risk of approximately 19% and a combined 10-year stroke, myocardial infarction, or vascular death risk of 43% (4% per year) [3].

There have been numerous attempts over the past decade to create a validated risk-stratification tool that is easy to apply and provides clinicians with realistic estimates of stroke risk after TIA. The California score (in 2000) [22], and the ABCD score (in 2005) [28] have both been shown to predict short-term risk of stroke well in independent populations of patients presenting acutely after a TIA.

The ABCD2 score published in 2007 [29] represents the combined efforts of the authors of the California and ABCD scores and has demonstrated the best predictive ability. This score was designed to be used in primary and emergency care settings by identifying high-risk individuals to facilitate triage to specialist care and target secondary prevention [4]. The ABCD2 score is based on clinical features identifiable at the time of initial assessment, before specialist evaluation, and deliberately does not include the results of brain imaging. However, although the ABCD2 score was developed for use in cohorts of patients before investigation, the possibility has been raised that prognostication might be improved after evaluation in secondary care by the incorporation of information from investigations, particularly the presence of brain infarction on imaging [25,30]. Therefore, to enhance the discriminative ability of the ABCD2 score, several imaging enhanced scores have recently been developed (Tables 1,2,3) [31-38]. Many authors consider the presence of a new infarct on brain imaging (which was consistent with the classic definition of TIA but would now lead to a diagnosis of stroke) more valuable than clinical scores [31-38]. Indeed positivity of DWI is associated with an approximately 2- to 15-fold increase in subsequent short-term risk of stroke. Although, several studies have shown that the presence of brain infarction on DWI is associated with individual elements of the ABCD system [35], others have also demonstrated that brain infarction provides additional prognostic information and that incorporation of an infarction component into the scoring system (ABCD2I) was justified [14]. Only the ABCD2-I score included CT data and found that it was equal to DWI-MRI in improving the predictive power of the ABCD2 score [14]. Evidence of vessel occlusion on acute brain magnetic resonance angiography also has been associated with a 4-fold increased short-term risk of stroke [34]. The ABCD2 scoring system, including brain and carotid imaging was subsequently suggested [36].

RISK STRATIFICATION AFTER TIA

There have been numerous attempts over the past decade to create a validated risk-stratification tool that is easy to apply and provides clinicians with realistic estimates of stroke risk after TIA. The California score (in 2000) [22], and the ABCD score (in 2005) [28] have both been shown to predict short-term risk of stroke well in independent populations of patients presenting acutely after a TIA.

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<table>
<thead>
<tr>
<th>Score</th>
<th>Date of Publication</th>
<th>Imaging modality</th>
<th>Summary of changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD2</td>
<td>July 2009</td>
<td>DWI-MRI or CT</td>
<td>-Scores 3 points for the addition of abnormal imaging, defined as acute or old infarction on CT or DWI-MRI</td>
</tr>
<tr>
<td>ABCD3</td>
<td>November 2010</td>
<td>DWI-MRI+carotids</td>
<td>-Scores 2 points for DWI-MRI lesions -Scores 2 points for history of previous TIA within the preceding 7 days -Scores 2 points for ≥50% ipsilateral carotid stenosis using ultrasound, CTA or MRA</td>
</tr>
<tr>
<td>ABCD+</td>
<td>January 2012</td>
<td>DWI-MRI</td>
<td>-Scores 3 points for DWI-MRI lesions and large artery atherosclerosis -Scores 1 point for cardioembolism, small arterial occlusion, or undetermined cause</td>
</tr>
</tbody>
</table>
Although the addition of early DWI-MRI has aided the overall short-term stroke risk prediction in patients with TIA, it adds little insight into the underlying vascular mechanism responsible for the event, and therefore is limited in prognosticating future events [15,37].

It is important to emphasize that there are different uses of the ABCD² score:

- One is a pre-hospital triage tool that can be viewed as a “surrogate” for investigations to predict the risk in places where emergent evaluation (within hours after the TIA onset) is not possible. However, when TIA units are available, triage based on actual findings of immediate investigations should be preferred.

- Some use the ABCD² score after complete initial evaluation as a triage tool to determine who should be observed in the hospital for more than 24 hours. It has been suggested that all patients with TIA be evaluated as early as possible within 24 hours of call to medical attention regardless of ABCD² score to detect all patients needing immediate treatment to prevent a stroke [37].

**HOSPITALIZATION AFTER TIA**

Because stroke risk after TIA is reduced by immediate medical or surgical intervention, emergent evaluation and treatment is warranted. Current guidelines recommend immediate evaluation and treatment of TIA patients by a specialized physician [8,9,10]. Therefore, structures able to provide services for acute stroke care should be available 24/7. Models vary among hospitals and both hospitalization and dedicated TIA evaluation units (often associated with an ED) have proven effective.

In many places, the best way to access this service is through the ED where immediate access to a specialist, laboratory testing, cardiac monitoring and brain imaging is readily available.

Hospitalization of all TIA patients is a definite way to accelerate evaluation and treatment. Additionally, close observation during hospitalization has the potential to allow more rapid and frequent administration of tPA should a stroke occur [39,40]. Other benefits of hospitalization include continuous telemetry monitoring, rapid diagnostic evaluation, and greater rates of adherence to secondary prevention interventions. However, hospitalization rates after TIA vary widely among practitioners, hospitals, regions, and countries [8-10,40-43]. A cost-utility analysis showed that hospitalization was cost-effective for patients with a 24-hour risk of stroke >4% (patients with ABCD² score ≥ 4) solely on this basis [39].

Theoretically, most TIA patients could be evaluated as outpatients and hospitalization may be avoided [42-44]. However, in many medical care systems, having the work-up accomplished as an outpatient within 48 hours is not logistically feasible. Alternatives to traditional hospitalization have been developed over the past 10 years and may offer as many advantages as inpatient evaluation, with a much lower cost.

Rapid-access TIA clinics, such as the ones described in the French SOS-TIA study [25] and the British EXPRESS study (Early use of Existing Preventive Strategies for Stroke) [26], provide outpatient alternatives (24-hour access to TIA clinics) to hospital admission and have been shown to reduce the 90-day risk of stroke by 80%. In the EXPRESS study model, there was a significant reduction of overall hospital bed days and associated health-care costs [45]. These rapid-access TIA clinics offer the advantage of ensuring rapid specialist evaluation, comprehensive testing, and an opportunity for direct referral from the patient’s primary care physician thereby bypassing the ED [25,26,45-47]. However, such models remain rare and it is difficult to provide 24/7 physician specialist coverage.

A more common model in the US is the use of ED-based observation units (EDOU) that use an accelerated diagnostic protocol (ADP) to evaluate patients with TIA [48,49]; similar units have been used for many years to evaluate patients with chest pain, and a national study of EDOU performed in 2010 showed that such units were found in more than one-third of EDs [50]. This number had increased compared with an estimated number of 19% in 2003 [50], confirming the popularity and success of such units. Similar to rapid-access TIA clinics, TIA evaluation in EDOUs have resulted in lower costs compared with inpatient admission, with comparable clinical outcomes [49].

**EVALUATION OF TIA (TABLE 4)**

**Brain Imaging**

Numerous studies have suggested that all patients with TIA (including those with isolated visual loss) should have immediate brain imaging looking for neuroimaging evidence of cerebral infarction; the presence of large vessel occlusion is also

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**Table 2: Scoring system for the ABCD²**

<table>
<thead>
<tr>
<th>Score ABCD²</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age ≥ 60 Years</td>
</tr>
<tr>
<td>1</td>
<td>Blood pressure ≥ 140/90 mmHg on first evaluation</td>
</tr>
<tr>
<td>2</td>
<td>Clinical symptoms of focal weakness with the spell (or) speech impairment without weakness</td>
</tr>
<tr>
<td>2</td>
<td>Durations ≥ 60 minutes</td>
</tr>
<tr>
<td>1</td>
<td>(or) 10 to 59 minutes</td>
</tr>
<tr>
<td>1</td>
<td>Diabetes</td>
</tr>
</tbody>
</table>

**Table 3: 2 day risk of stroke using ABCD² score**

<table>
<thead>
<tr>
<th>Score ABCD²</th>
<th>2 day-risk of stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0%</td>
</tr>
<tr>
<td>2-3</td>
<td>1.3%</td>
</tr>
<tr>
<td>4-5</td>
<td>4.1%</td>
</tr>
<tr>
<td>6-7</td>
<td>8.1%</td>
</tr>
</tbody>
</table>
a predictor of new events [8,9,19,29,32,34-36]. Although MRI is more expensive and not as widely available as CT, DWI-MRI of the brain is the imaging of choice and should be obtained when possible [8,9].

Among patients who present to the ED with a TIA, studies show that approximately 50 to 70% have a CT performed. In the northern California study, a new infarct was identified in 4% of patients [51]. A nonvascular pathology (tumors, subdural hematomas for example) was identified on CT in 1 to 5% of patients in various series.

MRI is obviously much more sensitive than CT in demonstrating both old and new infarcts in TIA patients. Across various studies, MRI has shown at least one infarct somewhere in the brain in 46 to 81% of TIA patients [52,53]. It is important to emphasize that these acute infarctions seen on DWI-MRI are often small and multiple and can be found anywhere in the brain, not necessarily corresponding to the clinical symptoms (for example, a patient with a retinal TIA may have an abnormal brain DWI-MRI, with acute infarcts obviously not corresponding to the clinical symptoms).

The inclusion of DWI sequences facilitates the detection of acute cerebral ischemia, and provides a more precise evaluation of ischemic insult in TIA patients compared with standard CT and MRI studies [54].

Several studies have shown that DWI positivity has important prognostic implications [55]. Indeed, TIA patients who have abnormalities on DWI-MRI have a higher risk of recurrent ischemic events than those without such abnormalities. DWI positivity correlates with the ABCD and California scores for predicting the risk of stroke after a TIA [35,56]. Patients with retinal ischemia and abnormal DWI-TIA have a higher risk of having an underlying vascular or cardiac abnormality responsible for the ischemic events [19].

These studies suggest that MRI can help triage patients with TIA. All TIA patients with positive DWI-MRI should be admitted to a stroke unit for immediate treatment and observation. DWI can also assist with stroke localization and understanding the mechanism of the stroke, and is therefore extremely useful acutely [8,56].

Vascular imaging

Ideally, patients with TIA should be evaluated expeditiously with tests assessing the extracranial and intracranial circulation. The choice of tests varies depending on local strengths and expertise. It is usually easy to perform a MRA of the intracranial and cervical vessels in conjunction with the initial brain MRI. In other cases, ultrasound and CT-angiogram are also very helpful in detecting cervical artery stenosis and occlusion. These tests are essential because lesions amenable to endarterectomy or stenting are common in patients with TIA [8].

Cardiac evaluation

All TIA patients should undergo an ECG looking for myocardial ischemia and arrhythmia. Cardiac monitoring is easily performed in the ED, TIA clinic or when the patient is hospitalized, and often replaces Holter monitoring [8].

Cardiac evaluation with echocardiography and Holter monitoring in patients with no cardiac history or absent signs of cardiac abnormalities on examination or ECG yields important abnormalities in a minority of patients. However, the yield of cardiac evaluation increases if other potential sources of cerebral symptoms have been ruled-out.

The echocardiographic method used is important. Transthoracic echocardiogram (TTE) is less sensitive than transesophageal echocardiogram (TEE) for atheroma of the aortic arch and abnormalities of the interatrial septum, atrial thrombi, and valvular disease. The use of contrast increases the detection of right to left shunts [8,57].

Routine blood tests

No systematic studies have been performed to assess the value of blood tests in patients with TIA. It is reasonable to perform the same routine blood tests in patients presenting with TIAs as in patients presenting with ischemic stroke. These include a complete blood count with platelets, chemistry panel, and basic coagulation studies (prothrombin time, partial thromboplastin time). These tests are useful to exclude TIA mimics (such as hypoglycemia) and can help identify less common causes of thrombotic events (such as polycythemia or thrombocytosis). A fasting lipid profile is also appropriate [8,9].

Specialized coagulation tests can be considered in younger patients with TIAs, particularly when no vascular risk factor exists and no underlying cause is identified [8,9].

TREATMENT OF TIA

The Effect of urgent treatment of TIA and minor stroke on early recurrent stroke (EXPRESS) [26] and effectiveness of round-the-clock access (SOS-TIA) [25] studies showed that urgent evaluation and initiation of preventive treatments such as antiplatelets, statins, anticoagulation, and carotid revascularization markedly reduce the risk of early stroke after a TIA or minor stroke.

Patients who have had a suspected TIA should have:

- Anti platelet agents started immediately.
- Specialist assessment and investigation within 24 hours of onset of symptoms.
- Measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.
  - Patients who had a TIA but who present late (more than 1 week after their last symptom has resolved) should be treated as though they are at lower risk of stroke.
  - Specific guidelines have been published by the American Heart Association and should be followed (even for patients with transient visual loss) [8,10,11].

When a TIA patient is found to have severe carotid stenosis:

Numerous studies have shown that carotid endarterectomy
is effective and cost-effective for the prevention of stroke in individuals with symptomatic stenosis. Patients with severe (>70%), men, and patients aged ≥ 75 years may be more likely to benefit from carotid endarterectomy [8,10,58,59].

A growing body of evidence also suggests an increased benefit related to the timing of surgery from the last symptom. As a consequence, guidelines have recommended that stable patients with TIA (or nondisabling stroke) and ipsilateral internal carotid artery stenosis of 50% to 99% should be offered carotid endarterectomy optimally within 2 weeks of the incident TIA or stroke [8,10,59]. This is unfortunately only rarely the case, as shown by a recent Canadian study in which only 7 of 92 symptomatic patients underwent carotid endarterectomy within the recommended 2 weeks of symptom onset [60]. Surgery was particularly delayed in the group of patients presenting with retinal TIA.

PART IV: THE SPECIFIC ISSUE OF TRANSIENT VISUAL LOSS

CLINICAL VIGNETTE 2:

A 65-year-old man calls his physician immediately after recovering from a 10 minute episode of complete loss of vision of the left eye only. His medical history is unremarkable. How should he be treated?

Is it the same situation as in clinical vignette 1?

-No exactly, for two reasons:

1) An oculary examination is necessary to rule-out an ocular problem. Telephone diagnosis of visual loss is impossible. Before being evaluated and treated for a retinal TIA, the patient needs an immediate oculary examination, which, ideally, should be performed in the ED or close to an ED of an institution with a stroke neurologist. Because many EDs do not have an ophthalmologist readily available, an emergent ophthalmic examination by an outside ophthalmologist may be necessary prior to referral to an ED.

2) Giant cell arteritis needs to be ruled-out before a TIA work-up is initiated. Immediate blood tests including CBC, platelet, ESR and CRP need to be obtained. If abnormal, then evaluation and treatment for GCA need to be initiated; if normal, then an immediate TIA work-up is necessary.

-Yes:

1) No matter what, an urgent evaluation is necessary and involves testing that cannot be done in an eye clinic alone. The patient should always be immediately directed to an ED where the appropriate workup can be performed.

RETINAL TIAS ARE SIMILAR TO CEREBRAL TIAS AND SHOULD BE MANAGED SIMILARLY

Transient retinal ischemia resulting in transient monocular visual loss is a form of anterior circulation TIA caused by decreased blood flow in the ophthalmic branch of the internal carotid artery. Transient occipital ischemia often results in isolated binocular visual loss (either diffuse or in a hemifield) and is a posterior circulation TIA.

Classically, patients describe vision loss as though a curtain were being lowered over the affected eye, although it can also present as a clouding or darkening of the visual field. Patients with a hemianopia from occipital ischemia often report visual loss in the eye with the temporal defect, and the only way to differentiate monocular from binocular visual loss is to ask the patient to describe the visual symptoms while closing one eye or the other (which is almost never done when the visual loss is transient). Although it is theoretically helpful to know if an episode of transient visual loss was binocular or monocular (that’s what we teach medical students...), most patients are not able to provide this information with certainty. From a practical standpoint, because current guidelines suggest the exact same workup and management for retinal and occipital TIAs, the most important part in the evaluation of an episode of transient visual loss is to try to determine whether the visual loss may have been vascular (transient arterial ischemia to the eye or the brain) or whether the visual loss can be explained by an another mechanism (such as ocular disorders, seizures or occipital migraine). Very sudden onset, complete blackout of vision, description of a shade or curtain, duration of at least 3 minutes, but less than 20 minutes and very rapid recovery of vision are highly suggestive of retinal or occipital TIAs [18].

Most health professionals and the public consider retinal TIAs benign with a low risk of subsequent stroke. This is incorrect and such belief only delays the evaluation of patients with visual loss as the main symptom of retinal or cerebral ischemia. A study from 1995 emphasized that average time of delay from the onset of TIA to treatment was much longer for patients with retinal TIAs than for patients with hemispheric TIAs (48.5 vs 15.2 days) [61]. The same finding was recently observed in a series of patients with carotid stenosis whose surgery was delayed when the symptom was a retinal TIA [60]. The NASCET study showed a high-risk of recurrent TIAs or stroke after a first retinal TIA, with up to 24.2% of retinal TIA patients developing a stroke at 3 years [62]. However, because this risk was still lower than for patients who had a cerebral TIA, emphasis was placed on the relative “good prognosis” of retinal TIAs compared with cerebral TIAs, contributing to the misconception that retinal TIAs are relatively benign. The NASCET study itself and other studies also confirmed that the overall vascular risk (including myocardial ischemia and cardiovascular death) is as high for patients with a retinal TIA as it is for those with a cerebral TIA, emphasizing the need for immediate evaluation and treatment after a retinal TIA [8].

Observed differences in terms of etiology, presumed mechanisms, and apparent prognosis of retinal TIAs compared with cerebral TIAs may be partly explained by the often extreme difficulty in diagnosing episodes of transient visual loss [18]. In our experience, non-vascular ocular causes and occipital migraine explain most episodes of transient visual loss [63,64,65]. Because most large studies evaluating the prognosis after a TIA were performed by neurologists, it is likely that retinal ischemia as the cause of
transient visual loss is overestimated in most studies, contributing to the apparent better vascular prognosis after a retinal TIA.

A recent study showed that retinal arterial ischemia (both transient and permanent) carries the same overall poor vascular prognosis as cerebral ischemia. The authors evaluated 129 patients with retinal ischemia similarly to cerebral TIA patients, and showed that one of every 4 patients with acute retinal ischemia has acute brain infarction on DWI-MRI [19]. When looking specifically at those with retinal TIAs, 18% had a positive DWI-MRI, and therefore were managed as having had a stroke per current guidelines (Table 4). These infarcts are typically small and often multiple, frequently occur in the hemisphere ipsilateral to the involved eye, and tend to remain asymptomatic. These infarcts indicate a high risk of having a major etiology as the cause of retinal TIA and confirm the need for emergent workup and treatment in a specialized center.

The American Heart Association/American Stroke Association guidelines [8] recommend that all patients with suspected retinal ischemia (whether transient or permanent) should undergo urgent brain imaging and etiologic testing similar to retinal ischemia (whether transient or permanent) caries the same overall poor vascular prognosis as cerebral ischemia. The authors evaluated 129 patients with retinal ischemia similarly to cerebral TIA patients, and showed that one of every 4 patients with acute retinal ischemia has acute brain infarction on DWI-MRI [19]. When looking specifically at those with retinal TIAs, 18% had a positive DWI-MRI, and therefore were managed as having had a stroke per current guidelines (Table 4). These infarcts are typically small and often multiple, frequently occur in the hemisphere ipsilateral to the involved eye, and tend to remain asymptomatic. These infarcts indicate a high risk of having a major etiology as the cause of retinal TIA and confirm the need for emergent workup and treatment in a specialized center.

The American Heart Association/American Stroke Association guidelines [8] recommend that all patients with suspected retinal ischemia (whether transient or permanent) should undergo urgent brain imaging and etiologic testing similar to patients with hemispheric TIAs (Table 4). This is certainly not routinely performed currently in the US where a large majority of patients with retinal ischemia are never sent to the ED or a stroke neurologist for immediate evaluation [66].

Table 4: Summary of recommendations from the American Heart Association (AHA), the National Stroke Association (NSA) [8], and from the National Institute for Health and Clinical Excellence (UK) (NICE) [9]

<table>
<thead>
<tr>
<th>Class I recommendations</th>
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<tbody>
<tr>
<td>1. Patients with TIA should preferably undergo neuroimaging evaluation within 24 hours of symptom onset. MRI, including DWI, is the preferred brain diagnostic imaging modality. If MRI is not available, head CT should be performed (Class I, Level of Evidence B).</td>
</tr>
<tr>
<td>2. Noninvasive imaging of the cervicocerebral vessels should be performed routinely as part of the evaluation of patients with suspected TIAs (Class I, Level of Evidence A).</td>
</tr>
<tr>
<td>3. Noninvasive testing of the intracranial vasculature reliably excludes the presence of intracranial stenosis (Class I, Level of Evidence A) and is reasonable to obtain when knowledge of intracranial steno-occlusive disease will alter management. Reliable diagnosis of the presence and degree of intracranial stenosis requires the performance of catheter angiography to confirm abnormalities detected with noninvasive testing.</td>
</tr>
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<td>4. Patients with suspected TIA should be evaluated as soon as possible after an event (Class I, Level of Evidence B).</td>
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<th>Class II Recommendations</th>
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<tr>
<td>1. Initial assessment of the extracranial vasculature may involve any of the following: carotid ultrasound/trans cranial doppler, MRA or CTA, depending on local availability and expertise, and characteristics of the patient (Class IIa, Level of Evidence B).</td>
</tr>
<tr>
<td>2. If only noninvasive testing is performed prior to endarterectomy, it is reasonable to pursue two concordant noninvasive findings; otherwise catheter angiography should be considered (Class IIa, Level of Evidence B).</td>
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<tr>
<td>3. The role of plaque characteristics and detection of microembolic signals is not yet defined (Class IIb, Level of Evidence B).</td>
</tr>
<tr>
<td>4. Electrocardiography should occur as soon as possible after TIA (Class I, Level of Evidence B). Prolonged cardiac monitoring (inpatient telemetry or Holter monitor) is useful in patients with an unclear etiology after initial brain imaging and electrocardiography (Class IIa, Level of Evidence B).</td>
</tr>
<tr>
<td>5. Echocardiography (at least transthoracic echocardiography) is reasonable in the evaluation of patients with suspected TIAs, especially when the patient has no cause is identified by other elements of the work-up (Class IIa, Level of Evidence B). Trans esophageal echocardiography is useful in identifying patent foramen ovale, aortic arch atherosclerosis, and valvular disease and is reasonable when identification of these conditions will alter management (Class IIa, Level of Evidence B).</td>
</tr>
<tr>
<td>6. Routine blood tests (complete blood count with platelets, chemistry panel, prothrombin time and partial thromboplastin time, and fasting lipid panel) are reasonable in the evaluation of patients with suspected TIAs (Class IIa, Level of Evidence B).</td>
</tr>
<tr>
<td>7. It is reasonable to hospitalize patients with TIA if they present within 72 hours of the event and any of the following criteria are present: –ABCD² score of ≥3, (Class IIa, Level of Evidence C). –ABCD² score of 0-2 and uncertainty that diagnostic work-up can be completed within 2 days as an outpatient (Class IIa, Level of Evidence C). –ABCD² score of 0-2 and there is other evidence that indicates the patient’s event was caused by focal ischemia (Class IIa, Level of Evidence C).</td>
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PART V: CONCLUSIONS AND RECOMMENDATIONS

Because stroke and permanent visual loss are devastating events that many patients consider worse than death [67,68], strategies aimed at preventing stroke by facilitating the immediate evaluation of patients with TIA are essential. The high very short term risk of stroke after a TIA supports an approach involving emergent evaluation and initiation of treatment in patients such as the ones described in the clinical vignettes. Many strokes occur in the first two days after a TIA, so even a short delay in treatment could have important consequences. Most patients should be sent to the ED (ideally to an EDOU) immediately after reporting symptoms suggestive of TIA, or to a rapid-access TIA unit where available. Hospitalization is indicated only if such facilities are not available, and the evaluation cannot be completed within 24 hours. Patients with visual loss should be managed similarly to those with cerebral ischemia. Education of healthcare providers is essential to promote the need for emergent evaluation and referral of all patients with suspected vascular visual loss [8,69]. The development of local networks prompting collaboration between optometrists, ophthalmologists, and stroke neurologists should facilitate such evaluations, whether in a rapid-access TIA clinic, an EDOU, or with hospitalization, depending on local resources.
CME ANSWERS

1. c
Retinal TIAs are as bad as hemispheric TIAs.

2. e
These are the guidelines from the AHA and the NSA.

3. e
The high risk of stroke justifies emergent evaluation and observation.

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43. Amarenco P. Not all patients should be admitted to the hospital for observation after a transient ischemic attack. Stroke 2012; 43: 1448-1449.


57. Amarenco P, Labreuche J, Lavallée PC. Patients with transient ischemic attack with ABCD2 <4 can have similar 90-day stroke risk as patients with transient ischemic attack with ABCD2 ≥4. Stroke 2012; 43: 863-865.


JOURNAL CLUB UPDATE: MYASTHENIA GRAVIS

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LEARNING OBJECTIVES
1. Participant will be aware of new literature regarding myasthenia gravis
2. Participant will be aware of scientific breakthroughs regarding myasthenia gravis
3. Participant will incorporate new information in patient care in the field of myasthenia gravis

CME QUESTIONS
1. Do statins cause myasthenia?
2. What is the latest blood test for myasthenia?
3. Do MuSK antibodies carry a higher or lower risk of thymoma?

KEYWORDS
1. Myasthenia gravis
2. Autoantibodies
3. Exacerbation
4. Thymoma
5. Immunomodulation

INTRODUCTION
What is the latest on Myasthenia?
Brief overview of major or interesting papers on the topic of Myasthenia Gravis in the last 2 years Review of the conclusion of the two major studies of the use of mycophenolate mofetil in myasthenia

DIAGNOSIS
Abstract: Patients with myasthenia gravis(MG) are divided into three groups: (1) acetylcholine receptor antibody positive MG: 80%, (2) muscle-specific receptor tyrosine kinase (MuSK) antibody positive MG: 5-10%, and (3) double seronegative MG. In 2011, autoantibodies (Abs) against low-density lipoprotein receptor-related protein 4(Lrp4) were identified in Japanese MG patients and thereafter have been reported in Germany and USA. In other Lrp4 Ab papers, Lrp4 Ab positive sera inhibited agrin-induced aggregation of AChRs in cultured myotubes, suggesting a pathogenic role regarding the dysfunction of the neuromuscular endplate. Anti-MuSK autoantibodies were revealed to block binding of collagen Q (ColQ) to MuSK. Anti-Kv1.4 antibodies targeting alpha-subunits(Kv1.4) of the voltage-gated potassium channel occurs frequently among MG patients with thymoma. Further understandings of neuromuscular junction structure and functions through newly discovered autoantibodies may provide more specific clinical information and treatments in MG.

Ann Neurol. 2011 Feb;69(2):418-22. doi: 10.1002/ana.22312. Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. Higuchi O, Hamuro J, Motomura M, Yamanashi Y . PMID: 21387385 Division of Genetics, Department of Cancer Biology, the Institute of Medical Science, the University of Tokyo, Japan.
Abstract: Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction, where acetylcholine receptor (AChR), muscle-specific kinase (MuSK), and low-density lipoprotein (LDL) receptor-related protein 4 (Lrp4) are essential. About 80% and 0% to 10% of patients with generalized MG have autoantibodies to AChR and MuSK, respectively, but pathogenic factors are elusive in others. Here we show that a proportion of AChR antibody-negative patients have autoantibodies to Lrp4. These antibodies inhibit binding of Lrp4 to its ligand and predominantly belong to the immunoglobulin G1 (IgG1) subclass, a complement activator. These findings together indicate the involvement of Lrp4 antibodies in the pathogenesis of AChR antibody-negative MG.

Abstract Myasthenia gravis (MG) is an autoimmune disorder characterized by a defect in synaptic transmission at the neuromuscular junction causing fluctuating muscle weakness with a decremental response to
implications of the anti-LRP4 antibody positivity remain to be clarified.

COMMENT

Not yet commercially available, but we continue to whittle away at the seronegative myasthenia gravis cohort.

Do acetylcholine receptor and striated muscle antibodies predict the presence of thymoma in patients with myasthenia gravis? Decroos EC, Hobson-Webb LD, Juel VC, Massey JD, Sanders DB. Muscle Nerve. 2013 Apr 27. doi:10.1002/mus. 23882. PMID: 23625360 Neuromuscular Section, Division of Neurology, Department of Medicine, Duke University Medical Center, DUMC 3403, Durham, North Carolina, 27710, USA.

Abstract Introduction: Acetylcholine receptor (AChR) and striated muscle antibodies (StrAbs) are found frequently in myasthenia gravis (MG) patients with thymoma. In this study we aimed to determine the positive predictive value (PPV) and negative predictive value (NPV) of these antibodies for thymoma in patients with MG. Methods: Antibody findings, thymic histology, and onset age were reviewed for 1141 patients with MG. PPV and NPV of these antibodies for thymoma were determined. Results: The PPV of AChR binding antibodies plus StrAbs was highest (50.0%) with onset before the age of 40 years. The PPV of all antibodies was low (<9%) after age 40. Higher StrAb levels did not increase the PPV. The NPV of AChR binding antibodies was high (99.7%) for all ages. Conclusions: Patients without AChR binding antibody are not likely to have a thymoma. StrAbs and AChR binding antibodies are not diagnostic for thymoma, but in early-onset MG their presence should raise the clinical suspicion for thymoma.

COMMENT

Antibodies predict thymoma in the under 40 population, and are not all that helpful after 40. Could help in decision making, but I think I will always order a CT chest in new myasthenia patients.

ICE TEST


Abstract Introduction: Several studies have reported high diagnostic sensitivity and specificity for the ice test in myasthenia gravis. All of the studies employed a case-control design, in which the diagnosis was already known at the time of the test for both patients and controls, leading to case selection bias. This suggests that the available literature substantially overestimates the diagnostic utility of these tests. Methods: A retrospective cohort study.
without selection bias was performed to examine the sensitivity and specificity of the ice test. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the ice test were determined by means of a 2 × 2 table. Results: The ice test has a sensitivity of 0.92 (95% CI 0.62-1.00), specificity of 0.79 (95% CI 0.56-1.00), PPV of 0.73 (95% CI 0.48-0.90), and NPV of 0.94 (95% CI 0.70-1.00). Conclusion: Due to its high negative predictive value the ice test is still a reliable and useful bed-side test.

J Neuroophthalmol. 2013 Jun;33(2):169-71. doi: 10.1097/WNO.0b013e31828bb19b. Variable ptosis after botulinum toxin type A injections to the brow and subsequently developed unilateral ptosis that was variable during examination and was transiently improved after the ice pack test. Ptosis gradually resolved spontaneously over approximately 3 months. This is the third patient to have variable ptosis documented after botulinum toxin type A injection to the brow and the second to have a positive ice test. The ice test is not completely specific for myasthenia gravis but may, at times, improve ptosis resulting from other defects at the neuromuscular junction. Wound botulism now is much more common because of illicit drug use, and the ice test also might be positive in this setting.

COMMENT

Ice test is becoming much more common than tensilon test in clinical practice. It is fast, accurate and safe. However, like any test, there are pitfalls. Take a good history!

TREATMENT


COMMENT

Letter to the editor describing prompt and sustained benefit from treatment with rituximab for MuSK positive generalized MG patients. Interesting that there was sustained post-treatment benefit lasting 1-3 years after last treatment.

Sugammadex is a modified gamma-cyclodextrin. Is a selective relaxant binding agent indicated to reverse the neuromuscular blockade induced during general anaesthesia. The mechanism of action of sugammadex differs from that of other commonly used reversal agents, such as neostigmine and edrophonium. It binds the rocuronium by encapsulating it, and preventing binding with the acetylcholine receptor. Sugammadex is approved in the EU, Australia, Iceland, New Zealand and Norway.

Abstract BACKGROUND: The use of neuromuscular blocking agents is still controversial in myasthenic patients but rocuronium could be useful after the introduction of sugammadex in myasthenic patients undergoing thoracoscopic thymectomy. METHODS: After ethical approval, 10 myasthenic patients undergoing videothoracoscopic-assisted thymectomy were enrolled in the study. Neuromuscular block was achieved with 0.3 mg/kg rocuronium and additional doses were given according to train-of-four (TOF) monitoring or movement of the diaphragm. Sugammadex 2 mg/kg was given after surgery. Recovery time (time to obtain a TOF value > 0.9) was recorded for all subjects. RESULT: All patients were extubated in the operating room after administration of sugammadex. Mean rocuronium dose was 48 mg and the average operation time was 62 min. Recovery time after sugammadex administration was 111 s (min 35; max 240). CONCLUSIONS: A rapid recovery of neuromuscular function was found in myasthenic patients receiving rocuronium when sugammadex was used for reversal. This combination could be a rational alternative for myasthenic patients for whom neuromuscular blockade is mandatory during surgery.

COMMENT

Letter to Editor - Report of 4 patients with ocular MG, successfully treated with tacrolimus, without steroids.

CLINICAL


Abstract: Statin-induced myopathy is well-known, but the effect of cholesterol-lowering agents on myasthenia gravis (MG) has not been studied in detail. We investigated statin information was systematically obtained from 170 patients being treated at the Neuromuscular Disease Clinic at the University of Alabama at Birmingham, Veterans Affairs Medical Center, Birmingham, Alabama, and clinical improvement occurred either with or without discontinuation of the statin medication. In 4 patients, additional treatment was needed to reverse MG worsening. Statins are safe in the majority of MG patients, but their use must be accompanied by close observation for possible MG worsening.

COMMENT
Consensus is growing that statins are potential trigger or aggravator of myasthenia.

REVIEW

Abstract: Background: A subset of myasthenia gravis (MG) patients is refractory to standard therapies. Identifying the characteristics of this population is essential as newer treatment strategies emerge that may be more effective in this group. Objective: The aim of our study is to describe the clinical features of refractory MG patients and compare them to those of non-refractory patients. Methods: A retrospective chart review was completed of 128 MG patients referred to a tertiary neuromuscular clinic from 2003 to 2011. Patients were classified as refractory or non-refractory based on predefined criteria, and clinical features were compared. Results: Nineteen out of 128 patients were classified as refractory (14.8 percent). Compared to the non-refractory patients, the refractory patients were more likely to be younger at onset, female, thymomatous, and MuSK-antibody positive. Conclusion: Refractory MG patients represent a small but distinct group for whom exploring newer therapeutic approaches and immunopathologic differences is warranted.
autoimmune diseases and related autoantibodies between thymus histology, coexisting autoimmune diseases and associated Abs in 83 MuSK-Ab-positive patients nationwide were investigated and were compared with those in AChR-Ab-positive patients followed at our institute (n = 83). As for the autoantibodies associated with thymoma, titin Abs were measured. RESULTS: Thymoma was not present in any of the MuSK-Ab-positive patients but presented in 21 patients (25.3%) amongst the AChR-Ab-positive patients. Titin Abs were absent in MuSK-Ab-positive patients but positive in 25 (30.1%) of the AChR-Ab-positive patients. Concomitant autoimmune diseases were present in eight MuSK-Ab-positive patients (9.6%) amongst whom Hashimoto’s thyroiditis and rheumatoid arthritis predominated, whereas 22 AChR-Ab-positive patients (26.5%) had one or more concomitant autoimmune diseases of which Graves’ disease predominated.

CONCLUSIONS: Differences in frequency of thymoma and thymic hyperplasia, coexisting autoimmune diseases and autoantibody positivity between MuSK-Ab-positive and AChR-Ab-positive MG were indicated, suggesting that, in contrast with AChR-Ab-positive MG, thymus does not seem to be involved in the pathogenic mechanisms of MuSK-Ab-positive MG.

COMMENT

No thymoma in MuSK positive MG.


We report a 60-year-old male with thymoma-associated myasthenia gravis with anti-MuSK antibodies. In October 2010, he had diplopia, ptosis, and dysphagia. He was diagnosed to have MG in February 2011. The neurological examination disclosed external ophthalmoplegia, bilateral ptosis, mild dysphagia, and fatigability. Repetitive nerve stimulation of the right facial nerve showed CMAP decrement greater than 10%. Patients showed an improvement in ptosis after administration of edrophonium. Anti-acetylcholine receptor antibody was negative, and anti-muscle specific receptor tyrosine kinase antibody was 66.8 nmol/l (cut-off value: 0.05 nmol/l). Prednisolone (50 mg every other day) were started. Contrast-enhanced chest MRI showed a mediastinal mass suggestive of thymoma. Extended thymectomy was performed in March 2011. Histological examination disclosed a type B1 thymoma. After resection of the tumor, the symptoms of MG improved with prednisolone (100 mg every other day). This is a rare case of MG with anti-MuSK antibodies and thymoma, which has been reported previously only in 2 cases.

COMMENT

Retrospective review that confirms the impression that it is the young women who have refractory disease.

PREGNANCY


Abstract: A national UK workshop to discuss practical clinical management issues related to pregnancy in women with myasthenia gravis was held in May 2011. The purpose was to develop recommendations to guide general neurologists and obstetricians and facilitate best practice before, during and after pregnancy. The main conclusions were (1) planning should be instituted well in advance of any potential pregnancy to allow time for myasthenic status and drug optimisation; (2) multidisciplinary liaison through the involvement of relevant specialists should occur throughout pregnancy, during delivery and in the neonatal period; (3) provided that their myasthenia is under good control before pregnancy, the majority of women can be reassured that it will remain stable throughout pregnancy and the postpartum months; (4) spontaneous vaginal delivery should be the aim and actively encouraged; (5) those with severe myasthenic weakness need careful, multidisciplinary management with prompt access to specialist advice and facilities; (6) newborn babies born to myasthenic mothers are at risk of transient myasthenic weakness, even if the mother’s myasthenia is well-controlled, and should have rapid access to neonatal high-dependency support.

COMMENT

Nice thorough review – keep a copy for patients to take to their high risk OB/GYN.

MUSK


Abstract: BACKGROUND AND PURPOSE: The differences in the characteristics of thymus histology, coexisting autoimmune diseases and related autoantibodies between anti-muscle-specific receptor tyrosine kinase (MuSK)-antibody (Ab)-positive myasthenia gravis (MG) patients, and anti-acetylcholine receptor (AChR)-Ab-positive MG patients are not clearly defined. METHODS: The types of thymus histology, coexisting autoimmune diseases and associated Abs in 83 MuSK-Ab-positive patients nationwide were investigated and were compared with those in AChR-Ab-positive patients followed at our institute (n = 83). As for the autoantibodies associated with thymoma, titin Abs were measured. RESULTS: Thymoma was not present in any of the MuSK-Ab-positive patients but presented in 21 patients (25.3%) amongst the AChR-Ab-positive patients. Titin Abs were absent in MuSK-Ab-positive patients but positive in 25 (30.1%) of the AChR-Ab-positive patients. Concomitant autoimmune diseases were present in eight MuSK-Ab-positive patients (9.6%) amongst whom Hashimoto’s thyroiditis and rheumatoid arthritis predominated, whereas 22 AChR-Ab-positive patients (26.5%) had one or more concomitant autoimmune diseases of which Graves’ disease predominated. CONCLUSIONS: Differences in frequency of thymoma and thymic hyperplasia, coexisting autoimmune diseases and autoantibody positivity between MuSK-Ab-positive and AChR-Ab-positive MG were indicated, suggesting that, in contrast with AChR-Ab-positive MG, thymus does not seem to be involved in the pathogenic mechanisms of MuSK-Ab-positive MG.
COMMENT
Or is there?

SCIENCE

Molecular Neurobiology Program, Helen L. and Martin S. Kimmel Center for Biology and Medicine at the Skirball Institute of Biomolecular Medicine, NYU Medical School, New York, NY 10016, USA.

Abstract: Muscle-specific kinase (MuSK) is essential for each step in neuromuscular synapse formation. Before innervation, MuSK initiates postsynaptic differentiation, priming the muscle for synapse formation. Approaching motor axons recognize the primed, or prepatterned, region of muscle, causing motor axons to stop growing and differentiate into specialized nerve terminals. MuSK controls presynaptic differentiation by causing the clustering of Lrp4, which functions as a direct retrograde signal for presynaptic differentiation. Developing synapses are stabilized by neuronal Agrin, which is released by motor nerve terminals and binds to Lrp4, a member of the low-density lipoprotein receptor family, stimulating further association between Lrp4 and MuSK and increasing MuSK kinase activity. In addition, MuSK phosphorylation is stimulated by an inside-out ligand, docking protein-7 (Dok-7), which is recruited to tyrosine-phosphorylated MuSK and increases MuSK kinase activity. Mutations in MuSK and in genes that function in the MuSK signaling pathway, including Dok-7, cause congenital myasthenia, and autoantibodies to MuSK, Lrp4, and acetylcholine receptors are responsible for myasthenia gravis.

COMMENT
Tells us what MuSK is doing there in the first place.

MYCOPHENOLATE MOFETIL

Abstract : OBJECTIVE: To test the hypothesis that mycophenolate mofetil (MMF) with prednisone provides better control of myasthenic weakness than prednisone alone in the initial management of generalized myasthenia gravis (MG). METHODS: Eighty immunosuppression naïve subjects with mild to moderate generalized, acetylcholine receptor positive MG at 13 centers were randomized to 2.5 g/day MMF plus 20 mg/day prednisone (n = 41) or placebo plus 20 mg/day prednisone (n = 39) and followed in a double-blind fashion for 12 weeks. Subjects over 18 years of age were included if judged to be candidates for immunosuppression; excluded were those with thymoma or severe oropharyngeal or respiratory muscle weakness. The primary measure of efficacy was change in the quantitative MG (QMG) score from baseline to week 12. Study completers could take open-label MMF for an additional 24 weeks, while prednisone was reduced to the minimally effective dosage. RESULTS: The mean change in QMG score was similar in the treated (-4.4 +/- 5.1) and placebo (-3.6 +/- 5.0) groups (p = 0.71). The dosage of prednisone was reduced by a similar amount in both groups during the open-label phase. Subjects tolerated the study drug well, without unexpected adverse events. CONCLUSIONS: This study demonstrated no benefit of mycophenolate mofetil (MMF) with 20 mg/day prednisone compared to 20 mg/day of prednisone alone after 12 weeks. This may be due to greater than predicted benefit from the prednisone dosage used, the short duration of the study, or the absence of any benefit of MMF in this population of patients with myasthenia gravis.


Abstract : BACKGROUND: This prospective, randomized, double-blind, placebo-controlled, phase III trial assessed the efficacy, safety, and tolerability of mycophenolate mofetil (MMF) as a steroid-sparing agent in patients with myasthenia gravis (MG). METHODS: Patients with acetylcholine receptor antibody-positive class II-IVa MG (MG Foundation of America [MGFA] criteria) taking corticosteroids for at least 4 weeks were randomized to MMF (2 g/day) or placebo for an additional 24 weeks, while prednisone was reduced to the minimally effective dosage. RESULTS: A total of 44% of MMF-treated (n = 88) and 39% of placebo-receiving (n = 88) patients achieved the primary endpoint (p = 0.541). Improvements in mean quantitative MG, MG activities of daily living, and 36-item Short-Form
health survey scores were similar in both groups. Numbers of adverse events were similar in both groups. The most commonly reported adverse events in the MMF-treated group were headache (12.5%) and worsening of MG (11.4%), and in the placebo group, worsening of MG (20.5%) and diarrhea (10.2%). CONCLUSIONS: Initiation of mycophenolate mofetil (MMF) treatment was not superior to placebo in maintaining myasthenia gravis (MG) control during a 36-week schedule of prednisone tapering. There were no significant differences in the primary or secondary endpoints between the study groups. MMF was well tolerated and adverse events were consistent with previous studies. Experience from this large, international, multicenter, phase III study employing full MG Foundation of America guidelines will aid the design of future MG studies.

COMMENT

Two studies showed no benefit of MM in improving MG control, or in reducing the dose of prednisone needed to control the disease.


Abstract: Two recent randomized, controlled trials failed to demonstrate a benefit of mycophenolate mofetil (MMF) over prednisone in the treatment of myasthenia gravis (MG). We reviewed our experience with MMF in MG to determine whether these trials may have been unsuccessful because of their short duration and the unpredicted benefit of prednisone. We reviewed outcomes and prednisone dosage for all our acetylcholine-receptor (AChR)-antibody positive MG patients treated with MMF alone or with prednisone for at least 3 months. The percentage of patients with a desirable outcome (MG-specific Manual Muscle Test score <4 or Myasthenia Gravis Foundation of America post-invention status of minimal manifestations or better) began to increase after 6 months; 80% of those followed for >24 months had a desirable outcome. Prednisone dose decreased after 12 months; after 25 months, 54.5% of patients took no prednisone and 75% took <7.5 mg/day. This retrospective analysis provides class IV evidence that MMF begins to improve AChR-positive MG after 6 months, both with prednisone and as monotherapy.

COMMENT

Undeterred, a retrospective study performed because of concerns the international study treatment was too short (although it was 9 months). Wouldn’t it have been good to compare the MM +/- prednisone patients with prednisone alone, or perhaps azathioprine +/- prednisone? More controlled studies in the offing perhaps?

CME ANSWERS:
1. Probably not
2. Anti-LRP4
3. Lower
LEARNING OBJECTIVES

1. To understand the current tests used to diagnose concussion
2. Describe the epidemiology of concussion
3. Understand the entity of chronic traumatic encephalopathy

CME QUESTIONS

1. The risk of recurrent concussion following a concussion is
   a. No increased risk
   b. Two fold
   c. Three fold
   d. Five fold
   e. Ten fold
2. This sideline test requires saccadic eye movements to perform
   a. Standardized assessment of concussion test
   b. Bess test
   c. Maddocks test
   d. King Devick test
3. Chronic traumatic encephalopathy is characterized by
   a. Amyloid deposition
   b. Alpha synuclein deposition
   c. Tau deposition
   d. TDP 43 deposition
   e. Prion deposition

KEYWORDS

1. Mild traumatic injury
2. Concussion
3. King Devick Test
4. Chronic traumatic encephalopathy

INTRODUCTION AND EPIDEMIOLOGY

Between 1.6 and 3.8 million sports-related mild traumatic brain injuries (mTBI) occur every year and the vast majority are concussions. This may be a gross underestimation as many patients do not seek medical attention. Concussions are induced by an impulsive force transmitted to the head resulting from an impact to the head, face, neck, or elsewhere. Direct head contact is not a requirement for a concussion and less than 10% of athletes lose consciousness. In similar sports, women appear to be more vulnerable to concussions. The clinical manifestations of concussion are diverse and include slowing of saccadic eye movements, double vision, balance or memory impairment, headache, confusion, amnesia, dizziness, nausea, slurred speech, fatigue, sensitivity to light, and sleep disturbances. These findings may be the end result of metabolic dysfunction resulting from impaired energy regulation.

It has become increasingly recognized that concussions may lead to devastating long-term sequelae and prolonged functional impairment including post-concussive syndrome, memory impairment, depression and chronic traumatic encephalopathy. In addition, returning to contact sports prior to complete recovery may have catastrophic consequences, including second impact syndrome. Athletes who sustain a concussion are three times as likely to sustain a second concussion in the same season, so proper concussion management is essential. Despite a variety of published guidelines, many medical professionals do not incorporate them for concussion assessment and management.

There are many concussion management and assessment tools available. The purpose of this neuro-ophthalmology journal club is to discuss the merits of some of the most widely used tests in order to provide an examination of available concussion tools and the scientific evidence that supports their use.

CONCUSSION TESTS:

Concussion tests are now broken into two broad groups: concussion assessment tools and concussion management tools. These tools can be further categorized as symptom lists, sideline assessment tools, balance assessment tools, computerized neurocognitive testing, and neuroimaging.

The Rivermead Post-Concussion Symptoms Questionnaire, Post-Concussion Symptom Score (PCSS), and Acute...
Concussion Evaluation were the most widely used symptoms checklists while the Modified Glasgow Coma Scale (GCS) was the most commonly employed examination tool. The Sport Concussion Assessment Tool (SCAT3)\textsuperscript{119}, Standardized Assessment of Concussion (SAC, a component of the SCAT3)\textsuperscript{119}, and King-Devick (K-D) test are commonly used sideline assessment tools. Similar in format to the PCSS and SAC portions of SCAT3, the Military Acute Concussion Evaluation (MACE)\textsuperscript{20} has been used to assess individuals in combat situations and may have applicability to athletes. The Balance Error Scoring System (BESS), also a component of SCAT 3, was the most frequent balance test employed. The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) is the main computerized neurocognitive testing that is commonly used. Magnetic resonance imaging (MRI), computerized tomography (CT), diffusion tensor imaging (DTI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single photon emission computed tomography (SPECT) are advanced neuroimaging techniques that utilized in the assessment of concussion.

**DISCUSSION**

**CONCUSSION ASSESSMENT TOOLS**

1. **SYMPTOMS CHECKLISTS**

Symptoms checklists allow athletes to self-report symptoms after concussion injury. They can be used on the sideline of an athletic field and serially during concussion recovery. Several symptom checklists have been assembled developed, including the Rivermead Post Concussion Symptoms Questionnaire\textsuperscript{21,22}, PCSS\textsuperscript{23,24}, Acute Concussion Evaluation (which also includes a physical examination), and the ImPACT post-concussion scale. These checklists list between 15 and 25 symptoms including headache, dizziness, blurred vision, balance problems, fatigue, confusion, difficulty concentrating or remembering, and sensitivity to light or noise\textsuperscript{25-27}. Responses are typically provided on a Likert scale. Some questionnaires ask whether the symptoms are exacerbated by physical or mental activity. Symptom checklists can differ in whether they query the severity of each symptom or how frequently the symptom occurs. In most scales, the responses are summated to provide a total symptom score. While the checklists contained slightly different sets of symptoms, most were very similar and there was no single “gold-standard”\textsuperscript{26}.

While these symptom checklists are comprehensive, their length can be burdensome for providers and athletes to complete. Piland and colleagues\textsuperscript{29,29} have demonstrated factorial and construct validity of a 9-item self-reported symptom instrument in both high school and college athletes. The 9 items are: headache, nausea, balance problems, sleeping more than usual, drowsiness, fatigue, feeling “slowed down”, feeling like “in a fog”, and difficulty concentrating.

Symptom checklists can be quickly administered and allow athletes and providers to identify common symptoms of concussion. However, it is well established that athletes tend to underreport symptoms in order to expedite return to play;\textsuperscript{2} therefore, symptom checklists may not accurately reflect an athlete’s true symptoms. One study found that 26% of athletes who reported being “symptom-free” on a symptoms checklist still were found to have cognitive changes\textsuperscript{20}. Therefore, the subjectivity of symptoms checklists potentially limited their usefulness for being included in return to play guidelines.

2. **SIDELINE ASSESSMENT TOOLS**

While many sideline tools currently employed incorporate other sub-tests that have been validated to various degrees, including assessments of cognition and balance, they are categorized as sideline assessment tests for the purposes of this review because they were developed specifically to help medical personnel, trainers and coaches recognize and diagnose concussion on the sideline of an athletic field.

**Sport Concussion Assessment Tool (SCAT3):** The SCAT3 is one of the most widely used sideline assessment tools. It contains a 22-item symptom checklist, cognitive and physical evaluation, GCS, Maddocks (recent event) questions\textsuperscript{31,115}, balance assessment (modified BESS), and the SAC. This scale was the product of an international working group on concussion\textsuperscript{18}. The SCAT3 takes 15 to 20 minutes to complete, and computes a composite score. The balance test in the SCAT3 can be significantly affected by high intensity exercise and muscle fatigue for up to 20 minutes following exercise\textsuperscript{32,33}. Perceived deficits in balance following head injury may be a result of muscle fatigue rather than concussion. Furthermore, McCrea et al. found that 26% of athletes who reported being “symptom free” according to the SCAT3 symptoms checklist still reported cognitive changes\textsuperscript{30}.

Scores in the SCAT3 are weighted to reflect the number of questions asked on each sub-section, rather than the importance of each symptom. For instance, the GCS has not been demonstrated to be effective at differentiating between concussed versus nonconcussed athletes, yet it accounts for a large number of points. The SCAT3 was designed to help providers recognize and diagnose concussion. A high score should not automatically clear an athlete to return to play as there are signs and symptoms of concussion not assessed by this tool and concussion symptoms can evolve over time.

One potential limitation of the SCAT3 symptoms checklist is the fact that athletes may under-report symptoms in order to avoid removal from the game or to expedite return to play. A recent anonymous online survey of collegiate athletes at the University of Pennsylvania revealed a substantial degree of under-reporting of concussion.\textsuperscript{122} Studies suggest that a lack of standardized knowledge may lead to under-reporting an under-treatment of sports-related concussion. However, there has been little
work done to establish how this knowledge may affect athletes’ behaviors towards reporting their concussions and removing themselves from play. We conducted an anonymous online survey was to assess athletes’ knowledge of signs and symptoms of concussion, and also sought to estimate the potential frequency of under-reporting in a collegiate athlete cohort. Among 262 athletes who responded to the survey, 43% of those with a past history of concussion reported that they had knowingly hid symptoms of a concussion to stay in a game, and 22% of athletes overall indicated that they would be unlikely or very unlikely to report concussion symptoms to a coach or athletic trainer in the future. These data suggest that there may be a substantial degree of under-reporting of concussion among collegiate athletes, despite most acknowledging that they have been formally educated about the risks of concussion.122

Head Impact Telemetry System (HITS): HITS is an investigational tool that may detect which athletes are at risk for concussion and to quantitate the impact of subconcussive hits. The HITS system incorporates a series of 6 accelerometers into a conventional football helmet and can identify the location and magnitude of impacts in real time34. This technology has demonstrated that several biomechanical variables including rotational acceleration greater than approximately 5500 rad/sec, linear acceleration greater than approximately 96 g, and impact on the front, top, or back of the helmet can yield a high predictive value for concussion34,35. Since HITS can identify the frequency and force of helmet impacts, it may be able to help identify athletes that are at risk for multiple sub-concussive injuries. One study found that football players who sustained a higher frequency of head impacts, even without diagnosed concussion, were more likely to exhibit concussive symptoms36. HITS may provide useful information in identifying athletes at risk for brain injury prior to being clinically diagnosed with a concussion.

While HITS may allow the identification of athletes who are at a high risk of brain injury based on frequency of impacts, individual variability in the ability to tolerate certain forces to the head and neck does not lead to an absolute relationship between force of injury and concussion34. Multiple studies have found no correlation between concussive impact magnitude and post-injury changes in symptoms, postural control, and cognitive function among high school or college athletes35,37. Athletes who sustain impacts well below the predicted concussion threshold still suffered concussions, and only 1 in 5 impacts above the predicted threshold resulted in concussion. Some experts have questioned the reliability of the rotational acceleration values since the accelerometers are not directly attached to the athlete. Therefore, HITS may be useful in identifying athletes at risk for concussion; however traditional measures must still be used to assess for concussion among athletes who sustain impacts below the injury threshold. This is important because there are currently no measures that are known to capture hits that are below the threshold but that might result in meaningful neurologic damage. Other sensor devices have been developed in mouth guards and patches that go behind the ear.

Standardized Assessment of Concussion (SAC): The SAC is an instrument designed to assess acute neurocognitive impairment on the sideline of an athletic contest. It is used as both a stand-alone test and as a component of the SCAT3 and MACE. The SAC includes measures of orientation, immediate memory, concentration, and delayed recall, which are domains of functions highly sensitive to concussion38-42. The SAC was designed for use by clinicians with no psychometric testing experience38,39, and can be administered in 5-7 minutes40, making it a practical sideline assessment tool. Little or no learning effect has been shown with the SAC42. Concussed players have been shown to perform significantly worse than baseline and worse than nonconcussed controls on all four domains of the SAC38,40, with 95% sensitivity and 76% specificity40. However, these results were obtained with an older definition of concussion that required an alteration of mental status.

Disadvantages of the SAC include that it only assesses a limited domain of neuro-cognitive functions, and there is a low correlation with other select neuropsychological tests, including Trails B, used to assess visuomotor tracking41. In addition, the SAC does not assess brainstem or cerebellar functions, which may be impaired in concussion7. Some athletes may have memorized sections of the tool, either from baseline testing or knowledge through teammates. While this is rare and may not have a significant impact on learning effects when shown in a large population of subjects, it may be of concern when assessing individual athletes. In addition, Grubenhoff et al. found that the SAC was not sensitive to changes after concussion in a pediatric population43. Finally, injured subjects have been found to demonstrate significant improvement in SAC scores 48 hours after injury, so the test may be best used and compared to baseline within the hours following concussion40.

King-Devick (K-D) Test: The K-D test is a rapid number naming test that captures impaired eye movements and saccades, attention, and language. These involve integration of functions of the brainstem, cerebellum, and cerebral cortex7,44. Impaired eye movements and saccades have been shown to correlate with suboptimal brain function, particularly in patients following concussion7,44,45. Because the K-D test does not require a medical professional and can be administered in 1-2 minutes, it is practical for sideline use at all levels of sports7. In a study of collegiate athletes found that on average, concussed athletes performed 5.9 seconds slower than their baseline, whereas controls performed on average almost 3 seconds faster7. In another study of boxers and mixed martial arts fighters, those suffering a concussion showed worsening of times required to read the three test cards of 5 seconds
or more compared to their own baseline. A third study performed in a cohort of amateur rugby players in New Zealand confirmed that athletes with concussion tested on the sidelines had 5-7-second increases in K-D time scores, consistent with worsening from baseline. In fact, unrecognized concussion may be more common than recognized concussion. At this time, any worsening of the KD score from baseline should suggest the presence of a concussion. In addition, K-D scores in studies of collegiate athletes were not negatively affected by prolonged exercise in the form of intense, two-hour scrimmage. One important consideration identified with the K-D was a learning effect associated with repeated testing. Nevertheless, the K-D has the potential to capture brain impairment not observed in standard neurocognitive testing.

3. BALANCE ASSESSMENT TOOLS

Balance Error Scoring System (BESS):

The BESS, which is also a component of the SCAT2, can identify post concussion balance deficits in and can be administered in 3-5 minutes. The test can easily be performed on the sideline or in a locker room and involves 3 different stances (double, single, and tandem) completed twice, once while standing on a firm surface and once standing on a piece of medium density foam. Each trial is 20 seconds long, and performance is scored by adding 1 error point for each error committed. Errors are recorded for lifting hands off hips, opening eyes, stepping, stumbling, falling, moving hip into more than 30° of flexion or abduction, lifting forefoot or heel, or remaining out of testing position for more than 5 seconds.

In one study, BESS identified only 36% of injured subjects immediately following concussion. In that study of over 1600 college football players, 94 sustained concussions that were identified by certified athletic trainers and team physicians. Sensitivity for the BESS was highest at the time of injury (sensitivity 34%). Specificity ranged from 91% to 96% across post injury days 1 to 7. Inter-rater and intra-rater reliabilities for the BESS were modest, with intra-class correlations of 0.57 and 0.74, respectively. These results suggest that scoring of BESS is difficult, and it may be best to have the same examiner perform the baseline and subsequent examinations. The authors concluded that overall BESS score is not highly reliable, but individual components, specifically the single leg stance, may have greater degrees of reliability in the setting of concussion.

BESS performance is affected by exertion and fatigue, the type of sport played, and a history of ankle injury or instability. In addition, healthy athletes typically demonstrate a learning effect.

Concussion Management Tools

1. COMPUTERIZED NEUROCOGNITIVE TESTING

Computerized neurocognitive tests are used primarily in the management of concussion. Some of the batteries are less practical to administer on the sideline because they require an environment free from distraction and can take 20 minutes to complete under ideal conditions. Nevertheless, they allow for the objective assessment of many brain functions that may be affected by concussion.

The Immediate Post-Concussion Assessment Cognitive Test (ImPACT): ImPACT is a widely used computerized neuropsychological test battery that measures attention, working memory, processing speed, response variability, and non-verbal problem solving. Deficits in neurocognitive function detected by ImPACT have been found to correlate with both traditional neuropsychological testing and altered activation of dorsolateral prefrontal cortex by fMRI. Because ImPACT is computerized, it can be administered by non-medical personnel, and it has numerous versions of each test and randomization procedures to reduce the possibility of practice effects. In addition, statistical techniques embedded within the software are used to help clarify data interpretation by accounting for things like practice effects and normal test score variability over time. Limitations of ImPACT include that it takes approximately 20 minutes to complete the battery, so collecting baseline data can be laborious and costly for large teams, concussed athletes may not have the stamina or attention to complete the entire battery, and the long testing session may cause symptom exacerbation. Test-retest reliability in a recent study was lower than had previously reported (intra-class correlation coefficient estimates from baseline to day 45 ranged from 0.15 to 0.39), and may influence the interpretation of some of the tasks. Additionally, up to 20-40% of athletes who were not concussed were found to have impairments on one of the five cognitive measures, and another study found that 17% of concussed athletes did not have any detectable cognitive abnormalities. While ImPACT reports five different cognitive measures, it has no associated algorithm for classifying overall performance as “impaired” or “recovered.”

Other products, such as the Axon Sports Computerized Cognitive Assessment Tool and the Automated Neuropsychological Assessment Metrics (ANAM), test athletes’ neurocognitive functions including processing speed, attention, working memory and learning are available, and overcome some of ImPACT’s limitations. Head to head comparisons are needed determine if any of these computerized batteries are superior at diagnosing concussion or monitoring recovery of neurocognitive deficits.
2. NEUROIMAGING

Conventional Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT): Conventional MRI and CT are structural imaging tools used to identify intracranial hemorrhage, contusion, mass effect, herniation, fractures, and other intracranial lesions, with MRI offering superior sensitivity compared to CT. The relatively recent development of susceptibility-weighted imaging has increased the sensitivity of MRI for evaluation of microhemorrhages, such as those associated with the diffuse axonal injury of more severe traumatic brain injury. However, conventional MRI and CT images often appear normal in concussed patients. Although sports-related concussion has been defined as a functional disturbance rather than a structural injury, more advanced MRI techniques have demonstrated associated functional and microstructure alterations. Determining the time course of MRI and CT changes following concussion will also be important to assess the usefulness of these techniques in athletes with minor head trauma.

Diffusion Tension Imaging (DTI): In a solution of pure water, water molecules diffuse in all directions equally. In fibrous tissues including white matter, water diffusion is relatively unimpeded in the direction parallel to the fiber orientation. Therefore, water diffusion is usually more anisotropic in white matter and isotropic in gray matter and cerebrospinal fluid. DTI exploits this phenomenon to measure the aggregate water movement in a voxel. DTI data can be analyzed in three ways to infer information regarding brain microstructure. The degree of anisotropy, which describes how much molecular displacements vary in space, is related to the presence of oriented structures; the mean diffusivity describes the overall mean-squared displacement of molecules and the overall presence of obstacles to diffusion; the main direction of diffusivity is linked to the structural orientation in space and is used in fiber tractography.

There are several scalar indices used to calculate diffusion anisotropy. One of these, fractional anisotropy (FA), is a measurement of the fraction of diffusion magnitude, and has been shown to be a reliable marker of white matter integrity. Neurodegenerative processes like demyelination are likely to cause significant decreases in fractional anisotropy. In patients with post-concussive symptoms, DTI has demonstrated a significant reduction in FA in the corpus callosum, corona radiata, longitudinal fasciculus, uncinate fasciculus, cingulum bundle, dorsolateral prefrontal cortex (DLPFC), rostral brainstem, and a number of other brain regions. The microstructural damage is thought to be the result of shearing axonal injury, misalignment of fibers, and milder axonal damage. Elevated mean diffusivities have been reported after traumatic brain injury, and Kinnunen, et al., demonstrated a correlation between elevated mean diffusivity and executive dysfunction. In addition, there is a significant correlation between structural white matter damage and neurocognitive performance in patients with mild traumatic brain injury (mTBI).

The use of DTI for evaluation of concussion appears to be promising, as it demonstrates higher sensitivity in detecting structural damage than conventional imaging methods. Although this robust technique is being utilized more frequently, its utility has not yet reached the level of routine diagnostic capabilities for mTBI.

Functional Magnetic Resonance Imaging (fMRI): In the brain, fMRI indirectly measures local neuronal hemodynamic changes with excellent temporal and spatial resolution by utilizing functional contrast agents. When a neuronal area is activated, an increase in blood flow follows in excess of the oxygen consumption, leading to an increase in oxygenated hemoglobin relative to deoxyhemoglobin. Blood oxygen level dependent (BOLD) imaging takes advantage of this phenomenon by detecting magnetic inhomogeneities caused by changes in the oxygenation state of hemoglobin.

Several fMRI studies have observed concussion-induced functional brain activation changes in both the acute setting and several months after injury in the absence of declines in behavioral performance. This phenomenon is postulated to arise as a result of increased recruitment of additional neural resources in response to higher processing demands. This increased neural recruitment can come from circuits in the same anatomical region or in different regions as those activated in control groups. Patients have shown reduced activation in the DLPFC, insular cortex, anterior cingulated cortex, anterior cingulated cortex, striatum, and medial frontal and temporal regions. The DLPFC has been consistently shown to display abnormal activity during working memory tasks. Patients with severe post-concussive symptoms have shown increased activity in the normal working memory networks, with the increased activity correlating with symptom severity. More highly symptomatic patients have been found to recruit additional cognitive resources during the acute phase of recovery from concussion.

fMRI has also been shown to correlate with other measures of concussion. Post-concussion symptom scores have been significantly associated with increased BOLD response in the premotor cortex and posterior parietal cortex. In addition, frequency of head blows detected by the Head Impact Telemetry System has been shown to correlate with BOLD response. While fMRI is promising for evaluation and treatment of concussed patients, one should be cautious with interpretation. Functional MRI measures a surrogate signal, subject to physical and biological constraints, with significant and substantial variability in the shape of responses collected across subjects. Cost and significant post-processing requirements may also limit availability and clinical usefulness. Nevertheless, fMRI...
has demonstrated clinical utility in determining return-to-baseline brain functioning as it relates to resolution of post-concussion syndrome symptoms.70

**Magnetic Resonance Spectroscopy (MRS):** MRS is a noninvasive MR imaging technique shown to accurately measure the concentrations of several compounds associated with brain metabolism.70,80 Changes in N-acetylaspartate (a neuronal marker), creatine (a marker for energy metabolism), choline (a marker for membrane disruption, synthesis, or repair), and lactate (associated with anaerobic glycolysis) have been documented in traumatic brain injury.70,80,97 In particular MRS has shown significantly lower levels of gray matter glutamine, N-acetylaspartate, and higher levels of white matter creatine in subjects with concussion relative to healthy controls.70,98,99

MRS has provided insight into metabolic brain recovery time after concussion. Studies have shown only modest brain metabolic recovery 15 days post-injury, with full recovery typically taking 30 days despite symptom resolution in as little as 3 days.99 In addition, athletes who received a second concussion within 15 days of the first did not show metabolic brain recovery until 45 days post-injury.99 MRS could play a clinical role in establishing guidelines with respect to when to initiate a graduated return to cognitive and physical activity during the concussion recovery period.99

While MRS is a promising functional imaging technique, its application in the domain of sports-related concussions is not well established, and the evidence for MRS in prognostication is not yet sufficient for use in routine clinical practice.89

**Positron Emission Tomography (PET):** PET is a functional imaging tool that utilizes radio-labeled metabolic analogues. The most widely used PET tracer is 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG), which has a half life of 110 minutes. After injecting this positron-emitting radionuclide into the bloodstream, FDG is partially metabolized by in the brain, and the rate of glucose metabolism can be measured using PET.70,80

Peskind et al. found that patients who experienced mTBI showed decreased glucose metabolism in the cerebellar vermis, pons, and medial temporal cortex compared to controls.100 The patients also displayed impairments in complex information processing, including verbal fluency, processing speed, attention, and working memory. The authors concluded that PET scanning may be an objective biomarker that correlates with neuropsychological symptoms of mTBI.

While PET may be an effective tool to measure metabolic and functional changes associated with concussion,70,80,100 there are several limitations. Although PET is sensitive for detection of functional abnormalities, underlying structural abnormalities may not be detected.101,102 It is therefore imperative to correlate PET images with structural imaging such as CT or MRI.101 PET is also time consuming and often more expensive than other traditional neuroimaging procedures. In addition, PET scanning requires intravenous access, and patients are exposed to ionizing radiation.70

Newly developed co-registered PET and MRI scanners hold promise to elucidate some of the mechanisms of concussive injury.

**Single Photon Emission Computerized Tomography (SPECT):** SPECT is an imaging technique that measures regional blood flow.70,74 After the intravenous injection of a radioisotope, images are acquired by a scintillation gamma camera.70,74 SPECT studies have demonstrated results similar to PET studies in traumatic brain injury.102 One study of mild to moderate brain injury demonstrated abnormal SPECT findings in 68% of patients with a normal head CT.103 Another SPECT study utilizing I123 iodoamphetamine demonstrated a good correlation between patient outcomes and CBF values.104 Since acute head trauma may result in the uncoupling of cerebral blood flow and metabolism,105 care must be taken when evaluating SPECT findings in the acute setting.101 Although one study of mTBI patients demonstrated SPECT abnormalities within the medial temporal lobe,24 a study investigating SPECT in sports-related mTBI has not been performed.106 Some disadvantages to SPECT include the need for intravenous access and exposure to ionizing radiation.70,74 Nevertheless, SPECT scanning is less expensive than PET imaging.

**Neuro-ophthalmological Testing:** A variety of neuro-ophthalmological testing is worth pursing in the study of patients with mild traumatic brain injury. Photophobia is quite common in this cohort and understanding the mechanisms of this complaint will be important. Furthermore, we and others have recognized retinal nerve fiber layer thinning by OCT in certain boxers, the significance of which is uncertain. However, retinal findings have been evident in athletes with CTE and in animal models of blast injury. Finally, Dr Randy Kardon has been examining the role of pupil reactivity in patients with head trauma.

### 3 BIOMARKERS

The correlation between mTBI and several biomarkers has been investigated recently to determine the biomarkers’ ability to indicate concussion or predict long-term outcomes. The biomarkers studied in the greatest depth are serum protein S100B and Apolipoprotein E (ApoE) and its promoter.

There has been little consensus whether any of these biomarkers can indicate increased chance of concussion or predict long-term outcomes. Several studies have found significant correlation between elevated S100B levels and worsened outcome anywhere from 1 week to 15 months post-injury.106-109 Other studies have found that S100B is a poor predictor of outcome.110-113
While most studies on ApoE2 and ApoE4 have found that neither genotype alone corresponds with an increased initial injury severity, risk of concussion, or outcome. Tierney et al. found that rare forms of the ApoE promoter correlated to an increased chance of multiple concussions. Furthermore, athletes with rare forms of the ApoE2, ApoE4, and ApoE promoter were 9.8 times more likely to report a previous concussion. Nevertheless, Gordon points to flaws in the Tierney study, namely the lack of validity in self-reported concussions, lack of an injured control group, lack of power (only four athletes reported all three rare alleles), and the need for replication and validation in genetic association studies.

**CONCLUSIONS**

This review highlights the merits of many tests used to evaluate concussions. While each test may be helpful in diagnosis or management, a single test that can reliably detect the presence of a concussion or complete recovery from a concussion has not been developed. Comprehensive computerized testing batteries are useful to help determine the athlete’s ability to return to play; however these tend to be time consuming. Furthermore, it is unclear which individual tests are most effective at identifying concussion, and how the results of these tests should be weighed. There still is a need for further research into a quick and reliable test validated by scientific investigation. The decision as to whether a concussion has occurred ultimately resides with the evaluating clinician.

There is also a need for concussion management tools that are both reliable and accessible. Many of the neuroimaging techniques discussed show promise in concussion management. Nevertheless these tools are expensive, time consuming, and the results are often not well understood. Further investigation will be essential in determining which imaging techniques and other tools are effective in the management of concussion and may be predictive of long term complications.

**Chronic traumatic encephalopathy**

Chronic traumatic encephalopathy is a degenerative disorder that appears to follow mild brain trauma. The disorder is characterized clinically by symptoms of irritability, depression, memory impairment and aggression. More severe cases may be associated with dementia, Parkinsonism and suicide. Neuropathologically, the changes of CTE are characterized by tau deposition in sulci of the cerebral cortex of the frontal and temporal lobes, diencephalon and mammillary bodies with subsequent involvement of the brainstem and spinal cord. There appears to be concentration of the tau deposition around blood vessels and in the subpial areas that are not present in Alzheimer’s disease. Further investigation is necessary to understand why for certain athletes and others prone to mild head trauma that there can be a devastating and subsequent dementing illness.

**CME ANSWERS:**

1. c
2. d
3. c

**REFERENCES**


LEARNING OBJECTIVES

1. To list the goals of treatment for nystagmus and saccadic intrusions
2. To identify potential weaknesses in clinical trials for nystagmus treatment
3. To list potential treatments for downbeat, acquired pendular, and congenital forms of nystagmus on the basis of recent clinical trials

CME QUESTIONS

1. Which of the following is least likely to require medical treatment?
   a. Downbeat nystagmus
   b. Acquired pendular nystagmus
   c. Periodic alternating nystagmus
   d. Oculopalatal tremor
   e. Square-wave jerks

2. Which of the following medications is most likely to suppress downbeat nystagmus?
   a. Baclofen
   b. Memantine
   c. Gabapentin
   d. 4-aminopyridine
   e. Carbamazepine

3. Which of the following medications is most likely to suppress acquired pendular nystagmus?
   a. Baclofen
   b. Memantine
   c. Valproate
   d. 4-aminopyridine
   e. Carbamazepine

KEYWORDS

1. Nystagmus
2. Saccadic intrusions
3. Oscillopsia

INTRODUCTION

Nystagmus is common, with a prevalence of approximately 24 per 10,000 in the general population. Because of the associated visual symptoms and negative impact on quality of life, many patients with nystagmus request treatment. Unlike physiologic nystagmus (e.g., during head movements), where slow phase drifts minimize retinal image slip, the slow phase drifts of pathologic nystagmus cause retinal image slip. When retinal image slip from pathologic slow phase drifts is greater than about 5 degrees per second, it can produce blurred vision, because the image of the object of interest no longer lies on the fovea, and illusory motion of the visual environment (oscillopsia). Saccadic intrusions also cause visual symptoms, such as difficulty reading, as they consist of inappropriate saccadic eye movements that take the image of the object of interest off the fovea.

GOALS OF TREATMENT AND GENERAL TREATMENT APPROACHES

GOALS OF TREATMENT

The primary goal of treatment is to reduce the patient’s visual symptoms by reducing the speed of nystagmus slow phases or frequency of inappropriate saccades. Treatments that stop the eyes from moving altogether (e.g., BOTOX® injections into the extraocular muscles or retrobulbar space) are not ideal, because they also impair physiologic eye movements (e.g., vestibulo-ocular reflex and vergence). Consequently, treatments that suppress the slow phase drifts or inappropriate saccades without affecting physiologic eye movements are preferred. Note that some types of nystagmus (e.g., gaze-evoked nystagmus) and saccadic intrusion (e.g., square-wave jerks) do not usually give rise to visual symptoms and, thus, do not require specific treatment.
**GENERAL APPROACHES TO TREATMENT**

Many treatments for nystagmus and saccadic intrusions have been proposed, including medical, optical, and surgical treatments, but few have been evaluated in prospective, masked, and controlled clinical trials.3-5 Commonly prescribed drug treatments and their doses are listed in Table 1.5 The aim of this journal club session is to review the results of recent trials evaluating treatments for nystagmus and saccadic intrusions.

Table 1: Drug treatments for acquired nystagmus

<table>
<thead>
<tr>
<th>Nystagmus Type</th>
<th>Treatment (dose, frequency)</th>
<th>Common Side-Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Vestibular Nystagmus</td>
<td>Treatment of underlying vestibular disorder</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Downbeat Nystagmus</td>
<td>4-aminopyridine (5-10mg, tid-qid)</td>
<td>Dizziness, paresthesias, incoordination</td>
</tr>
<tr>
<td></td>
<td>3,4-diaminopyridine (10-20mg, tid)</td>
<td>Dizziness, paresthesias, incoordination</td>
</tr>
<tr>
<td></td>
<td>Clonazepam (0.5-1mg, bid)</td>
<td>Drowsiness, dizziness, incoordination</td>
</tr>
<tr>
<td>Upbeat Nystagmus</td>
<td>Memantine (10mg, qid)</td>
<td>Lethargy, dizziness, headache</td>
</tr>
<tr>
<td></td>
<td>4-aminopyridine (5-10mg, tid-qid)</td>
<td>Dizziness, paresthesias, incoordination</td>
</tr>
<tr>
<td></td>
<td>Baclofen (5-10mg, tid)</td>
<td>Drowsiness, dizziness, incoordination, lethargy</td>
</tr>
<tr>
<td>Torsional Nystagmus</td>
<td>Gabapentin (300mg, qid)</td>
<td>Dizziness, incoordination, drowsiness</td>
</tr>
<tr>
<td>Seesaw Nystagmus</td>
<td>Alcohol Clonazepam (0.5-1mg, bid) Memantine (10mg, qid)</td>
<td>Drowsiness, incoordination, vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drowsiness, dizziness, incoordination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lethargy, dizziness, headache</td>
</tr>
<tr>
<td>Periodic Alternating Nystagmus</td>
<td>Baclofen (5-10mg, tid)</td>
<td>Drowsiness, dizziness, lethargy</td>
</tr>
<tr>
<td></td>
<td>Memantine (5-10mg, qid)</td>
<td>Lethargy, dizziness, headache</td>
</tr>
<tr>
<td>Acquired Pendular Nystagmus in MS</td>
<td>Gabapentin (300mg, qid)</td>
<td>Dizziness, incoordination, drowsiness</td>
</tr>
<tr>
<td></td>
<td>Memantine (10mg, qid)</td>
<td>Lethargy, dizziness, headache</td>
</tr>
<tr>
<td>Acquired Pendular Nystagmus in OPT</td>
<td>Gabapentin (300mg, qid)</td>
<td>Dizziness, incoordination, drowsiness</td>
</tr>
<tr>
<td></td>
<td>Memantine (10mg, qid)</td>
<td>Lethargy, dizziness, headache</td>
</tr>
<tr>
<td></td>
<td>Trihexyphenidyl (5-20mg, tid)</td>
<td>Dry mouth, blurred vision, dizziness</td>
</tr>
</tbody>
</table>

**Abbreviations:** bid, twice daily; MS, multiple sclerosis; OPT, oculopalatal tremor; qid four times daily; tid, three times daily

**POTENTIAL PITFALLS IN INTERPRETATION OF TREATMENT TRIALS**

Although the primary goal of treatment is to reduce patient’s visual symptoms, most trials use eye movement recordings as well as measures of visual function (e.g., visual acuity) to quantify any treatment effect. Factors that need to be considered in the interpretation of treatment trials for nystagmus and saccadic intrusions include the following:

1. **Subject numbers:** many trials include only a small number of subjects, because of the rarity of many forms of nystagmus and saccadic intrusions. Few multi-center trials have been completed, because the required eye movement recording equipment is not readily available and recording conditions can be difficult to standardize.

2. **Calibration of eye movement recording system:** the eye movement recording system often requires an in vivo calibration, where the patient looks toward a visual target at a known angle away from the central fixation point, such that the signal that is recorded by the system can be appropriately scaled. Since steady fixation is often not possible during the calibration in a patient who has nystagmus or saccadic oscillations, the accuracy of the findings becomes less certain. Consequently, eye movement recording systems that do not require in vivo calibration, such as the magnetic search coil system, are preferred. In the case of the magnetic search coil system, the search coil is calibrated in vitro (e.g., on a gimbal device) before the search coil is placed on the eye and an in vivo calibration is not required.

3. **Resolution of eye movement recording system:** an adequate sampling rate (ideally greater than 250 Hz) is required to accurately calculate the amplitude and speed of eye movements. Eye movement recording systems with sampling rates less than 100 Hz are inadequate for quantification of slow phases or saccades. Inadequate sampling rate can also result in aliasing, where high-frequency components of the data are inappropriately interpreted as being lower-frequency components. An adequate spatial resolution (e.g., less than 0.5 degrees) is also desirable.
4. Control of head and fixation position: many forms of nystagmus vary depending on head orientation relative to gravity, eye-in-head position, and vergence angle. Ideally, the head should be immobilized in a consistent position during the recording sessions, with the eye movement recording taken with the patient looking toward a fixation target at a set distance from the patient and at a set location in the visual field. In congenital forms of nystagmus that have a null point or null zone, the eye movements should be recorded in a variety of gaze positions, so that the location and breath of the null zone can be determined.

5. Visual symptoms may not correlate with nystagmus speed or intensity: in congenital forms of nystagmus, visual symptoms will often correlate better with the frequency and duration of “foveation” periods than with slow phase speed. Thus, quantification of the frequency and duration of “foveation” periods might be preferred over quantification of the slow phase speed or other measures of nystagmus intensity.

6. Other relevant outcome measures may not be reported: ability to function, quality of life, and cosmetic aspects are often not considered as outcome measures in nystagmus treatment trials, yet may be relevant to the patient’s concerns and goals for treatment.2

DOWNBEAT NYSTAGMUS

Downbeat nystagmus causes vertical oscillopsia and affected patients frequently seek treatment. The aminopyridines (3,4-diaminopyridine and 4-aminopyridine; K+ channel blockers) can suppress downbeat nystagmus;6,7 4-aminopyridine is thought to be more effective due to better central nervous system penetration.8 Three recent clinical trials merit discussion.


ABSTRACT: Objective: The effects of 4-aminopyridine (4-AP) on downbeat nystagmus (DBN) were analysed in terms of slow-phase velocity (SPV), stance, locomotion, visual acuity (VA), patient satisfaction and side effects using standardised questionnaires. Methods: Twenty-seven patients with DBN received 5 mg 4-AP four times a day or placebo for 3 days and 10 mg 4-AP four times a day or placebo for 4 days. Recordings were done before the first, 60 min after the first and 60 min after the last drug administration. Results: SPV decreased from 2.42 deg/s at baseline to 1.38 deg/s with 5 mg 4-AP and to 2.03 deg/s with 10 mg 4-AP (p<0.05; post hoc: 5 mg 4-AP: p=0.04). The rate of responders was 57%. Increasing age correlated with a 4-AP-related decrease in SPV (p<0.05). Patients improved in the ‘get-up-and-go test’ with 4-AP (p<0.001; post hoc: 5 mg: p=0.025; 10 mg: p<0.001). Tandem-walk time (both p<0.01) and tandem-walk error (4-AP: p=0.054; placebo: p=0.059) improved under 4-AP and placebo. Posturography showed that some patients improved with the 5 mg 4-AP dose, particularly older patients. Near VA increased from 0.59 at baseline to 0.66 with 5 mg 4-AP (p<0.05). Patients with idiopathic DBN had the greatest benefit from 4-AP. There were no differences between 4-AP and placebo regarding patient satisfaction and side effects. Conclusions: 4-AP reduced SPV of DBN, improved near VA and some locomotor parameters. 4-AP is a useful medication for DBN syndrome, older patients in particular benefit from the effects of 5 mg 4-AP on nystagmus and postural stability.

COMMENT: The study confirms, in a larger number of patients and with a more rigorous study design, that the slow phase velocity of downbeat nystagmus can be significantly decreased in some patients with 4-aminopyridine. As suggested by prior studies, those with idiopathic downbeat nystagmus responded better than those with other causes for their nystagmus. Older patients tended to respond better than younger patients. Some patients also showed improvement in postural and locomotion parameters. Side effects were similar to those reported with placebo. For unclear reasons, use of a higher dose (10 mg) of 4-aminopyridine did not result in an amplified treatment effect.


ABSTRACT: We investigated the effects of dalfampridine, the sustained-release form of 4-aminopyridine, on slow phase velocity (SPV) and visual acuity (VA) in patients with downbeat nystagmus (DBN) and the side effects of the drug. In this proof-of-principle observational study, ten patients received dalfampridine 10 mg bid for 2 weeks. Recordings were conducted at baseline, 180 min after first administration, after 2 weeks of treatment and after 4 weeks of wash-out. Mean SPV decreased from a baseline of 2.12 deg/s ± 1.72 (mean ± SD) to 0.51 deg/s ± 1.00 180 min after first administration of dalfampridine 10 mg and to 0.89 deg/s ± 0.75 after 2 weeks of treatment with dalfampridine (p < 0.05; post hoc both: p < 0.05). After a wash-out period of 1 week, mean SPV increased to 2.30 deg/s ± 1.6 (p < 0.05; post hoc both: p < 0.05). The VA significantly improved during treatment with dalfampridine. Also, 50% of patients did not report any side effects. The most common reported side effects were abdominal discomfort and dizziness. Dalfampridine is an effective treatment for DBN in terms of SPV. It was well-tolerated in all patients.

COMMENT: The study demonstrates that the sustained-release form of 4-aminopyridine (i.e., Ampyra® in the United States) can significantly decrease the slow phase velocity of downbeat nystagmus and improve visual acuity.
The magnitude of the improvement was greater than reported in previous studies using 4-aminopyridine. The study has several shortcomings, however. It was neither masked nor placebo-controlled. Furthermore, only patients with idiopathic downbeat nystagmus and cerebellar degenerations were studied, so it is unclear if those with downbeat nystagmus from other etiologies might respond.


ABSTRACT: Objective: Downbeat nystagmus (DBN) is the most frequent form of acquired persisting fixation nystagmus with different symptoms such as unsteadiness of gait, postural instability, and blurred vision with reduced visual acuity (VA) and oscillopsia. However, different symptomatic therapeutic principles are required, such as 3,4-diaminopyridine and 4-aminopyridine, that effectively suppress DBN. Chlorzoxazone (CHZ) is a nonselective activator of small conductance calcium-activated potassium (SK) channels that modifies the activity of cerebellar Purkinje cells. We evaluated the effects of this agent on DBN in an observational proof-of-concept pilot study.

Methods: Ten patients received CHZ 500 mg 3 times a day for 1 or 2 weeks. Slow-phase velocity of DBN, VA, postural sway, and the drug’s side effects were evaluated. Recordings were conducted at baseline, 90 minutes after first administration, and after 1 or 2 weeks. Results: Mean slow-phase velocity significantly decreased from a baseline of 2.74°/s ± 2.00 to 2.29°/s ± 2.12 (mean ± SD) 90 minutes after first administration and to 2.04°/s ± 2.24 (p < 0.001; post hoc both p = 0.024) after long-term treatment. VA significantly increased and postural sway in posturography showed a tendency to decrease on medication. Fifty percent of patients did not report any side effects. The most common reported side effect was abdominal discomfort and dizziness. Conclusions: The treatment with the SK-channel activator CHZ is a potentially new therapeutic agent for the symptomatic treatment of DBN. Classification of Evidence: This study provides Class IV evidence that CHZ 500 mg 3 times a day may improve eye movements and visual fixation in patients with DBN.

COMMENT: The study demonstrates that chlorzoxazone (traditionally used as a muscle relaxant) can significantly decrease the slow phase velocity of downbeat nystagmus, but the treatment effect was not as substantial as for 4-aminopyridine. Half of the patients did not report side effects. The study has several shortcomings. Firstly, a reversal of the treatment effect was not confirmed following a “wash out” period. Secondly, the study was not masked or placebo-controlled. Lastly, only patients with idiopathic downbeat nystagmus and cerebellar degenerations were included.

ACQUIRED PENDULAR NYSTAGMUS

Acquired pendular nystagmus (e.g., due to multiple sclerosis or with oculopatalal tremor) causes intractable oscillopsia and affected patients often seek treatment. Gabapentin and memantine appear to be effective treatments for acquired pendular nystagmus in the setting of multiple sclerosis, but most trials have used a video-based eye movement recording system rather than the magnetic search coil system. 12-14 One recent clinical trial merits discussion.


ABSTRACT: We conducted a masked, crossover, therapeutic trial of gabapentin (1,200mg/day) versus memantine (40 mg/day) for acquired nystagmus in 10 patients (aged 28-61 years; 7 female; 3 multiple sclerosis [MS]; 6 post-stroke; 1 post-traumatic). Nystagmus was pendular in 6 patients (4 oculopatalal tremor; 2 MS) and jerk upbeat, hemi-seeaw, torsional, or upbeat-diagonal in each of the others. For the group, both drugs reduced median eye speed (p < 0.001), gabapentin by 32.8% and memantine by 27.8%, and improved visual acuity (p < 0.05). Each patient improved with 1 or both drugs. Side effects included unsteadiness with gabapentin and lethargy with memantine. Both drugs should be considered as treatment for acquired forms of nystagmus.

COMMENT: Using the magnetic search coil technique, the study shows that both gabapentin and memantine reduce slow phase speed and improve visual acuity in patients with acquired pendular nystagmus due to multiple sclerosis or with oculopatalal tremor. However, the response was idiosyncratic, with some patients showing dramatic improvement to one or both drugs and others showing only mild improvement. Only a small number of patients were included and, thus, larger studies are required to define factors that predict a response to treatment.

CONGENITAL FORMS OF NYSTAGMUS

Some patients with congenital forms of nystagmus do not have visual symptoms and most do not report oscillopsia. Asymptomatic patients do not require treatment for the nystagmus, but it may be requested due to concerns about the cosmetic appearance of the nystagmus. 9 Some patients might have impaired vision due to associated afferent visual system anomalies (e.g., optic nerve or foveal hypoplasia), such that suppression of the nystagmus does not produce a significant improvement in vision. However, those patients with visual symptoms who have an intact afferent system anomalies (e.g., optic nerve or foveal hypoplasia), such that suppression of the nystagmus does not produce a significant improvement in vision. However, those patients with visual symptoms who have an intact afferent visual system will sometimes benefit from treatments that suppress the nystagmus. 12-14 Optical, surgical, and medical treatments have been proposed for the treatment of congenital forms of nystagmus, but remain controversial due to a lack of well-designed prospective masked clinical
trials and difficulties with measuring treatment effect. One recent study merits discussion.


ABSTRACT: Purpose: To report a systematic approach to, and the visual and electrophysiological effect of, eye muscle surgery in 100 patients with infantile nystagmus syndrome (INS). Methods: Prospective, interventional case cohort analysis of clinical and eye movement data in 100 patients with INS who had virgin extraocular eye muscles operated upon for nystagmus with or without combinations of strabismus and an anomalous head posture. All patients were followed at least 9 months after surgery. Outcome measures, part of an IRB approved study, included binocular visual acuity, head position, strabismic deviation, and eye movement recordings, from which waveform types and an Automated Nystagmus Acuity Function (ANAF) was calculated. Computerized parametric and non-parametric statistical analysis of data were performed using standard software on both individual and group data. Results: There were 9 consistent surgical procedures used with the most common being that for a horizontal head posture alone (22%). Age at surgery averaged 14 years with 11 months follow-up. Sixty-eight percent had associated eye disease (optic nerve, retinal, amblyopia, cataracts). Group means in binocular acuity, strabismic deviation, head posture, and ANAF measures from eye improved for all procedures. There were 12 (12%) reoperations without any serious surgical complications. Individual analysis revealed only age and head posture differences in outcome measures between the 9 procedures. Conclusions: Using this approach, surgery on the extraocular muscles in patients with INS results in improvements in multiple aspects of ocular motor and visual function.

COMMENT: The study demonstrates that strabismus surgery (including tenotomy and reattachment) can be effective in improving binocular visual acuity, strabismic deviation, head posture, and nystagmus waveform in patients with congenital forms of nystagmus, even in those with afferent visual system anomalies. However, the study highlights that the choice of procedure needs to be tailored to the individual patient. Data were obtained prospectively and in a standardized fashion, but there was no masking or control group and the eye movement recordings were obtained using a video-based eye movement recording system.

CME ANSWERS:

1. e
2. d
3. b

REFERENCES

LEARNING OBJECTIVES

1. Describe the spectrum of paraneoplastic syndromes with neuro-ophthalmic features
2. Define the challenges in diagnosis of the paraneoplastic syndromes
3. Explain the therapeutic options for treatment of these diseases

CME QUESTIONS

1. The presence of serum antibodies against recovering
   a. Are pathognomonic for CAR
   b. Are found in the majority of patients with lung cancer
   c. May be responsible apoptotic cell death in CAR patients
   d. Are best detected by immunofluorescent studies on retina

2. Which of the following is correct regarding therapy for paraneoplastic neuro-ophthalmic disease:
   a. Steroid therapy may be helpful in control of disease
   b. Should be initiated only after there is validation for the presence of autoreactive antibodies
   c. Cytoreduction of the primary tumor is not helpful in controlling the autoimmune component
   d. Biologic immunomodulatory agents have no role in therapy

3. Lambert-Eaton myasthenic syndrome is associated with which of the following:
   a. Symptoms and signs that are indistinguishable from myasthenia gravis
   b. Antibodies against the acetylcholine receptor
   c. Absence of autonomic symptoms in the majority of patients
   d. Clinical response to 3,4-diaminopyridine

KEYWORDS

1. Paraneoplastic
2. Cancer associated retinopathy
3. Melanoma associated retinopathy
4. Lambert Eaton syndrome
5. Opsoclonus/Myoclonus

INTRODUCTION

Neuro-ophthalmic consequences of paraneoplasia may involve multiple aspects of the afferent visual pathway from the uvea to the optic nerve and the efferent pathways for eye movement.1-6 It is important to understand the spectrum of signs and symptoms that can result from a tumor-stimulated immune process in order to both suspect, diagnose and treat these diseases.

CLINICAL DISEASE SPECTRUM

When should the astute clinician consider a diagnosis of paraneoplastic syndrome? In terms of afferent symptoms, an unexplained, painless, progressive vision loss is typical. In the retinal diseases, there may be photopsias, night blindness, or ring scotomas. In the optic neuropathies there is most commonly bilateral disc swelling often accompanied by a vitritis. Efferent symptoms include myasthenic-like presentation or the presence of opsoclonus-myoclonus. Associated systemic neurologic symptoms, such as encephalitis, cerebellar degeneration, myelitis, or sensory neuropathies, increase suspicion for a paraneoplastic syndrome. Pertinent negatives include lack of alternative explanation for the symptoms such as a known genetic condition, history of ocular surgery, infection, trauma, mass lesion, or toxic exposures. A history of cancer may heighten the suspicion for a paraneoplastic syndrome, but the real challenge is to help diagnose a potentially treatable cancer in patients who do not already carry that diagnosis.

AFFERENT SYMPTOMS

Autoimmune paraneoplastic retinopathy. Three types of syndromes of autoimmune paraneoplastic retinopathy have been described in the literature: cancer associated retinopathy (CAR), melanoma associated retinopathy (MAR) and, bilateral diffuse uveal melanocytic proliferation (BDUMP).7-14 CAR was the first of these syndromes to be recognized, appears to be the most common of the
paraneoplastic retinopathies, and remains a significant diagnostic and therapeutic challenge.\(^7\)

Visual dysfunction in CAR typically involves a bilateral, progressive and painless loss of vision with photopsias.\(^9,15\) Patients complain of a rapid onset of night blindness and flickering lights associated with progressive vision loss over weeks to months. However, the signs and symptoms depend on whether rod or cone function is primarily disrupted. In rod disease, there is often constriction of the visual field with impaired dark adaptation. In contrast, when there is primarily cone dysfunction, central scotomas, dyschromatopsia, and loss of visual acuity are more prominent. There may be an associated uveitis. Retinal findings may be unexceptional, alternatively arteriolar narrowing, thinning or mottling of the retinal pigment epithelium (RPE), or pallor of the optic disc may be observed in these patients. Electroretinography (ERG) confirms photoreceptor dysfunction but is not pathognomonic for CAR. CAR may occur in patients with known malignancies, however it may also occur before the diagnosis of cancer, and thus prompt recognition of this disease may lead to early diagnosis and cure for patients with specific types of malignancies. Although the most common tumor associated with CAR is small cell lung carcinoma, other tumors originating in many organs including the prostate, bladder, colon, thymus, ovary, endometrium, breast, and cervix have also been implicated in CAR (Table 1).

Visual symptoms in MAR have a rapid onset and include loss of visual acuity, presence of photopsias, and central or paracentral scotomas.\(^16,17\) The vision loss is usually mild with acuities generally in the 20/60 range. Ophthalmoscopy may be initially normal but ERG abnormalities are present, including reduced scotopic a-wave and decreased or absent dark-adapted b-wave. In a large review of more than 60 patients with MAR, vitreous cells were present in 30% of affected patients.\(^17\) However, the fundus evaluation was initially normal in more than 40%. Similar to CAR, disc pallor and retinal vascular attenuation may be observed. Patients with MAR usually have a diagnosis of malignant melanoma that predates the retinal disease by several years.

BDUMP is rare but distinctive in its proliferation of melanocytes in the uveal tract along with bilateral loss of vision. These patients are present with sudden and bilateral visual loss and may have exudative retinal detachment and progressive cataracts. This entity is rare and the patients reported typically had a short life span, less than 15 months following diagnosis on average. Visual disturbance may precede diagnosis of malignancy, and although multiple types of cancers have been identified in association with BDUMP, the most common are lung or gynecologic in origin.

**Paraneoplastic optic neuropathy.** Paraneoplastic optic neuropathy (PON) is an unusual but serious cause of bilateral, painless loss of vision. In 2003 a cohort of 16 patients were identified as being positive for the antibody against CRMP-5.\(^18\) More than 90% of these patients, in concordance with others reported since then in the literature, have a prominent complaint of vision loss, which is painless and either acute or subacute. Similar to patients with CAR and MAR, photopsias may be present. Ophthalmoscopic findings in these patients classically include optic disc edema and vitreous cells, but patients may present with optic atrophy as well. Retinitis may also be present, and ERG in these patients may show abnormalities in scotopic rod, scotopic combined rod-cone, or photopic cone response. Vitreous cells appear small, without clumping, and without evidence for an intermediate uveitis. Evaluation of vitreous cells reveals pleomorphic lymphocytes. One of the original 16 patients described also had anterior chamber cells, an unusual finding in this disease. In addition, disorders of eye movement including vertical gaze disturbance, internuclear ophthalmoplegia, and opsoclonus have been observed in affected patients. Systemic neurologic symptoms are present in essentially all of the patients during their illness and may include seizures, dementia, cognitive abnormalities, cerebellar findings and a wide variety of motor and sensory abnormalities. Concomitant Lambert-Eaton syndrome has also been described in association with PON. The most common associated cancer in these patients is small cell lung carcinoma. Less common associations include other lung cancers, renal cell carcinoma, colon cancer, papillary thyroid cancer, breast, uterine, and neuroendocrine tumors.

**EFFERENT SYMPTOMS**

*Opsoclonus/myoclonus syndrome.* Myoclonus is defined by short, sudden involuntary jerking movements which may involve lower or upper extremities and may be induced or worsened by a change in posture. Opsoclonus is the ocular concomitant or myoclonus, and is characterized by rapid, involuntary, horizontal and vertical eye movements without intersaccadic delays. In children, up to 43% of cases of the opsoclonus-myoclonus syndrome (OMS) were associated with a paraneoplastic syndrome associated with neuroblastoma.\(^19\) In 2011 a series of adults with OMS was described in conjunction with a review of all reported cases of adult OMS.\(^20\) In this series the age range for the newly reported patients was 27-78 years and symptoms consisted of dizziness/balance difficulties in 67%, nausea/vomiting in 48%, and abnormalities of vision from opsoclonus in 28% of patients. Neuroimaging was normal in all except one patient with metastatic disease. Evaluation of CSF revealed abnormalities in more than 50% including elevated protein and/or increased white cells (lymphocytes) in the majority; in about a third of cases there may be an increased IgG index or oligoclonal bands. Etiologies for OMS included cancer in 15% (breast adenocarcinoma and small cell lung cancer) and parainfectious in the remaining patients; notably in the review of the literature lung cancer was responsible for 28% of cases and breast cancer for 6% of cases. Other non-malignant causes of OMS in adults are less common and include toxic/metabolic or other autoimmune etiologies.
Lambert-Eaton myasthenic syndrome. In the Lambert-Eaton myasthenic syndrome (LEMS) there is a decrease in acetylcholine release leading to decreased activity of the neuromuscular junction. Although LEMS is typically characterized by decreased deep tendon reflexes, autonomic dysfunction, and proximal muscle weakness, symptoms of diplopia and ptosis may be common.\textsuperscript{5,21} In fact, the autonomic symptoms develop in about 90\% of affected patients within the first three months of disease onset and are very helpful in identifying the diagnosis as LEMS. To distinguish LEMS from myasthenia gravis (MG), clinical findings, such as slight increases in strength on prolonged effort, and electromyography, showing facilitation in repetitive stimulation testing, when present may help make the diagnosis. Ocular symptoms generally occur after onset of other disease symptoms such as generalized weakness and ultimately occur in about half of patients with LEMS. Ocular findings reported in patients with LEMS, that are not generally seen in MG include involuntary lid closure, decreased ptosis with prolonged upgaze, dilated pupils, and poorly reactive pupils.\textsuperscript{5} Ductions are typically full in LEMS, but may be limited in MG. More than 50\% of patients with LEMS have cancer, commonly lung cancer, but also lymphoproliferative diseases as well as cancers of the prostate or thymus have been disease associated.

PATHOPHYSIOLOGY
The paraneoplastic syndromes discussed in this session involve antibodies against normal proteins that are also typically expressed in the tumor. To date a virtual alphabet soup of proteins have been identified as potential immune targets and in some cases these proteins have been validated as playing a significant role in the pathophysiology of the disease (Table 1). For other candidates, the pathophysiological role played by the immune response against a particular autoantigen is not entirely clear.

Recoverin, a 23 kDa protein, is one of the first antigenic targets identified that is associated with CAR. The protein is widely expressed in the majority of lung cancer samples, irrespective of retinopathy. Serum autoantibodies against recoverin may be present in small subset of patients with lung cancer, but only a small fraction of those develop CAR. Alpha-enolase, another common protein that is found both in lung cancer and the retina elicits an antibody in a larger percentage of patients with lung cancer (estimated at 13–65\%); however only a small subset of these patients will develop CAR.\textsuperscript{1,22,23} Alpha-enolase antibodies are also found in many other diseases, including autoimmune hepatitis, rheumatoid arthritis, and mixed cryoglobulinemia, but also can be found in normal individuals as well, thus the presence of the antibody alone does not indicate disease or causation of symptoms.

Therefore, how are these antibodies associated with disease pathophysiology? It is believed that high-titer antibodies may traverse the blood-retinal barrier, leading to exposure to retinal cells. There is also some evidence for different antigenic epitopes within a protein with differential consequences with regards to pathology. In addition, the immunologic phenomenon of epitope spreading is postulated to be associated with differences in pathogenic sequelae. In the retina there is some evidence that the antibody may be engulfed through an endocytic mechanism into retinal cells.\textsuperscript{24} Once internalized, the antibody engages its corresponding antigen and this binding leads to downstream signalling resulting in apoptotic cell death. This observation was initially made in vitro using retinal cells in culture, but has also been replicated in vivo using either intravitreal or intravenous injections of antibodies against recoverin. Apoptosis was activated through caspase 3 and caspase 9.\textsuperscript{25} It is believed that an increase in free Ca\textsuperscript{2+} precedes apoptosis, a mechanism that was also observed in studies using antibodies against enolase. In studies using anti-enolase antibodies there is a decrease in glycolytic adenosine triphosphate with resultant increase in the intracellular Ca\textsuperscript{2+}. Therefore, this mechanism is a plausible common pathway leading to cell death. However additional studies will be required to definitively understand the disease pathophysiology. Many other potential antigens have also been identified but it is yet unknown whether the antibodies against these antigens play an important role in disease pathogenesis.

In LEMS there is a well-characterized antibody against P/Q, voltage-gated calcium channels (VGCC), present on the presynaptic nerve terminal at the neuromuscular junction. This antibody reproduced the disease in in vivo animal models and the disease can be transmitted passively from mother to child. It is believed that the antibody causes a loss in the VGCC, leading to a decrease in Ca\textsuperscript{2+} internalization and subsequent decrease in release of acetylcholine containing vesicles, thus there is less available acetylcholine at the neuromuscular junction.

LABORATORY EVALUATION
For the well-characterized antigens in disease pathophysiology, such as CRMP-5 and recoverin, the presence of antibodies is helpful in making the diagnosis. The challenges are primarily: 1) interpreting and identifying possible disease-associated antibodies against other possible antigens, and 2) understanding the sensitivity and specificity for the known antigens in helping to make the diagnosis of a paraneoplastic condition. Laboratory evaluations for the presence of antibodies are performed using multiple techniques. In immunofluorescence testing, a section of tissue is exposed to sera from the patient and then the bound antibodies are visualized using a fluorescently tagged second antibody that globally recognizes the type of bound antibody, for example IgG. Immunofluorescence testing simply identifies whether or not the serum binds to a tissue, but does not identify the antigens. Particular patterns of binding, types of cells or subcellular preferences (nuclear, cytoplasmic, perinuclear) may be helpful in identifying a likely type of antibody. In immunofluorescence testing the...
origin and type of tissue, fixation protocol, and incubation time with the serum, and serum dilution are all critical in obtaining an interpretable result. In Western blot testing, a mixture of proteins, generally obtained from cell culture or tissue homogenization are separated on a gel using an electric current, transferred to a nitrocellulose membrane, exposed to the serum, and the bound antibody is identified using a tagged second antibody that allows for visualization. Here the pitfalls are many and include the tissue or cells of origin, the way that the proteins are extracted from the tissue or cells, the dilution and exposure time to the serum, blocking of the membrane to enhance specificity, and the size of the antigen which determines whether it is bound or transferred adequately from the gel to the membrane. In Western blot one identifies the size of the protein, which may be suggestive but is not confirmatory for the identity of the antigen. ELISA testing typically will use a purified protein as the target for antibody detection and therefore provides the greatest specificity when identifying an antibody. The protein is immobilized, exposed to the serum at multiple dilutions, and a tagged secondary antibody is used for visualization. As in the other types of antibody testing, the technique is important. In all of these tests, it is important to understand the limitations of the testing strategy and the false positive and false negative potential for particular evaluations.

Antibodies against self-proteins are fairly common, using Western blot as a criteria the majority of control individuals have immunologic reactivity against at least one protein in whole retinal extracts. A report in 2008 included a review of the literature about antiretinal antibodies and this report suggested that standardization among laboratories was lacking and therefore results were not always concordant between different testing sites. In fact, in a paper published in 2013, serum from 14 patients who were diagnosed as having autoimmune retinopathy was sent to two different laboratories for evaluation of the presence of antiretinal antibodies by Western blot. One laboratory used human retina extract with a positive control and the other used pig retinal extract with a panel of normal controls (without antiretinal activity). They tested serum from all 14 patients and found that antibodies were detected by both laboratories in 64%, of the remaining 5 patients, 4 were positive for antiretinal antibodies as detected by one laboratory and one was positive as detected by the other laboratory. Furthermore, for the 64% that were positive, there was only a single patient whose sera gave the same results (within 1 kDa of size of the band) from both laboratories. Therefore the testing for antiretinal antibodies is not currently standardized and may result in data that is confounding at best.

What antibodies are known to be disease-associated? Disease-associated, validated antigenic targets of antibodies have been described in several of the paraneoplastic neuro-ophthalmic syndromes (Table 1). However there are other antigens that have also been identified as potential immunologic targets, but the pathologic significance of these antibodies is uncertain. What testing is recommended when you encounter a patient with a suspected paraneoplastic syndrome with neuro-ophthalmologic symptoms?

If you suspect CAR then antibodies against retinal proteins are initially tested through Western blot and/or immunofluorescence. As noted above however, it might be important to send materials to different laboratories for investigation. It is likely that over the next several years, there will be standardization of testing, however this is not yet a reality. If the testing is negative, you must consider the possibilities that the patient is negative for antiretinal antibodies or that the technique used was not sufficiently sensitive to uncover the reactivity. In one of the largest series of CAR patients described in the literature, only 61% had antibodies against defined retinal proteins, of which the antigenic targets were alpha-enolase in about half of the patients, followed in descending percentages by transducin, carbonic anhydrase II, and recoverin. In fact, antibodies against recoverin, the best characterized antibody, were found in only 10% of the patients. If the clinical suspicion for CAR remains high, but the antibody testing is negative, then one might try empirical therapy for treatment of CAR, in particular in the setting of known malignancy, to determine if there is improvement in visual symptoms (see management below). What systemic evaluation should be performed for an occult malignancy? Certainly one would obtain a chest CT scan to identify lung or mediastinal lesions. Breast examination and mammography should be performed. Pelvic and abdominal CT would reveal many other cancers that are associated with CAR. Pelvic examination, prostate examination, and colonoscopy should be considered in the appropriate patients. Serologic testing for cancer markers may also have a role in the evaluation. These tests are perhaps best ordered through a collaborative care of the patient with their primary care provider. Whole-body positron emission tomography using fluorodeoxyglucose (FDG-PET) can be performed in patients in whom other testing was not revealing, however FDG-PET will reveal “hot-spots” that are associated with inflammatory and infectious diseases as well as neoplastic disease and therefore the sensitivity may lead to enhanced patient morbidity in terms of additional testing.

If antibody testing is positive, you need to determine whether the results fit the observed clinical picture prior to making the diagnosis. In addition to the high incidence of un-named retinal antibodies mentioned above, antirecoverin antibodies, the best-studied antibody associated with CAR, has also been observed in 1% of patients with retinitis pigmentosa. Therefore the presence of these antibodies is not pathognomonic for CAR.

Patients with MAR most commonly produce antibodies that react with retinal bipolar cells, as visualized by immunofluorescence, however specific antigenic targets are not well-defined although several candidates antigens have been identified. Therefore, MAR is primarily a clinical
diagnosis, based on the presenting signs and symptoms, the history of melanoma, and ERG findings that are consistent with the disease. If there is no history of melanoma, but your clinical suspicion is high for MAR, then the patient should be referred for a full dermatologic evaluation and one should consider whether additional testing, such as FDG-PET or other imaging, is prudent.

In the case of PON, antibodies against the CRMP-5 antigen are present and detectable by immunofluorescence studies or Western blot.18,29

Patients with the opsoclonus/myoclonus syndrome generally do not have positive paraneoplastic antibody evaluations in the serum or CSF.20 However, antibodies against ANNA-2, NMDA receptor, nuclear antigens, and neuronal calcium channels have all been seen in subsets of these patients.19,30-32 In fact recent data suggests that antibodies against Purkinje cells may be responsible for disease pathogenesis in some patients.32 If testing is desired, then serum should be sent for a full paraneoplastic evaluation that will typically use immunofluorescence, for reactivity against brain, and enzyme-linked immunosorbent assay (ELISA), for reactivity against specific antigenic targets as an initial screen followed by additional testing for antigens of high specificity. Given that an antibody is typically not identified, consideration of a paraneoplastic syndrome is pursued by evaluation for occult malignancy.

Specific testing for antibodies against the VGCC should be done in patients who are suspected to have LEMS. These studies are generally available through both academic and community laboratory services as ELISA tests with good specificity. Antibodies against the P/Q-type VGCC are present in 85-90% of patients with LEMS but may also be seen in up to 4% of patients with small cell lung cancer in the absence of neurologic disease. In addition LEMS patients may have antibodies against N-type VGCC (in up to 30-40%) or L-type VGCC (in up to 25%).20 Occult malignancies in these patients are performed as described for CAR, above. The starting point should be a chest CT, which would reveal the more commonly associated lung or thymus cancer, however male patients will require prostate evaluations, and lymphoproliferative diseases should also be considered in this paraneoplastic condition.

**MANAGEMENT**

A common thread among all of the paraneoplastic syndromes is that treatment of the underlying tumor may be beneficial to the neuro-ophthalmological symptoms and signs. Treatment targeting the antibody mediated paraneoplastic syndrome and symptomatic therapy has also shown some utility.

In addition to cytoreduction of tumor, the mainstay for treatment for CAR is use of oral or intravenous corticosteroids or a combinatorial therapy of cyclosporine, azathioprine, and prednisone with a reported response rate of up to 70%.31 Newer therapies have included rituximab.34 Many types of therapies have been used with variable success in MAR. Use of local or systemic corticosteroids was generally unsuccessful whereas a single patient received benefit from steroids and several patients received benefit from IVIG, alone or in combination with cytoreduction of tumor burden.17 Successful treatment has been reported with combinatorial therapy such as oral prednisone, plasmapheresis, azathioprine, and gabapentin or the combination of intravenous steroid with plasmapheresis. The total numbers of affected patients are small and therefore best practice is not yet determined for these patients. BDUMP is quite rare but there have been reports of improvement with plasma exchange with or without concomitant corticosteroid.35

Paraneoplastic optic neuropathy in association with CRMP-5 is unusual and is typically also accompanied by a mixed T cell lymphocytic cellular infiltrate at the vitreous and optic nerve.36 Although the usual therapy will include primary tumor treatment as well as systemic corticosteroids, the authors presented two patients in whom disease improvement was tied to the use of intravitreal triamcinolone.

In the opsoclonus-myoclonus syndrome, patients generally respond favorably to treatment with intravenous corticosteroids and/or IVIG.20 In addition to the treatment of the primary tumor with surgery and/or chemotherapy and/or radiation, it is believed that early treatment is associated with a better response to therapy. A wide variety of other agents have been used in small numbers of patients with some success. If long-term corticosteroids are required then steroid-sparing agents could be tried.

Suggested therapy for LEMS includes 3, 4-diaminopyridine, intravenous immunoglobulin (IVIG), plasma exchange, steroids, and immunosuppressive agents.37-40 According to a Cochrane publication that reviewed trials through 2010, there is good evidence for the use of 3,4-diaminopyridine, an agent that increases the release of acetylcholine, and a single trial that demonstrated benefit from IVIG.37 The use of steroid and azathioprine in addition to 3,4-diaminopyridine may be advised, but this is not based on prospective clinical trials.39 In 2013 a new calcium channel agonist, with selectivity for both the N-type and P/Q type VGCC was used in an experimental model of LEMS, with promising results.40 If these results can be replicated in humans then this would give additional therapeutic options.

In conclusion, the paraneoplastic disorders in neuro-ophthalmology may predate identification of a malignancy. These patients require careful discussion about the possibility of an underlying disease such as cancer and also will require periodic follow up. Treatment consists of control of tumor itself followed by symptomatic relief and targeted use of immunomodulatory drugs. The expectation is that new modalities for a standardized diagnosis and targeted therapy will be developed over the next few years.
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**not otherwise discussed in this report

**CME ANSWERS

1. c
2. a
3. d

**REFERENCES


LEARNING OBJECTIVES
At the conclusion of this talk, the attendee will be able to:

1. Differentiate toxic and nutritional optic neuropathies from conditions that mimic them.
2. Identify the clinical manifestations of toxic and nutritional optic neuropathies.
3. Understand the controversy surrounding certain presumed toxic optic neuropathies.

CME QUESTIONS
1. All of the following are typical hallmarks of a toxic or nutritional optic neuropathy except:
   a. Bilateral and symmetric
   b. Dyschromatopsia
   c. Altitudinal field loss
   d. Temporal disc pallor

2. The optic neuropathy that most often is mistaken for a toxic or nutritional optic neuropathy is:
   a. Leber optic neuropathy
   b. Acute optic neuritis
   c. Ischemic optic neuropathy
   d. Compressive optic neuropathy

3. An optic neuropathy associated with the use of a TNF-alpha inhibitor is most likely due to:
   a. Ischemia
   b. Infection
   c. Demyelination
   d. Nutritional deficiency

KEYWORDS
1. Toxic Optic Neuropathy
2. Nutritional Optic Neuropathy
3. Optic Neuropathy
4. TNF-Alpha Inhibitor
5. Leber Optic Neuropathy
6. Amiodarone, Toluene Abuse

INTRODUCTION AND TWO CASES
Physicians have known for centuries that the anterior visual pathways are vulnerable to damage from nutritional deficiency and chemicals. The resulting disorders share many signs and symptoms, and several appear to have a multifactorial etiology in which both under-nutrition and toxicity play a role.

Although certain optic neuropathies have an obvious toxic or nutritional etiology (eg, ethambutol, methanol), the toxic or nutritional basis of others is merely presumptive, and the attribution may ultimately prove false. Consider the following two cases:

CASE #1:
In 1978, a 31-year-old otherwise healthy man sued the United States government, claiming that shortly after receiving the “swine flu” vaccine in September of 1976, he lost vision in both eyes. An examination at this time revealed acuity of CF OU with dense central scotomas and some peripheral field constriction. Both optic discs were said to be pale. A diagnosis of “toxic” optic neuropathy due to the influenza vaccine was made, and the patient’s case was actually published in the literature under the title “Bilateral Optic Nerve Atrophy and Blindness Following Swine Influenza Vaccination.” I was a witness for the defense and testified that it was likely that the patient had Leber hereditary optic neuropathy (LHON). It was subsequently shown in court that the patient’s visual loss had begun several weeks before the vaccine was available to the public (mass vaccinations were not begun until October of 1976). Following publication in 1988 of Doug Wallace’s seminal paper on the genetics of LHON, I contacted the patient’s attorney and recommended that the patient undergo genetic testing. As expected, he had the 11778 (Wallace) mutation.
CASE #2
A 28-year-old woman was evaluated at Johns Hopkins because of progressive decreased vision in both eyes that she indicated had occurred shortly after gastric bypass surgery for morbid obesity. A diagnosis of presumed nutritional deficiency-related optic neuropathy had been made but vitamin assays had shown no deficiency. When examined by me, the patient indicated that her visual loss had occurred rather rapidly and that she had experienced some mild ocular discomfort at onset. She had visual acuity of 20/100 OD and 20/200 OS. Color vision was markedly diminished. The patient had bilateral small central scotomas. There was no RAPD. The temporal aspects of both optic discs were pale. A CT scan (MRI was not available at this time) was unremarkable, and a lumbar puncture revealed no abnormalities in the CSF. The patient was discharged on vitamin supplements; however, 3 months later, she developed numbness and tingling of her extremities, and a repeat LP showed elevated protein and six oligoclonal bands in the CSF. A diagnosis of multiple sclerosis was made and subsequently supported several years later by MRI. In the meantime, the patient was treated with systemic steroids with improvement in her vision to 20/40 OU.

These cases illustrate the pitfalls of diagnosing toxic or nutritional optic neuropathies. Conversely, it also is likely that a few of the optic neuropathies now considered idiopathic or ascribed to some other etiology, actually result from toxicity or nutritional deficiency. Nevertheless, there are cases in which it is clear that there is a toxic and/or nutritional etiology.

SUBACUTE MYELO-OPTIC NEUROPATHY (SMON): “KOCH’S POSTULATES (VAR)” CONFIRM A TOXIC OPTIC NEUROPATHY
The primary issue in patients suspected of having a toxic optic neuropathy is whether or not they were exposed to a substance that has been proved to damage the optic nerve by the same route of exposure. Visual loss may occur from either acute or chronic intoxication depending upon the agent, but there should not be a long interval between the cessation of the exposure and the onset of symptoms. The patient must have symptoms and signs that are compatible with a toxic optic neuropathy and typical of those in other patients proved to have suffered loss of vision from the same agent. Of course, the symptoms cannot have preceded the exposure.

The response of patients to re-challenge is helpful in evaluating the validity of presumed intoxications and in helping to establish the cause of the patient’s optic neuropathy. If a patient who has recovered vision following cessation of exposure to a drug or chemical loses vision again when re-exposed, the recurrent loss of vision tends to verify the neurotoxic nature of the agent and the toxic etiology of the visual loss. Epidemiologic data, especially those showing correlation of changing disease incidence when and where specific drugs or chemicals are introduced or withdrawn, can also prove quite useful. A perfect example of these issues is the optic neuropathy that occurred in patients treated with halogenated hydroxyquinolines for various gastrointestinal disorders producing severe diarrhea.

The halogenated hydroxyquinolines are amebacidal drugs. One of these (iodochlorhydroxyquin) was promoted in some parts of the world for preventing or treating traveler’s diarrhea and chronic diarrheas. Between 1956 and 1970, an epidemic of 10,000 cases of a new neurologic syndrome--subacute myelo-optic neuropathy (SMON)--occurred in Japan. Although the epidemic was recognized promptly and a multidisciplinary search for the etiologic agent was begun, it was not until 1970 that careful retrospective case-control and cohort studies implicated a halogenated hydroxyquinoline, iodochlorhydroxyquin, as the agent responsible. Tsubaki et al. observed neurologic symptoms in 35.4% of patients taking this drug for more than 14 days and also found that of 171 patients examined with evidence of SMON, 166 (96%) had taken the drug prior to the onset of neurologic symptoms. Nakae et al. conducted a nationwide survey and collected 1839 cases of SMON of which 75% had received iodochlorhydroxyquin. In the meantime, in September of 1970, the Japanese government removed all halogenated hydroxyquinolines from the market, and the epidemic ended precipitously. In addition to the Japanese experience, numerous authors from other countries reported SMON or isolated optic atrophy (with diiodohydroxyquin) associated with ingestion of halogenated hydroxyquinolines including Great Britain, Australia, Switzerland, Sweden, Denmark, the Netherlands, and the United States. Of most significance is that not only do several reports demonstrate the potential for reversal of the visual loss once the drug is stopped but also recurrence of visual loss when the drug was restarted. For example, Etheridge and Stewart reported a young child who was treated with diiodohydroxyquin in a dose of 3200 mg daily for 2 years. The patient developed visual loss in the range of 20/200 bilaterally with optic atrophy 1 month after an increase in the dosage to 3600 mg/day. When the dose was lowered, the patient’s vision improved and then worsened when the dose was raised. Billson et al. reported an 18-year-old woman with ulcerative colitis who developed progressive blurred vision in both eyes after 9 months of treatment with Clioquinol at a dosage level of 2000 mg/day. On initial examination, the patient had visual acuity of 20/200 in each eye with bilateral cecocentral scotomas and normal fundi. Clioquinol was stopped, and the patient’s vision gradually improved to 20/80 in the right eye and 20/40 in the left eye with diminution in the size of the scotomas. About 1 year later, the patient was restarted on Clioquinol because of exacerbation of her colitis. Two days after restarting the drug at a dosage of 2000 mg/day, she patient noted severe loss of vision and presented with visual acuity of 20/600 in the right eye and 20/200 in the left eye, large, bilateral cecocentral scotomas, and bilateral, severe optic atrophy. The drug was immediately stopped, and within 2 days there was dramatic improvement in the patient’s visual acuity to 20/200 in the
right eye and 20/120 in the left eye. Within the next 2 weeks, visual acuity had improved and stabilized at 20/120 in the right eye and 20/40 in the left eye (this case was reported in more detail by Reich and Billson). The “SMON Story” is one of the best examples of proof of a clear-cut toxic optic neuropathy. Not all such cases are as clear. Take the case of amiodarone.

## Amiodarone-Associated “Toxic” Optic Neuropathy

Amiodarone is a benzofuran derivative that is primarily used to treat atrial or ventricular tachyarrhythmias that are unresponsive to other anti-arrhythmic agents. Amiodarone’s therapeutic mechanism of action is related to its ability to prolong the duration of action potentials and the refractory period in cardiac conducting tissues. The most common ocular side effect is the formation of verticillate, pigmented, corneal epithelial deposits that eventually occur in most patients (70–100%) treated with the drug. The amount of corneal epithelial deposits observed in a given patient, as well as the incidence of these deposits in a group of patients, is related to the dose of the drug and the duration of treatment. With discontinuation of the drug, the deposits resolve over several months as amiodarone has a long half life of up to 100 days. Other ocular side effects from amiodarone include anterior subcapsular lens opacities, multiple chalazia, and keratitis sicca. Fortunately, these ocular side effects rarely cause significant visual impairment and do not constitute a reason for discontinuing the drug.

Amiodarone sometimes is associated with an optic neuropathy that has many characteristics similar to nonarteritic anterior ischemic optic neuropathy (NAION). Indeed, in 1982, Chew et al. were the first to mention a case of what was thought to be NAION in a patient taking amiodarone, although they gave no details about the case as the point of their paper was to describe the corneal edema. Subsequently, Gittinger and Asdourian reported this association in two patients treated with therapeutic doses of amiodarone. They described a 45 year old man who had unilateral, hemorrhagic disc edema noted on a routine examination 8 months after starting treatment with amiodarone. He was asymptomatic and had normal visual acuity, color vision, and visual fields. His disc edema resolved 1 month later despite continued treatment with the drug. The other patient was a 61 year old man who complained of hazy vision in his right eye two months after starting treatment with amiodarone. He had a visual acuity of 20/25 OU, a right RAPD and hemorrhagic disc edema in the right eye. Several days later, he developed hemorrhagic disc edema in the left eye. Three months later, he still had bilateral, hemorrhagic disc edema and his dosage of amiodarone was reduced. Five months after his visual loss, he had a visual acuity of 20/20 OU, an inferior arcuate defect in the right visual field, disc edema OD, and resolution of his disc edema OS.

Feiner et al. subsequently described 13 patients who developed an optic neuropathy during treatment with amiodarone. The amiodarone dosage ranged from 200 to 600 mg/day and the time interval between initiation of amiodarone therapy and the manifestation of optic neuropathy ranged from 1–72 months. Three patients had no visual symptoms and disc edema was noted on a routine examination. The remaining 10 patients complained of blurry or decreased vision and presented with visual acuities ranging from 20/20 to 20/400. Nine patients had visual field deficits including arcuate scotomas, altitudinal deficits, centrocecal scotomas, enlarged blind spot, and visual field constriction. Among the 13 patients, 12 had disc edema and five had bilateral ocular involvement. Three patients had recovery of vision after amiodarone was discontinued, whereas patients had a final visual acuity of 20/100 or worse.

Several other investigators have described patients that developed an optic neuropathy while being treated with amiodarone. In 1997, a 50 year old man who became legally blind from a bilateral optic neuropathy that developed 6 weeks after the initiation of amiodarone therapy was awarded a $20 million judgment in a lawsuit against the pharmaceutical company that sold the drug at that time.

The nature of the association of optic neuropathy and amiodarone treatment is controversial. Many of the patients described in the above reports developed an optic neuropathy that is indistinguishable from nonarteritic anterior ischemic optic neuropathy (NAION). Feiner et al. noted that the 1.79% incidence of optic neuropathy among patients treated with amiodarone at the Mayo Clinic was significantly higher than the 0.3% incidence of ischemic optic neuropathy in the general population 50 years of age or older in Olmsted County, Minnesota. However, patients treated with amiodarone often have severe vascular disease and probably have a higher risk of developing anterior ischemic optic neuropathy compared with the general population.

The lawsuit described above stimulated Macaluso et al. to try to establish criteria with which to distinguish “amiodarone-associated optic neuropathy” from NAION (one of the authors was a witness at the trial!). These investigators reviewed data from 73 patients who developed an optic neuropathy while taking amiodarone. They noted that patients with amiodarone induced optic neuropathy tend to have insidious bilateral visual loss and protracted, bilateral simultaneous disc edema that resolves several months after the drug is discontinued. These findings were echoed by Purvin et al. In contrast, patients with typical NAION tend to have acute unilateral visual loss and disc swelling that resolves several weeks after visual loss. Despite these distinctions, there is certainly overlap in the clinical spectrum of these two entities.

Adding to the controversy surrounding amiodarone is a study by Joel Mindel and co-workers. These investigators assessed 1669 subjects receiving either weight-determined doses of closed-label amiodarone (n=837) or placebo (n=832) in a prospective double-masked fashion. Closed-label amiodarone subjects were followed, unless death
occurred, for a minimum of 27 months. Median follow-up in survivors was 45.5 months. The end point was removal from the study because of bilateral visual loss. In fact, NO SUBJECT was removed from the study because of bilateral vision loss. The authors concluded that “at the doses commonly used clinically, bilateral visual loss from amiodarone toxic optic neuropathy occurs infrequently, if at all.”

Despite the findings of Mindel et al., it is important to remember the dictum of William Cowper, the great English poet: “Absence of proof is not proof of absence.”44 Some patients in this study may have experienced a unilateral or bilateral optic neuropathy caused by amiodarone but either not recognized by the patient because it was too subtle or attributed to something else, such as developing cataracts.

The mechanism of amiodarone induced optic neuropathy—assuming that it exists—may be related to the fact that amiodarone binds phospholipids within lysosomes and forms a complex that is not degradable by phospholipase enzymes25,45. The amiodarone phospholipid complex accumulates within lysosomes and forms cytoplasmic lamellar inclusions. These lamellar inclusions have been observed in the cytoplasm of many tissues including corneal epithelial, stromal, and endothelial cells; lens epithelium; conjunctival epithelium; extraocular muscle fibers; scleral cells; uvea; blood vessel endothelial cells; retinal ganglion cells; retinal pigment epithelium; and optic nerve axons. Indeed, these inclusions are likely responsible for the corneal and lens deposits noted above.

The available data are insufficient to make firm recommendations regarding a screening protocol for patients treated with amiodarone. Macaluso et al.42 recommended obtaining a baseline examination on all patients prior to starting amiodarone treatment and repeating the examination every 6 months during treatment. I believe that all patients taking amiodarone should be told of the potential for visual issues and the need to contact their ophthalmologist immediately should they experience any visual sensory disturbance. Amiodarone may be a life saving treatment, and the occurrence of an optic neuropathy is therefore not an absolute contraindication to further treatment; however, in patients who have an optic neuropathy while on amiodarone, discontinuation of amiodarone and treatment with an alternative drug should be considered. A superb overview of this issue was published by Murphy and Murphy.46

**TOXIC OPTIC NEUROPATHY ASSOCIATED WITH TNF-ALPHA INHIBITORS**

TNF-α is known to play a crucial role in the pathogenesis of many chronic inflammatory diseases. Elevated levels of TNF-α have been demonstrated in Crohn disease (CD), psoriasis (Ps), psoriatic arthritis (PsA) and rheumatoid arthritis (RA), suggesting a role for TNF-α in their pathogenesis55-51 and providing a rationale for the treatment of these diseases with drugs that inhibit it.

TNF-α blockers have demonstrated efficacy in large, randomized controlled clinical trials, either as monotherapy or in combination with other anti-inflammatory or disease modifying anti-rheumatic drugs (DMARDs).32,33 At the time this syllabus was written, five TNF-α inhibitors were available for clinical use: infliximab, adalimumab, etanercept, golimumab and certolizumab pegol. All of these drugs block the biologic effects of TNF-α although there are some differences in their structure, pharmacokinetics and mechanisms of action (Figure 1).34

**Figure 1. Anti-TNF molecules bind to and neutralize the activity of TNFα.** Infliximab and adalimumab are monoclonal antibodies. Infliximab is a mouse/human chimera that joins the variable regions of a mouse antibody to the constant region of human IgG1, and adalimumab is a human IgG1 antibody. Etanercept is a dimeric fusion protein that joins the human p75 TNF receptor to the Fc domain of human IgG1. Reprinted from Shukla R, Vender RB. Pharmacology of TNF inhibitors. In Weinberg JM, Buchholz R (eds) . TNF-alpha Inhibitors. Birkhäuser Verlag. Switzerland, 2006; pp. 23-44.

The efficacy and safety profile of the TNF-α inhibitors can be considered, in general, as a class effect. Nevertheless, some differences exist among the five agents. Infliximab is a chimeric human/murine IgG1 monoclonal antibody (mAb) directed against TNF-α, that has been approved in combination with methotrexate (MTX) for the treatment of RA. The ATTRACT and ASPIRE studies confirmed that infliximab (3 mg/Kg intravenously at weeks 0-, 2- and 6- and 8-weekly thereafter) plus MTX provided greater clinical and functional benefits than treatment with MTX alone for the treatment of RA.53 Infliximab alone (5 mg/Kg) also has been approved for the treatment of Ps, PsA, AS, CD and ulcerative colitis refractory to conventional drugs.53,56,57 Furthermore, infliximab is considered the treatment of choice for fistulizing CD.57 Colombel et al. reported that infliximab plus azathioprine was the most effective treatment, for moderate-to-severe CD.58 Episodic therapy with infliximab
on relapse of CD is possible but is less efficacious and frequently is associated with problems resulting from the formation of antibodies to infliximab. If treatment is episodic, maintenance therapy with immunosuppression (azathioprine, MTX) is mandatory.59

Adalimumab is a fully recombinant human IgG1 anti-TNF-α-specific mAb approved for the treatment of Ps, PsA, RA, AS and CD.53,60 The PREMIER study demonstrated that adalimumab (40 mg subcutaneously every other week) plus MTX was significantly superior to either MTX alone or adalimumab alone in improving signs and symptoms and inhibiting radiographic progression of early, aggressive RA.60,61 In addition, Colombel et al. demonstrated that continuous treatment with adalimumab was more effective than induction dosing followed by re-initiation of adalimumab with clinical deterioration for maintenance of clinical remission, improved quality of life outcomes, reduced flares and a decrease in the number of surgeries and risk of hospitalization in patients with active CD.52

Golimumab is a human gamma-1 immunoglobulin-k anti-TNF-α monoclonal antibody and is administered as a 50-mg subcutaneous injection once a month.59 Golimumab was approved for use with MTX in adults with moderate to severe RA, and with or without MTX or other DMARDs in adults with active PsA or active AS. Boyce et al. confirmed the efficacy of golimumab.63

Certolizumab pegol differs from the other anti-TNF-α agents by its structure, composed of the Fab antigen-binding domain of a humanized monoclonal anti-TNF-α antibody combined with polyethylene glycol to increase its half-life in the body.54 Certolizumab pegol in combination with MTX is indicated for the treatment of moderate to severe, active RA, and it also has been recommended for the treatment of CD.65,66

Etanercept is not a monoclonal antibody, but a fusion protein that acts as a ‘decoy receptor’ for TNF-α and acts competitively to inhibit the binding of TNF-α to its cell surface receptor.53 It has been approved for the treatment of Ps, PsA, AS and juvenile RA.53

The differences in the mechanism of action of the TNF-α inhibitors are reflected by the variable response rate observed in patients with CD who respond well to infliximab and adalimumab but not to etanercept. In addition, patients who fail to tolerate one TNF-α inhibitor can be switched to another TNF-α inhibitor if allowed by the nature of the adverse event.

Although TNF-α inhibitors are generally well tolerated, all have potential adverse effects.67,68 The most frequent adverse effects are: 1) infusion reactions with infliximab, 2) injection-site reactions to subcutaneously administered drugs, and 3) mild infusion reactions (i.e., headache, itch, urticaria, nausea) and cutaneous injection-site reactions (i.e., local erythema and swelling) that usually subside within 24 hours and that can be treated with premedication with anti-histaminic drugs and, when needed, with glucocorticoids.69 Severe infusion reactions (i.e., angioedema and shock) have been reported in patients under infliximab therapy. As infliximab is a chimeric human/mouse anti-TNF-α antibody, it may induce the synthesis of neutralizing antibodies that could reduce the efficacy of the drug. MTX usually is co-administered to control both the rheumatic disease and the development of neutralizing antibodies.53 Despite its fully human sequence, the production of antibodies to adalimumab also has been reported, and this may reduce the efficacy of the drug and induce the development of adverse drug reactions and exanthema.67 Malignancies (i.e., lymphomas), autoimmune diseases and demyelinating diseases (see below) have been reported in patients taking TNF-α inhibitors. Finally, TNF-α inhibitors may cause reactivation of latent tuberculosis and increase the overall risk of opportunistic infections such as those caused by Histoplasma capsulatum, Coccidioides immitis, Listeria monocytogenes, and invasive fungi such as Aspergillus and Candida species.67

There have been infrequent reports of central nervous system (CNS) demyelinating disorders during treatment with anti-TNF-α agents. Several of these cases have been temporally related to anti-TNF therapy and have resolved when treatment was withdrawn.68 Mohan et al.69 reviewed the occurrence of neurologic events suggestive of demyelination during anti-TNF-α therapy for various inflammatory arthritides. The Adverse Events Reporting System of the Food and Drug Administration (FDA) was queried following a report of a patient with refractory RA who developed confusion and difficulty with walking after receiving etanercept for 4 months. 19 patients with similar neurologic events were identified from the FDA database, 17 following etanercept administration and two following infliximab administration for inflammatory arthritis. All neurologic events were related temporally to anti-TNF therapy, with partial or complete resolution on discontinuation. One patient exhibited a positive re-challenge phenomenon. The authors concluded that further surveillance and that studies were required to better define risk factors for and frequency of adverse events and their relationship to anti-TNF therapies. Until more long-term safety data are available, rheumatologists advise that consideration be given to avoiding anti-TNF therapy in patients with pre-existing multiple sclerosis and to discontinuing anti-TNF therapy immediately when new neurologic signs and symptoms occur, pending an appropriate evaluation.68,69

As far as optic neuropathies associated with anti-TNF-α treatment are concerned, it would appear that they are not “toxic” in the normal sense of the word, but rather due to demyelination stimulated by the agents. Be that as it may, there is some evidence that patients taking TNF-α inhibitors are at increased risk from a unilateral or bilateral optic neuropathy that may be a form of optic neuritis. Winthrop et al.70 performed a retrospective, population-based cohort study in which they identified new users of anti-TNF-α
therapy (etanercept, infliximab, or adalimumab) or non-biologic DMARDs during 2000–2007 from several data sources. Within this cohort, they used validated algorithms to identify cases of optic neuropathy occurring after onset of new drug exposure. They then calculated and compared the incidence rates between exposure groups. They identified 61,227 eligible inflammatory disease patients with either new anti-TNF-α or new nonbiologic DMARD use. Among this cohort, they found three cases of optic neuropathy among anti-TNF-α new users, occurring a median of 123 days (range, 37–221 days) after the start of therapy. The crude incidence rate of optic neuropathy across all disease indications among this cohort was 10.4 (95% CI 3.3–32.2) cases per 100,000 person-years. In the cohort with current or past anti-TNF-α or DMARD use, they identified a total of six optic neuropathy cases: three among anti-TNF-α users and three among DMARD users. Crude ON rates were similar between the two groups: 4.5 (95% CI 1.4–13.8) and 5.4 (95% CI 1.7–16.6) per 100,000 person-years, respectively. The authors therefore concluded that new-onset optic neuropathy/optic neuritis is rare among those who begin treatment with TNF-α inhibitors and occurs with similar frequency among those with nonbiologic DMARD exposure. This validity of this conclusion was questioned by Eggenberger,71 who emphasized a number of potential inaccuracies in the way the diagnosis of “optic neuritis” was made and pointed out that there was, in fact, biological plausibility with respect to a causal association between TNF-α inhibitors and the development of demyelinating events including true optic neuritis. Several years ago, I was retained by Pfizer to assess cases reported to the company of possible optic nerve damage in patients using etanercept (Enbrel®). Although there were several cases of true optic neuropathy, many of the histories and examination results were so vague that one could not determine what was going on. Even worse, some cases clearly either were not examples of optic nerve damage at all and others were not consistent with a demyelinating event. Nevertheless, there are in the literature several case reports that suggest a potential for the development of a unilateral or bilateral optic neuropathy in patients taking TNF-α inhibitors, some of which were associated with other manifestations of multiple sclerosis. In particular, Li et al.72 reported a case of optic neuritis and multiple sclerosis and identified 21 cases of unilateral or bilateral anterior or retrobulbar optic neuritis (or at least optic neuropathies) associated with TNF-α inhibition (see Table 1 in Li et al.72). Among these cases, 36% with available MRI results had evidence of other demyelinating lesions in the CNS. I agree with those who say that such agents should be used with caution—if at all—in patients with multiple sclerosis and, as in the case of patients beginning treatment with amiodarone, patients about to placed on one of the TNF-α inhibitors should be told about the possibility of visual loss and told to contact their ophthalmologist immediately should they experience any visual sensory or neurologic symptoms or signs.

**TOXIC/NUTRITIONAL OPTIC NEUROPATHIES FROM SUBSTANCE ABUSE: YOUR PATIENT MAY NOT/WILL NOT TELL YOU!**

**A. ALCOHOL-RELATED OPTIC NEUROPATHY**

Perhaps the most common toxic or deficiency optic neuropathy in the United States is that once termed “tobacco-alcohol amblyopia.” Optic neuropathy related purely to tobacco abuse appears no longer to exist, and many individuals believe this relates to “safer tobacco” without contaminants, but alcohol-related optic neuropathy continues to appear on a regular basis. Most of the patients who develop alcohol-related optic neuropathy are males, and symptoms begin at a later age than that associated with the majority of cases of optic neuritis. Patients with presumed alcohol-related optic neuropathy do not show spontaneous improvement but may improve to a variable degree once alcohol consumption is halted, dietary habits are improved, and treatment with vitamin supplement is begun (see below).

Quigley et al.73 studied the number and distribution of human optic nerve axons in a patient with presumed alcohol optic neuropathy. The patient was a 51-year-old man who died of lung carcinoma. He had abused alcohol throughout his adult life and suffered from cirrhosis, pancreatitis, systemic hypertension, and diabetes mellitus. The patient’s left eye developed uncontrolled open-angle glaucoma and lost all vision. Intraocular pressures in the patient’s right eye averaged 18 mm Hg, but visual acuity in that eye varied from 20/50 to 20/100 with a full peripheral field and a central scotoma. Although the cup/disc ratio of the right optic disc was only 0.4, there was significant temporal disc pallor. Quigley and co-workers found that the right optic nerve contained fewer than one-half the normal number of fibers. There was a striking loss of the temporal quadrant of nerve fibers; however, in the other three quadrants, nerve fiber loss was also significant, averaging about 40%. Thus, the selective damage to the temporal quadrant—presumably the papillomacular bundle—was accompanied by a diffuse loss of axons in the other quadrants as well.

The etiology of this bilateral, primarily retrobulbar, optic neuropathy is controversial. At the heart of the controversy is one issue: Is there a direct toxic effect of alcohol on the optic nerve or is this condition, in reality, a nutritional disorder related to a deficiency of vitamin B12, folic acid, thiamine, or some other substance. One of the major problems in deciphering the precise cause of the amblyopia is that patients who develop the disorder often are generally malnourished. Thus, the separation of critical factors is often impossible. Nevertheless, several investigators have attempted to isolate the factors involved in the production of this disorder (these disorders). Alcohol is known to reduce the absorption of vitamin B12 and this, as well as simple dietary insufficiency of vitamin B12, folic acid, thiamine, etc. may, individually or together, be responsible; however, controlled studies have yet to be performed.
Carroll\textsuperscript{75} studied 25 patients with presumed “tobacco-alcohol ambylopia.” The patients were allowed to drink and smoke in their usual manner, providing that they ate a nutritious diet supplemented with B vitamins and folic acid. All of the patients recovered vision completely or almost completely. In addition, several investigators\textsuperscript{76,77} have found low levels of red blood cell folate but normal levels of vitamin B12 in patients with presumed alcohol-related optic neuropathy and documented improvement in visual parameters when such patients are treated with folate alone. The importance of assessing red blood cell folate rather than serum folate in patients with suspected alcohol-related optic neuropathy cannot be overemphasized.

**B. TOLUENE (METHYLBENZINE)**

Toluene, or methylbenzene, a colorless, sweet, and pungent-smelling liquid naturally present in crude oil, is produced in enormous amounts worldwide.\textsuperscript{78} Although some toluene remains in gasoline and motor fuel products, much of the toluene content of crude oil is extracted in refineries. This toluene then is sold for use in the production of chemicals, like benzene, and in the formulation of paints, graphic pigments, adhesives, lacquers, paint strippers, printing ink, spot removers, cosmetics, perfumes, and antifreeze.\textsuperscript{79} In addition to these traditional uses, toluene may be inhaled to achieve instantaneous intoxication. This is done by “sniffing” (i.e., inhaling vapors from an open container), “bagging” (i.e., inhaling more concentrated vapors from a closed container), or “huffing” (i.e., breathing through a solvent-soaked cloth).\textsuperscript{80} Cheap, legal, and readily available, products with substantial toluene content, typically glues or paint thinners, offer optimal substances of abuse for those without access to other illicit drugs. Consequently, toluene abuse is most prevalent in adolescents, particularly those of lower socioeconomic backgrounds.\textsuperscript{76} Lifetime prevalence rates of inhalant abuse ranging from 8 to 25\% among high school students.\textsuperscript{80} In addition, more than half of those reporting a history of inhalant use have done so multiple times, and 77\% state they have abused inhalants for more than 1 year.\textsuperscript{81}

The tremendous morbidity and mortality associated with this behavior are often under-appreciated. From 1987 to 1996 in Virginia alone, there were 39 inhalant-related deaths (two died abusing pure toluene or products containing mostly toluene and several more died abusing products that contained toluene as a key ingredient).\textsuperscript{82} Chronic toluene abuse can cause irreversible renal, hepatic, cardiac, and pulmonary toxicity;\textsuperscript{78,79} however, the magnitude and range of toluene’s CNS effects eclipse its peripheral toxicity profile. Coordination and gait impairment occur in chronic toluene abusers\textsuperscript{78} as may slurred speech, intention tremors, rigidity, spasticity, and hyperreflexia.\textsuperscript{84,85} Ocular motor dysfunction, including pendular nystagmus, ocular flutter, opsoncosus, and bilateral internuclear ophthalmoplegia also have been described.\textsuperscript{84,87,88} Correspondingly, both cerebellar atrophy and cerebellar tract damage as well as diffuse white matter changes have been documented by neuroimaging in these patients.\textsuperscript{84,85,90,91}

As far as optic nerve damage is concerned, Keane\textsuperscript{89} reported the case of a 20-year-old man who gave a 3-year history of inhaling a spray paint mixture containing metallic copper, toluene, and xylene as solvents and isobutane propane and methylene chloride as propellants, The patient developed progressive ataxia and bilateral visual loss with acuities of 4/200 in :ach eye, dyschromatopsia, moderately constricted visual fields, sluggish pupillary responses to direct light stimulation, and normal fundi. Following cessation of paint sniffing, the patient’s neurologic symptoms slowly subsided, and within 2 months, his visual acuity had improved to 20/30- in each eye, his color vision was mildly impaired as tested with pseudosichromatic color plates, and his visual fields were full. Although his fundi were said to be normal, pattern-reversal visual evoked responses showed prolonged, although improved, latencies. It seems likely that this case represents a true toxic reaction to toluene, particularly as a similar case of reversible optic neuropathy was reported after industrial exposure to vinyl benzene (styrene).\textsuperscript{89} Other patients have had permanent visual loss. Ehyai and Freemon\textsuperscript{90} reported the case of a 27-year-old man who developed progressive ataxia, sensorineural hearing loss, and bilateral optic atrophy over a 5-year period during which he sniffed glue extensively. At the time his visual loss began, the optic discs were observed to be normal in appearance, indicating a retrolubar process. Other investigators have reported similar cases.\textsuperscript{84,95-100}

A more recent article by Gupta et al.\textsuperscript{91} emphasized the problem making the diagnosis of a toluene-induced optic neuropathy in the setting of other white-matter disease. These authors described two patients with bilateral optic neuropathies. One, a 28-year-old man, also had progressive ataxia, weakness, and numbness. He underwent an extensive evaluation that culminated in a brain biopsy that showed demyelination and reactive gliosis. Despite years of denial of drug abuse or toxin exposure, the patient finally admitted to recreational inhalation of spray paint for 13 years. The second patient was a painter who had been exposed to paint products, some of which contained toluene or toluene products, for 27 years. Gupta et al. emphasized that the optic neuropathy caused by toluene exposure is characterized by a slow progressive decline in visual acuity ranging from 20/20 to 4/200 with associated diminished color vision in most patients.\textsuperscript{88,92,93} The initial optic disc appearance usually is normal, but patients gradually develop optic atrophy. Visual fields reveal enlargement of the blind spot and central depression.\textsuperscript{92,93} Treatment with vitamins, steroids, gabapentin, or cessation of toluene exposure results in an improvement in visual acuity and symptoms in about half the patients;\textsuperscript{92,94} however, in general, the visual prognosis is poor.

Evidence suggests that, despite important inconsistencies in the literature, toluene exerts an effect on the mesocorticolimbic system that likely involves dopaminergic (especially, D2), cholinergic, GABAergic, and serotonergic neurons, but how and why it damages neurons and astrocytes, leading to significant white-matter (including...
optic nerve) damage remains unknown; however, it is clear that chronic toluene intake results in widespread demyelination including demyelination of the optic nerves.\textsuperscript{95,96}

C. NATIVE MEDICINES
Catha edulis Forsk, or khat, is a member of the family Gelastraceae and has been grown for centuries in parts of eastern Africa and southern parts of the Arabian peninsula.\textsuperscript{97} The fleshy, pinnate leaves are chewed by millions of inhabitants of these countries for the drug’s ability to produce euphoria, combat fatigue, and as part of social gatherings (Figure 2).

Figure 2. Catha edulis (Khat). The leaves of this plant are chewed to produce euphoria and to combat fatigue.

Khat grows at 3000 to 6000 feet (900-1800 m) above sea level and reaches a height of 20 feet (6 m). It can survive drought, and the leaves can be harvested throughout the year. The plant is seedless, and this may explain its limited geographical distribution. Extensive thin-layer and gas-liquid chromatographic analyses of the fresh leaves of the khat plant have isolated three major compounds: cathine (i.e., norpseudoephedrine or phenylpropanolamine), cathinone (i.e., α-aminopropiophenone), and norephedrine.\textsuperscript{97-99} Both cathine and cathinone are similar in structure to amphetamine (Figure 3).\textsuperscript{97}

Cathine was identified in 1930, and for a long time it was believed to be the only active stimulant in khat. Cathinone was isolated in 1975. It is a ketone congener of cathine, and it is now believed that it is the main active principle responsible for khat’s stimulant properties.

Khat induces amphetamine-like sympathomimetic and central stimulant effects in users. The pharmacological effects include mydriasis, tachycardia, extra systoles, hypertension, conjunctival congestion, headaches, and increased respiration. Anorexia and insomnia also are common in habitual users.

Several cases of bilateral optic neuropathy have been reported in individuals in whom Khat abuse was the only potential cause. For example, Baird\textsuperscript{100} reported the occurrence of a bilateral anterior optic neuropathy in two khat abusers in Somalia in whom visual function improved and optic disc swelling resolved upon withdrawal of khat. Roper\textsuperscript{101} reported the development of a bilateral optic neuropathy in two patients who, although they were longstanding users of the leaves of Catha edulis, had chewed larger quantities than usual over a short period of time. Both patients had bilaterally decreased visual acuity, central scotomas, sluggish pupillary responses without a relative afferent defect, loss of retinal nerve fibers in the papillomacular bundle, and optic atrophy. One of the patients also had some retinal pigmentary abnormalities. Neither individual had any other risk factors for the development of a nutritional, toxic, or metabolic optic neuropathy. Thus, Roper concluded that the cause of the optic neuropathies in both patients was related to Khat abuse. Although one might assume that it would be rare for someone living in the Western hemisphere to see patients who experience a toxic reaction to a drug not normally present in that area, due to increasing air transportation and the loosening of customs restrictions, it is now readily available in the Western Countries, mainly used by...
immigrants from khat-growing areas. In addition, the fact that the stimulants in khat have a structure similar to that of amphetamine suggests that abusers of similar drugs (e.g., methylenedioxymethamphetamine aka MDMA aka ecstasy) could present with similar findings, as it is known that MDMA stimulates the production of reactive oxygen species, leading to oxidative damage. Ingestion of MDMA also promotes disruption of mitochondrial membrane potential and activates the caspase cascade, leading to apoptosis. Ingestion of MDMA also may increase the extracellular concentration of glutamate, and this may mimic impaired activity of the EAAT1 glutamate transporter, recently linked to mtDNA mutations of LHON. The resulting exocytotoxic damage to both optic nerves and retinal ganglion cells. Indeed, Cardaioli et al. reported the case of a 17-year-old boy who experienced acute, bilateral, asymmetric, painless visual loss after two consecutive treatments with telithromycin and simultaneous abuse of cocaine and ecstasy. On examination, the patient had visual acuity of 20/100 OD and 20/200 OS, with bilaterally reduced color vision, bilateral cecocentral scotomas, no relative afferent pupillary defect, and optic discs with telangiectatic vessels. The patient was subsequently found to harbor the 14484 Leber mutation. It was suspected that the use of cocaine and ecstasy may have rendered the patient susceptible to the effects of the mutation, resulting in his becoming symptomatic.

**CLINICAL CHARACTERISTICS OF TOXIC AND NUTRITIONAL OPTIC NEUROPATHIES**

Individuals of all ages, races, places, and economic strata are vulnerable to the toxic and nutritional deficiency optic neuropathies. Certain groups are at higher risk because they are under treatment with drugs, because of occupational exposure, or because of habits such as smoking and drinking. Nutritional deficiency optic neuropathy is more likely to occur in the economically disadvantaged and during times of war and famine. The value of taking a thorough history, including dietary intake, exposure to drugs, use of tobacco, and social and occupational background is obvious.

The symptoms and signs of nutritional and toxic optic neuropathy are similar and resemble those of most of the other optic neuropathies, primarily those that occur bilaterally and simultaneously. No single characteristic or combination of characteristics is pathognomonic. Toxic and nutritional optic neuropathies are not painful. Thus, one should inquire carefully about this symptom since the presence of pain would suggest some other diagnosis.

Dyschromatopsia is present early and may be the initial symptom in observant patients. Some patients notice that certain colors, such as red, are no longer as bright and vivid as previously. Others experience a general loss of color perception.

Patients with nutritional or toxic optic neuropathies often initially notice a blur, fog or cloud at the point of fixation, following which the visual acuity progressively declines. The rate of decline can be quite rapid. Although vision can decrease to any level, total blindness or vision limited to light perception is unusual in cases of nutritional optic neuropathy, even if the patient is neglected. With the exception of methanol, which typically produces complete or nearly complete blindness, visual loss less than 20/400 is unusual in the toxic optic neuropathies. Bilaterality is the rule, although in the early stages, one eye may be affected before the other becomes symptomatic. Profound loss of vision in one eye with completely normal findings in the other eye should cast doubt on the diagnosis of a toxic or nutritional optic neuropathy.

Patients with toxic or nutritional optic neuropathies typically have central or centrocecal scotomas with sparing of the peripheral visual field. Some perimetrists claimed that centrocecal scotomas with “nuclei” between fixation and the physiologic blind spot were the hallmark of toxic optic neuropathy, especially the variety blamed on tobacco. There are who doubt this, and most authorities now recognize that both central and centrocecal scotomas may be encountered in either disorder. Some patients have a central scotoma in one eye and a centrocecal scotoma in the fellow eye. Peripheral constriction and altitudinal visual field loss are rare.

Because of the symmetric and bilateral visual impairment in toxic and nutritional optic neuropathies, a relative afferent pupillary defect is not a common finding in affected patients. When the patient is blind or nearly so—e.g., as a consequence of methanol poisoning—the pupillary light response will be absent or weak and the pupils will be dilated. Otherwise the pupils are likely to have relatively normal responses to light and near stimulation.

In the early stages of toxic and nutritional deficiency optic neuropathy, the disc may be normal, slightly hyperemic, or swollen. It is unusual to find the physiologic blind spot.107 There are many who doubt this, and most authorities now recognize that both central and centrocecal scotomas may be encountered in either disorder. Some patients have a central scotoma in one eye and a centrocecal scotoma in the fellow eye. Peripheral constriction and altitudinal visual field loss are rare.

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**DIFFERENTIAL DIAGNOSIS**

When an individual complains of bilateral visual loss that refraction cannot correct, and has an otherwise normal examination, there are many diagnostic possibilities in addition to the toxic and nutritional optic neuropathies. Certain maculopathies can present in this guise. With time, the fundus will show abnormalities, but until then, fluorescein angiography, multifocal electroretinography, pattern electroretinography, autofluorescence, or a combination of these techniques may be the only means of establishing the diagnosis of a retinal process. Ganzfeld electroretinography may be helpful when there is a diffuse retinal process, but if the process is focal, involving less than 25% of the retina, it will not reveal the defect. It also should be emphasized that an abnormal ERG often will result in an abnormal VEP. Thus, in most instances of unexplained visual loss, it is best to obtain an ERG when ordering a VEP. If both tests show abnormal results, the electrophysiologist and
you will have to decide if the changes in the VEP are primary and responsible for the patient’s visual loss or if the retina is responsible and the VEP changes merely reflect abnormal retinal function causing abnormal transmission from the retina to the optic nerve.

One should be alert to the possibility of a conversion disorder or malingering in cases of bilateral visual loss. The absence of optic atrophy is an important clue when the visual loss is long standing. In the acute phase, the characteristics of the visual field defects may help the clinician recognize that the loss of vision is nonorganic. The visual field defects in the toxic and nutritional optic neuropathies are typically central or centrocecal. Such defects are exceptional in patients with a conversion reaction or who are malingering. In conversion reaction and malingering, the visual fields are usually constricted and may show spiraling or have a tubular configuration.

Autosomal-dominantly inherited (Kjer) and mitochondria-inherited (Leber) optic neuropathies can be confused with nutritional optic neuropathy if no other family members are known to be affected. The confusion is most likely to occur in patients who are first evaluated late in their course. Autosomal-dominant optic neuropathy progresses much more slowly than the nutritional and toxic optic neuropathies, and optic atrophy is an early finding. In Leber optic neuropathy, the onset of visual loss not infrequently is symmetric or nearly so, and this disorder must therefore be considered in any patient in whom a toxic or nutritional optic neuropathy is thought to be present. Appropriate testing for mitochondrial DNA mutations may be required in some cases.

It can be tragic to mistake a compressive or infiltrative lesion of the optic chiasm for nutritional or toxic optic neuropathy. There are few instances in which one should be so confident of the diagnosis of toxic or nutritional optic neuropathy that neuroimaging is omitted. Centrocortical scotomas and the bitemporal visual field defects of chiasmal disease resemble each other, and there are many examples of bilateral central and even centrocecal scotomas from tumors.

If a demyelinating, inflammatory, or infectious optic neuritis begins simultaneously in both eyes, there may be confusion with the toxic and nutritional optic neuropathies. The visual field defects are similar, but there is pain in about 90% of cases of optic neuritis. In some cases, magnetic resonance (MR) imaging will indicate the nature of the lesion. In others, however, it may be necessary to examine the cerebrospinal fluid, perform specific tests for syphilis, sarcoidosis, or systemic vasculitis, and perform a complete neurologic examination.

**EVALUATION**

In most cases, analysis of the symptoms and signs obtained from a detailed history and physical examination will establish the diagnosis of a toxic or nutritional optic neuropathy. As stated above, it is prudent to obtain neuroimaging unless one is absolutely confident of the diagnosis. MR imaging before and after intravenous injection of gadolinium diethylenetriamine pentaacetic acid (gadolinium DTPA) with special attention to the optic nerves and optic chiasm, is the optimum investigation in most cases. A vitamin B_{12} level should be determined to identify pernicious anemia, and red blood cell folate levels provide one marker of general nutritional status. In addition, in patients with a low or low-normal serum vitamin B_{12} level, assays for homocysteine and methylmalonic acid also may be appropriate.

When a specific intoxicant is suspected, one should try to identify the toxin or its metabolites in the patient’s tissues or fluids. The advice of a toxicologist is invaluable in such instances. In cases of suspected intoxication, one should attempt to evaluate or obtain information about other persons who have had similar exposure. The resulting information has potential public health implications and can help to validate the toxicity of chemicals not previously recognized as dangerous to the human optic nerve.

**CME ANSWERS**

1. c
2. a
3. c

**REFERENCES**


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IgG WHAT IS IT GOOD 4?

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LEARNING OBJECTIVES

1. The attendee will learn the current diagnostic criteria for IgG4-related disease
2. The attendee will understand the potential pathophysiologic mechanisms of tissue injury for IgG4-RD
3. The attendee will know when to consider screening for IgG4-RD in a clinical setting

CME QUESTIONS

1. What are the most common neuro-ophthalmic manifestations of IgG4-related disease?
2. What is the sensitivity of serum IgG4 in IgG4-related disease?
3. True or False: IgG4 activates the classic complement pathway

KEYWORDS

1. IgG4
2. Orbital inflammatory syndrome
3. Pachymeningitis

INTRODUCTION

IgG4-related disease is an increasingly recognized condition which can mimic other, immune-mediated inflammatory diseases. The diagnostic criteria are still evolving and a number of previously unclassified or eponymous diseases are now falling under the category of IgG4-related disease. This condition has several distinct neuro-ophtalmic manifestations, including orbital inflammatory syndrome and pachymeningitis, and others may follow. Neuro-ophthalmologists should have increased awareness of this condition and be familiar with diagnostic testing for, and treatment of, IgG4 related disease.

IgG4-related disease (IgG4-RD) is an increasingly recognized condition characterized by sclerosing inflammation, a lymphoplasmacytic infiltration full of IgG4-positive plasma cells, and frequently associated with elevated serum IgG4 concentrations. It was first described as a systemic condition in 2003 when extrapancreatic manifestations were identified in patients with autoimmune pancreatitis, a condition known to be associated with elevated levels of IgG4. Since that discovery, the presence of IgG4-related inflammation has been detected in virtually all organs, particularly the pancreas, liver, kidney, lung, and thyroid. Over the past several years, more and more previously unclassified or eponymous conditions have been reclassified as IgG4 related disease, several of which are particularly relevant to neuro-ophthalmologists. The increased awareness of this condition has led many clinicians to search for IgG4 RD in patients, either by screening with serum IgG4 levels, or re-reviewing previous pathology specimens. However, the diagnostic criteria for IgG4-RD are still evolving, and to some degree remain a moving target. Indeed, the nomenclature for IgG4-RD varies considerably in the literature— it is variably referred to as IgG4-RD, IgG4-associated disease, IgG4 sclerosing disease, and others. Serum IgG4 levels may be elevated in other, unrelated autoimmune and infectious diseases, and some (but not all) of the pathologic findings are non-specific.

HISTORICAL BACKGROUND

The first reported manifestation of IgG4-RD was autoimmune pancreatitis, initially described as a possible immune mediated condition by Sarles et al in 1961. Harano et al found increased IgG4 levels in patients with a subtype of autoimmune pancreatitis—lymphoplasmacytic sclerosing pancreatitis. This condition typically affects elderly men, with a prevalence of ~2-11% among patients with chronic pancreatitis. Characteristic pathologic features, which serve as the basis for the diagnostic criteria for IgG4-RD, include interstitial infiltration by plasma cells, small lymphocytes, and some eosinophils. The infiltrate is organized in a storiform (matted and whorled) pattern, and obliterative phlebitis is a frequent feature, although this may vary depending upon the target tissue. Response to steroids is usually good and there are multiple reports of favorable response to a variety of immunomodulatory agents. As more patients with IgG4 related sclerosing pancreatitis were identified, it became clear that extrapancreatic involvement was common, in some series in up to 80% of cases. More and more organ systems were implicated, as pathologic specimens in extra-pancreatic sites showed similar histologic features. Indeed, blind biopsies of clinically normal organs can show increased IgG4 plasma cells.
Figure 1a-b: Pathology specimen from a dural biopsy in a patient with pachymeningitis. Figure 1a is a high-power view (100X) demonstrating mature appearing plasma cells, singly dispersed and clustered. Figure 1b shows a section with IgG4 staining. The stain is positive in the majority of the plasma cells, with over 20+ cells/HPF. The IgG4 to IgG ratio is markedly increased.

The epidemiology of IgG4-RD is almost exclusively drawn from the Japanese literature, focusing primarily on IgG4-related autoimmune pancreatitis. The epidemiology of non-pancreatic IgG4-RD, and particularly IgG4 related eye disease, is poorly studied. However, a recent review of 1,014 cases of orbital lymphoproliferative disease in Japan found that nearly 25% of cases had histopathologic features consistent with IgG4 related disease.

The diagnostic criteria for IgG4-RD are evolving. An international symposium was held in Boston, MA in 2011 to generate a consensus statement on the nomenclature, pathologic features, and diagnostic criteria for IgG4-RD. The diagnosis of IgG4-RD cannot be established with certainty without increased numbers of IgG4 plasma cells (or elevated IgG4/IgG ratio) in tissue and an appropriate histological appearance (Figure 1a-b). This represents the current “gold standard” for confirmation of the diagnosis of IgG4-RD. They propose a three-tiered approach to diagnosis, acknowledging the while the general histologic features of IgG4-RD are broadly similar across organ systems, some sites vary (Figure 2). Therefore, careful examination of the biopsy specimen by an experienced pathologist who is expert in that organ system is crucial. IgG4 serum levels are not included in this histopathology based diagnostic criteria.

To complicate matters further, elevated IgG4 and IgG4-mediated immune dysfunction can be seen in variety of conditions that are clearly distinct from IgG4-RD, including pemphigus vulgaris, idiopathic membranous glomerulonephritis, and possibly thrombocytopenic thrombotic purpura. Therefore, it is possible that IgG4-RD may be overdiagnosed or misdiagnosed by relying solely upon clinical findings and serum IgG4 levels. Serum IgG4 levels are still useful as a rapid, easily performed screening test, but should not be used in isolation to make the diagnosis.

**SYSTEMIC MANIFESTATIONS OF IgG4-RD**

Table 1 summarizes the major organ systems that have been implicated in IgG4-RD (excluding neuro-ophthalmic conditions). Allergic condition such as bronchial asthma and chronic sinusitis may occur in up to 40% of patients with IgG4 RD, perhaps providing a clue to diagnosis. Indeed, many patients with IgG4 RD have allergic manifestations such as atopy, eczema, and asthma.

The clinical manifestations of extra-pancreatic IgG4-RD are...
Table 1: IgG4-related disease: Reported organ specific involvement

<table>
<thead>
<tr>
<th>Organ</th>
<th>Manifestion</th>
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<tbody>
<tr>
<td>Salivary gland</td>
<td>Sclerosing sialoadenitis</td>
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<tr>
<td>Lung</td>
<td>Interstitial pneumonia</td>
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<tr>
<td>Kidney</td>
<td>Tubulointerstitial nephritis</td>
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<td>Liver</td>
<td>Inflammatory pseudotumor, sclerosing cholangitis</td>
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<tr>
<td>Lacrimal gland</td>
<td>Sclerosing dacyoadenitis</td>
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<tr>
<td>Retroperitoneum</td>
<td>Retroperitoneal fibrosis</td>
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<tr>
<td>Cardiovascular</td>
<td>Inflammatory aortic aneurysm</td>
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<td>Prostate</td>
<td>Prostatitis</td>
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<tr>
<td>Thyroid</td>
<td>Thyroiditis</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Lymphadenopathy</td>
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Table 2: Eponymous diseases reclassified as IgG4-related disease

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Target organ/tissue</th>
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<tbody>
<tr>
<td>Miculicz’s syndrome</td>
<td>Salivary and lacrimal glands</td>
</tr>
<tr>
<td>Kuttner’s tumor</td>
<td>Submandibular glands</td>
</tr>
<tr>
<td>Riedel’s syndrome</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Ormond’s syndrome</td>
<td>Retroperitoneum</td>
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</tbody>
</table>

Involvement

The development of multi-system involvement can occur simultaneously, or evolve over many years. This highlights the need for thorough systemic evaluation once IgG4-RD has been found in a single target organ.

A number of previous eponymous diseases have now been reclassified as IgG4-RD (Table 2). In one review, 92-100% of cases of chronic sclerosing sialoadenitis (Kuttner tumor) were IgG4 related. Mikulicz disease is characterized clinically by bilateral, painless, symmetric swelling of the lacrimal, parotid, and submandibular glands. Recent reports suggest that IgG4-RD is a major cause of Mikulicz disease. Ormond syndrome is a condition characterized by the proliferation of fibrous tissue in the retroperitoneum. This condition has several associations, including Riedel thyroiditis, sarcoi.d, and malignancy. Comings et al reported retroperitoneal fibrosis, Riedel thyroiditis, orbital pseudotumor, and sclerosing cholangitis in two family members, perhaps one of the earliest reported cases of multi-system IgG4 related disease with neuro-ophthalmic features. Further reports described the co-occurrence of 2 or more of these entities in a single patient. These lesions share histologic features of lymphoplasmacytic infiltrate, sclerosis, and phlebitis. Many of these cases have been shown to harbor large numbers of IgG4 plasma cells, and may represent another manifestation of IgG4-RD. It should be noted that many of these reports do not fulfill the consensus statement defining the histopathologic criteria for IgG4-RD, and in some cases may best be termed “Probable IgG4-RD”.

It is expected that with increasing awareness of IgG4-RD, more and more previously uncategorized or poorly categorized conditions and syndromes may be reclassified as IgG4-RD. However, as noted, neither the presence of IgG4 plasma cells in the biopsy specimen nor increased IgG4 serum levels alone is specific enough to warrant classification as IgG4-RD. A careful review of pathology and exclusion of alternate diagnoses (such as sarcoidosis, lymphoma, Wegener’s, and others) remains paramount.

NEURO-OPHTHALMIC MANIFESTATIONS OF IgG4-RD

Of particular importance to neuro-opthalmologists are the conditions which present with visual dysfunction that have now been shown to be associated with IgG4-RD. We will review the conditions that have now been reported to occur in association with IgG4-RD, and also discuss currently poorly categorized disorders which might potentially be candidates for IgG4-RD.

ORBITAL INFLAMMATORY SYNDROME

Orbital inflammatory syndrome is a heterogeneous disorder characterized by inflammation in the orbit and ocular adnexal tissues. It is best thought of not as a specific syndrome but as a localized response secondary to a number of different causes. Up to 8% of patients have no identifiable underlying disease, even with biopsy, and are classified as idiopathic Orbital Inflammatory Syndrome (IOIS). This has traditionally been considered a diagnosis of exclusion.

In 1993, an association between IOIS and systemic fibrosclerosis (a condition now known to be one of the IgG4 related conditions) was reported. Over the past decade, more reports have emerged, largely from Japan, linking IOIS with IgG4-RD. Sato et al, in 2008, reviewed 112 cases of ocular adnexal lymphoproliferative disease; 78 were orbital and 34 had conjunctival involvement. 21/112 (19%) had >10 IgG4 positive plasma cells/tissues section. All of these patients had orbital lesions but no conjunctival involvement. Of this group, 17 had lacrimal gland involvement, 12/17 bilateral. The majority had elevated serum IgG4 levels, but these were obtained from stored samples, and several of these patients had undergone treatment, which could potentially alter serum IgG4 levels. It should be noted that the criteria used for the diagnosis of IgG4 RD in this paper (<10 IgG4 cells/hpf) is less strict than current proposed criteria, which require >30/hpf. Matsuo et al, in 2010, reported a series of 9 cases of lymphoproliferative disease of the orbit and ocular adnexa. Bilateral lacrimal gland lesions were present in 7/9 cases, with orbital extension in 4 of these. Four cases showed >10 IgG4 plasma cells/hpf,
with pathology showing lymphoplasmacytic infiltration, fibrosis and atrophy of tissue. A group of investigators reviewed the pathology of orbital specimens collected between 1993 and 2006. Of this group, 11/21 (53%) had increased IgG4+ cells (using the criterion of >10/hpf). A review of these patients’ medical records revealed that they had associated diagnoses of asthma (5/11), idiopathic pancreatitis (1/11), inflammatory pseudotumor of the liver (1/11) and cholangitis (1/11). These disorders either preceded or followed the orbital biopsy. Of this group, 3/11 had stored serum samples available for analysis, and 2/3 showed elevated serum IgG4. Clinical findings on the IgG4+ patients included eyelid edema, bilateral orbital involvement, and a more prolonged course than the IgG4− group. Histology in the IgG4+ group compared with the IgG4− group showed a higher degree of follicular hyperplasia, background fibrotic changes, plasma cells, and eosinophilia.

These reports and others suggest that IgG4-RD can present in a manner indistinguishable from IOIS. Multisystem involvement is not rare in the reported cases, suggesting that other organ involvement should raise suspicion of IgG4 RD in patients with presumed IOIS; or conversely, patients with IgG4 related OIS should undergo screening for other systemic involvement. This may include standard bloodwork including metabolic panel, body scanning with CT or PET-CT, or involving the patient’s primary care physician to coordinate the systemic evaluation.

IDIOPATHIC PACHYMENINGITIS
Hypertrophic pachymeningitis is, similar to IOIS, a heterogeneous group of disorders, characterized in this case by localized or diffuse thickening of the dura (cranial, spinal, or both). A wide range of infectious, inflammatory, and neoplastic disorders are included in the differential diagnosis, and must be excluded through neuroimaging, laboratory testing, lumbar puncture, and often dural biopsy. When no identifiable cause is found, this condition is known as Idiopathic Hypertrophic Pachymeningitis (IHP).

Dural biopsies in cases of IHP show histologic features including lymphoplasmacytic infiltrate with fibrosis, a pattern seen with IgG4-RD. There are now numerous reports of IgG4-RD presenting as IHP (Figure 3a-b). Wallace et al reviewed 14 cases of pachymeningitis at their institution, 6 of which were classified as IHP. They used the consensus criteria published in 2012 to validate the diagnosis of IgG4-RD. Of the 14 cases, 4 met criteria for IgG4-RD. All had been previously classified as IHP. They also highlighted the importance of finding the characteristic pathologic features of IgG4-RD rather than relying upon serum or tissue IgG4 levels: they described IHP due to granulomatous polyangiitis, rheumatoid arthritis, neurosarcoidosis, and lymphoma all demonstrating 10 IgG4+ plasma cells in biopsied tissue. They even found elevated IgG4+/IgG+ plasma cells in several of the non-IgG4-RD cases. The crucial distinguishing feature was the histopathology. They also reviewed CSF contents and MRI findings for all cases, and found no features distinguishing the IgG4-RD cases and the non-IgG4-RD cases, although IgG4 levels were not tested in the CSF. One IgG4-RD case showed sinus disease contiguous with dural thickening, a feature also seen in granulomatous polyangiitis. They concluded that IgG4-RD may account for a substantial

Figure 3a-b: These images show T1, post-gadolinium sagittal (3a) and axial (3b) MRI cuts of a patient presenting with headache, weight loss, and profound visual loss. They demonstrate diffuse leptomeningeal enhancement and thickening, suggesting pachymeningitis. The arrow highlights subtle perineural enhancement of the optic nerve. Subsequent dural biopsy confirmed IgG4-related disease.
number of so-called IHP cases, and that careful review of pathologic specimens is a critical part at arriving of the diagnosis of IgG4-RD.

Patients with IgG4-RD pachymeningitis may also have other organ involvement. Lipton et al\(^\text{26}\) reported a case of IgG4-RD presenting with pachymeningitis and aortitis. The patient responded to a combination of corticosteroids and methotrexate. They acknowledged that, based upon the consensus criteria for IgG4-RD, their cases would qualify as “probable histologic features of IgG4-RD”.

Not all patients with central nervous system IgG4-RD fit well into a specific category of pachymeningitis or IOIS. Moss et al\(^\text{27}\) described two cases of IgG4-RD presenting with dural based mass lesions and cranial nerve palsies. Both cases met pathologic criteria for IgG4-RD, and responded to an immunosuppressive regimen which included mycophenolate mofetil.

**CANDIDATE NEURO-OPHTHALMIC DISORDERS FOR IgG4-RD**

There are a large number of syndromes and conditions we see frequently in neuro-ophthalmology that remain poorly classified or defined. It is tempting to consider the possibility that some of these disorders may fall within the spectrum of IgG4-RD. These include Lymphocytic Hypophysitis (LH), scleritis, Tolosa-Hunt syndrome (THS), Chronic Relapsing Inflammatory Optic Neuropathy (CRION), Autoimmune Optic Neuropathy (AON), Gradenigo syndrome, and others. To date, only Lymphocytic Hypophysitis and scleritis have been reported to occur in the setting of IgG4-RD\(^\text{28,29}\). One obvious issue with many of these conditions (particularly those isolated to the optic nerve) is that a tissue specimen is usually lacking, as biopsy is either technically challenging, or too high a risk. Still, some patients with progressive optic neuropathy undergo biopsy of an NLP nerve, so adding stains for IgG4 and reviewing the pathology for features suggestive of IgG4 could be considered in these uncommon situations.

**PATHOGENESIS OF IgG4-RD**

Although the pathogenesis of IgG4-RD remains incompletely understood, more precise mechanisms of tissue injury are becoming clearer over time. Some of the clues likely lie in the distinct histopathologic features of this condition, as well as the unique molecular feature of IgG4. Eosinophilia and elevated IgE levels (both features of allergic disorders) are present in approximately 40% of patients with IgG4-RD\(^\text{30}\). These responses are mediated primarily by cytokines produced by Th-2 cells. These cells (Th2) produce cytokines (IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13) which promote recruitment of eosinophils, and inhibit some of the antimicrobial activity of Th1 cells\(^\text{31}\). In contrast to many autoimmune conditions, activation of T regulatory cells is common with IgG4-RD. These cells can produce transforming growth factor beta (TGF-B), which may play a central role in the development of fibrosis in IgG4-RD. Stone et al\(^\text{1}\) provided a comprehensive overview of the current theories of pathogenesis in a recent review article.

**IGG4 MOLECULE**

Immunoglobulins are protein complexes comprised of 4 peptide chains (Figure 4), two heavy chains and two light chains. They are secreted by plasma cells. There are 5 major immunoglobulin isotypes, or classes: IgA, IgD, IgE, IgM, and IgG. Immunoglobulin G (IgG) is the most abundant antibody class in humans, accounting for ~75% of immunoglobulins found in the circulation. IgG molecules are major players in the humoral immune response and help control infection of body tissues. This occurs via several immune mechanisms: IgG-mediated binding of pathogens causes their immobilization and binding together via agglutination; IgG coating of pathogen surfaces (known as opsonization) allows their recognition and ingestion by phagocytic immune cells; IgG activates the classical pathway of the complement system, a cascade of immune protein production that results in pathogen elimination.

The IgG4 molecule is distinct from other immunoglobulins in structure and function. It accounts for <5% of total IgG and is by far the least abundant IgG subclass. The serum IgG4 concentrations vary by a factor of more than 100 in normal adults, a feature not shared by other IgG subclasses\(^\text{1,31}\).

![Figure 4: Schematic diagram of the basic unit of immunoglobulin (antibody)](image)
The IgG4 subclass also has unique immunologic features, related in part to its molecular structure. First, amino acid differences within the second constant domain result in poor binding to Clq and Fc-gamma receptors. This suggests that IgG4 does not activate the classic complement pathway, and historically, IgG4 has been thought to play a limited role in immune activation. Second, as opposed to other IgG subclasses, the disulfide bonds between the heavy chains of IgG4 are unstable. It is estimated that ~50% of IgG4 molecules have heavy chains linked weakly by non-covalent forces. This means that the chains may separate and recombine randomly, resulting in an inability to form immune complexes. The production of IgG4 is controlled primarily by type 2 T helper cells (Th2), with Th2 cytokines shifting the balance of between IgE and IgG4, favoring IgG4. The precise role of IgG4 in normal immune function is still unclear. It may play a significant role in allergic reactions. It may also act as a protective blocking antibody in IgE-mediated responses to parasitic infection.

The specific role of IgG4 antibodies in IgG4-RD is still open to debate. They may simply act as tissue-destructive immunoglobulins. However, the tendency for IgG4 antibodies to promote anti-inflammatory responses and the fact that disease-specific IgG4 autoantibodies have not yet been identified in IgG4-RD could suggest that the overabundance of IgG4 molecules in this condition is a response to an as yet unknown primary inflammatory stimulus.

Autoimmunity (whether due primarily to IgG4 molecules or another stimulus) remains the most widely accepted explanation for the Th2 response associated with IgG4-RD. Serum IgG4 obtained from patients with IgG4-RD binds to the normal epithelia of the pancreatic ducts, bile ducts, and salivary gland ducts. Ultrastructural studies have identified electron-dense granular deposits at the basement membrane of renal tubules and pancreatic ducts in patients with IgG4-RD. However, it is unclear whether these deposits are involved in immune-complex mediated tissue injury or are a bystander phenomenon. Further, the degree to which the interaction between IgG4 and IgG is involved in the formation of these immune deposits is not clear.

As with many immune-mediated diseases, there may be genetic factors contributing to IgG4-RD. The HLA haplotypes DRB*0405 and DQB*0401 appear to confer increased risk of IgG4-RD in the Japanese population. Other non-HLA genes which have been implicated are single nucleotide polymorphisms which encode proteins such as T-lymphocyte associated antigen 4, tumor necrosis factor alpha, and Fc receptor-like 3.

SEROLOGIC STUDIES IN IgG4-RD

The incidence of elevated serum IgG4 levels in IgG4-RD varies widely. Most studies suggest that ~70% of patients have increased serum IgG4 levels. However, most of this data is drawn from patients with Autoimmune Pancreatitis. There is a great deal of heterogeneity, depending upon organ involvement, and less than strict adherence to the consensus guidelines for pathologic diagnosis of IgG4-RD. Although screening for IgG4-RD with serum IgG4 levels is a reasonable first line strategy, the sensitivity and specificity of this test, particularly for extra-pancreatic disease, is yet to be determined. The validity, as well as the sensitivity and specificity, of CSF IgG4 levels also remains unknown.

It is also unclear whether, in patients who have confirmed IgG4-RD, serum IgG4 levels can be used to monitor treatment or disease activity. The literature shows conflicting data. A large, multi-center Japanese study showed that IgG4 levels failed to normalize in 115/182 patients (63%) treated with corticosteroids. Some patients in that study remained in remission, despite persistent elevation in serum IgG4 levels. Monitoring of serum IgG4 may predict early relapse in some patients, but relapse occurs in up to 10% of patients with normal IgG4 levels, and most studies assessing the predictive value of serum IgG4 concentrations suffer from limited follow up.

NEUROIMAGING IN IgG4-RD:

The neuroimaging of IgG4-RD is dependent upon the clinical presentation and primary organ/soft tissue involvement.

Orbital involvement typically involves the lacrimal glands. Concurrent salivary gland involvement is common. The abnormalities are usually bilateral and relatively non-specific. The affected tissues show soft tissue attenuation on CT and hypointensity on T1 weighted images on MRI. One feature perhaps more distinct to IgG4-RD is low signal intensity on T2 weighted images due to increased cellularity and fibrosis. Perineural spread may occur, as well. Ohshima and colleagues studied 71 cases of orbital lymphoproliferative disorders, assessing the frequency of infra-orbital nerve enlargement on MRI. Of these cases, 16 met criteria for IgG4-RD. The incidence of infra-orbital nerve enlargement was significantly more frequent in the IgG4-RD cases than the non-IgG4-RD patients, suggesting that this radiologic sign might be a marker of IgG4-RD. In contrast to fungal infections and Wegener’s granulomatosis, involvement of the paranasal sinuses with IgG4-RD is rare. When it occurs, CT demonstrates infiltration with soft tissue attenuation with or without bony destruction. MRI demonstrates hypointensity on T2 weighted images relative to the normal nasal and paranasal mucosa.

Pachymeningitis due to IgG4-RD is best detected with MRI, pre and post gadolinium. Typical findings include meningeal enhancement, best seen on coronal and sagittal, post contrast T1 weighted images. The pattern of meningeal enhancement is variable: it has been reported as homogenous or heterogenous enhancement, diffuse or multi-focal, smoothly textured or nodular. There may or may not be associated mass effect.
Wallace et al referred 14 cases of pachymeningitis at their institution, 6 of which were classified as IHP. Of the 14 cases, 4 met criteria for IgG4-RD, using the consensus criteria published in 2012. They reviewed the MRI findings for all cases, and found no features distinguishing the IgG4-RD cases and the non-IgG4-RD cases. Other studies have found that, although the pattern of meningeal enhancement is variable in IgG4-RD, focal or pauci-focal distribution with associated mass effect may be more common that diffuse, homogeneous enhancement.

Involvement of the pituitary stalk can occur, with an appearance similar to lymphocytic hypophysitis, as noted previously. Typical MRI imaging findings include thickening or mass formation within the pituitary stalk, less commonly in the pituitary gland itself. Post contrast T1 weighted images usually demonstrate homogeneous enhancement. These findings are non-specific, and can be seen in a wide variety of other inflammatory disorders, including sarcoidosis, Langerhans cell histiocytosis, and tuberculosis. Pachymeningitis may occasionally co-exist with hypophysitis.

TREATMENT OF IgG4-RD
There are no high quality evidence based guidelines for the management of IgG4-RD. Treatment should be individualized, and based upon existing medical literature.

For example, not all systemic manifestations of IgG4-RD need to be treated. IgG4-related lymphadenopathy is usually asymptomatic, and may persist for years with no consequences. Some patients may have widespread disease which remains indolent, and not require treatment, whereas a patient with single organ involvement may have devastating consequences and require aggressive therapy. Patients with vision-threatening manifestations such as pachymeningitis and orbital inflammatory syndrome (particularly with optic nerve involvement) often need more aggressive treatment once the diagnosis has been established.

Corticosteroids are the first line of treatment in most cases. Although steroids are effective initially in IgG4-RD, relapses during taper are common, and many patients require long term steroid sparing therapy. A consensus statement from 17 referral centers in Japan (primarily related to IgG4-related autoimmune pancreatitis) recommended starting prednisone at a dose of 0.6 mg/kg daily for 2-4 weeks, with a taper over the next 3-6 months to 5 g daily, and continued treatment with prednisone for up to 3 years.

The choice of a steroid sparing agent is also highly individualized, as no evidence based treatment guidelines exist, and there is no clear evidence favoring one treatment over another. Azathioprine, mycophenolate mofetil, and methotrexate have all been used successfully for IgG4-RD.

Since IgG4-RD is (presumably) mediated by plasma cells, B cell depletion with rituximab has been advocated. Rapid and dramatic clinical responses have been reported, with marked decline in serum IgG4 levels, and clinical improvement. This must be balanced against the potential for serious side effects with the use of this medication.

Treatment response may be influenced by organ involvement, severity of disease and perhaps most importantly, the degree of fibrosis within the affected tissue. In patients with well established fibrosis, treatment response is usually minimal, although there are reports of clinical improvement after treatment in patients with widespread fibrotic disease.

SCREENING FOR IgG4-RD IN NEURO-OPHTHALMOLOGY
Given the increasing attention that IgG4-RD has received, it is tempting to consider this condition in any patient with an unexplained inflammatory process involving the visual pathways. However, it should be noted that the diagnostic criteria for IgG4-RD remain a moving target, and there is a risk of over-diagnosis, particularly if the diagnosis rests solely upon serum IgG4 levels.

At this time, the consensus statement establishing diagnostic criteria for IgG4-RD should be considered the “gold standard”, until new data emerges. This means that careful histopathologic examination is critical before arriving at a definitive diagnosis of IgG4-RD. Good communication with the neuropathologist reviewing the specimen is also of vital importance.

Screening for IgG4-RD with serum IgG4 levels should be strongly considered in patients with the two most frequently reported neuro-ophthalmic manifestations: orbital inflammatory syndrome and pachymeningitis. Lymphocytic hypophysitis likely falls within this category as well, perhaps scleritis also, although only two cases to date have been reported. Screening for IgG4-RD in some of the other conditions mentioned above (optic perineuritis, Tolosa-Hunt syndrome, etc) should be considered on a case-by-case basis.

Since there is no high quality evidence guiding treatment of IgG4-RD, it could be argued that management of IgG4 related OIS or pachymeningitis would not differ from management of the idiopathic forms of OIS or hypertrophic pachymeningitis- that is, exclusion of infectious and neoplastic etiologies, initial treatment with corticosteroids, and steroid sparing therapy in refractory patients. However, there are rational arguments for pursuing a diagnosis of IgG4-RD:

1. Other organ involvement. Since multi-organ involvement is frequent, once IgG4-RD disease is identified in one organ, screening for other organ involvement may identify potentially serious disease and prevent future complications.

2. Limiting further testing. Any disease which includes the term “idiopathic” carries a degree of uncertainty regarding the accuracy of the diagnosis. This often results in periodic re-testing.
and re-evaluation, with further expense and lost time for the patient. Achieving a specific, biopsy-supported diagnosis may preclude “re-inventing the wheel” during monitoring and treatment, particularly with treatment failure.

3. More confidence instituting potentially toxic treatments.

4. Less uncertainty for the patient, as it is often helpful for the patient to have a “named” disease.

**SCREENING FOR OTHER SYSTEMIC INVOLVEMENT**

All patients with confirmed IgG4-RD in one target organ should be suspected of harboring disease in other organs as well, particularly the pancreas. A thorough physical examination, and selective laboratory and imaging evaluation for other organ involvement should be considered once the initial diagnosis is secured. It is clear that this condition evolves over time, so if the initial surveillance screening for other organ involvement is negative, periodic re-evaluation may be considered. This may require the involvement of the patient’s primary care physician or specific consultation with specialists or subspecialists, depending upon specific organ-involvement.

**CME ANSWERS**

1. Orbital inflammatory syndrome and pachymeningitis

2. The true sensitivity is still unclear, but approximately 70% of patients with IgG4-related autoimmune pancreatitis have elevated serum IgG4 levels

3. False

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LEARNING OBJECTIVES
1. To critically appraise the treatment options currently available for Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (DOA)
2. To understand the concepts behind experimental strategies such as gene therapy and the prevention of germline transmission for pathogenic mitochondrial DNA mutations
3. To become aware of the “alternative” therapies for LHON and DOA that patients will come across on the internet

CME QUESTIONS
1. True or False? The marked sex bias in LHON could be due to the protective effect of female sex hormones, in particular oestrogens.
2. True or False? Idebenone and EPI-743 are officially licensed for clinical use in patients with LHON.
3. True or False? There is evidence to support the use of hyperbaric oxygen therapy after the onset of visual loss in LHON.
4. True or False? Gene therapy for LHON based on allotopic gene expression involves the direct transfer of genetic material into mitochondria.
5. True or False? Pronuclear transfer and metaphase II spindle transfer are two fertilisation techniques that could prevent the germline transmission of pathogenic mtDNA mutations.

KEYWORDS
1. Autosomal dominant optic atrophy
2. Genetic counselling
3. Leber hereditary optic neuropathy
4. Mitochondrial genetics
5. OPA1

INTRODUCTION
Hereditary optic nerve disorders result in significant chronic visual morbidity and the minimum prevalence of affected individuals in the population has been estimated at 1 in 10,000.1 Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (DOA) are the two classical paradigms for this group of disorders and they comprise nearly half of all the inherited optic atrophy cases seen in clinical practice. LHON is caused by mitochondrial DNA (mtDNA) point mutations whereas in DOA, the majority of cases are due to pathogenic mutations in the OPA1 gene, which codes for an inner mitochondrial membrane protein.1, 2 Strikingly, both LHON and DOA share the same characteristic pathological features with selective degeneration of the retinal ganglion cell (RGC) layer leading to progressive optic nerve degeneration and the onset of visual symptoms.3 RGCs are therefore exquisitely sensitive to mitochondrial dysfunction and the elucidation of the mechanisms involved is opening the way for therapeutic interventions targeting different stages of the disease process. In this review, recent advances in our understanding of LHON and DOA will be discussed, in addition to the practical management of this group of patients and emerging treatment options.

MITOCHONDRIAL GENETICS
Mitochondria are unique in possessing their own genetic material in the form of a double-stranded circular DNA molecule about 16,569 base-pair long.4, 5 MtDNA molecules are located within the matrix compartment where they are packaged within intricate physical structures known as nucleoids.6 The mitochondrial genome is very compact with limited capacity, but it codes for structural and functional components that are indispensable for normal mitochondrial function, including two ribosomal RNAs (12S and 16S rRNA), 22 transfer RNAs (tRNAs), and 13 polypeptide subunits of the mitochondrial respiratory chain complexes (I, III, IV and V). Overall, mitochondria have limited genetic autonomy and they rely heavily on the nuclear genome for the vast majority of proteins required for mtDNA replication, transcription and translation.4, 5

Another remarkable feature of mitochondrial genetics is its very high copy number with several thousands of mtDNA molecules being present in metabolically active cells such as neurones. Unlike nuclear DNA, mtDNA replicates continuously in dividing as well as in non-dividing cells,
and this process occurs independently of the cell cycle. As a result of this relaxed replication machinery, a cell’s total mtDNA content can be adjusted according to its bioenergetic requirements under both physiological and pathological conditions. Furthermore, the large number of mtDNA molecules present in each cell creates two possible genetic situations, referred to as homoplasy or heteroplasy. In the heteroplasmic state, two or more mtDNA variants are present at a specific nucleotide position and this genetic admixture has been implicated in the variable disease expression that typifies mitochondrial disorders. Most pathogenic mtDNA mutations are heteroplasmic and mitochondrial respiratory chain activity becomes compromised when the level of the mutant species exceeds a critical threshold (60-80%), which is both mutation and tissue specific.

LEBER HEREDITARY OPTIC NEUROPATHY

1. MOLECULAR GENETICS

LHON (OMIM 535000) is the most common of the primary mitochondrial DNA (mtDNA) disorders and the minimum prevalence has been estimated at 1 in 31,000 in the North of England. Comparable prevalence figures of 1 in 39,000 and 1 in 50,000 have been reported in epidemiological studies from the Netherlands and Finland, respectively. The majority of cases (90%) are due to one of three mtDNA point mutations: m.3460G>A (MTND1), m.11778G>A (MTND4), and m.14484T>C (MTND6), which affect key complex I subunits of the mitochondrial respiratory chain. The m.11778G>A mutation is by far the most common pathogenic mutation accounting for ~ 70% of all LHON cases worldwide. The one notable exception to this rule is the preponderance of the m.14484T>C mutation (~ 90%) in patients of French Canadian descent secondary to a mutational founder event.

2. CLINICAL FEATURES

Disease conversion in LHON is characterised by acute or subacute, painless, central visual loss in one eye, followed weeks to months later by the fellow eye. The median inter-eye delay is six to eight weeks and the second eye is invariably affected within one year of disease onset. Bilateral simultaneous onset occurs in a proportion of patients (~ 25%) with the caveat that some individuals are probably unaware that visual loss had been ongoing unnoticed in one eye prior to the second eye being involved. Although there are rare case reports of unilateral optic nerve involvement in LHON, it is important to exclude other underlying pathological causes in these highly atypical presentations. The peak age of onset is in the second and third decades of life and it is unusual for LHON carriers to experience visual loss beyond the age of 50 years. Off-chart vision worse than 20/200 is the norm at the visual nadir and there is an associated dense central or centrocecal scotoma with profound dyschromatopsia. Interestingly, the pupillary light reflexes are relatively preserved in LHON due to the sparing of a special class of melanopsin-containing RGCs that are more resistant to mitochondrial dysfunction.

The overall visual prognosis in LHON is poor and the majority of patients will remain legally blind with a significant detrimental impact on their overall quality of life. Spontaneous visual improvement is most likely within the first year, but remarkably, it has also been reported several years or even decades following the initial visual loss. Visual recovery is usually heralded by the appearance of small islands of vision in the central visual field and as the scotoma gets concurrently less dense, these fenestrations can greatly help with scanning vision and peripheral navigation. LHON carriers harbouring the m.14484T>C mutation have the best visual prognosis with a partial visual recovery rate of 37-58%, compared with 4-25% for the m.11778G>A mutation. Other reported positive prognostic factors for visual recovery in LHON include an earlier age of onset (< 20 years), especially among young children; a subacute presentation with slow visual deterioration; and a relatively large optic disc.

LHON is typically a monosymptomatic disease but additional features such as cardiac conduction defects, peripheral neuropathy, dystonia, and myopathy have been reported to be more common among LHON carriers compared with controls. There is also a well-reported association between the three primary mtDNA LHON mutations and a multiple sclerosis (MS)-like illness, especially among female carriers.

3. INCOMPLETE PENETRANCE AND SEX BIAS

Not all LHON mutation carriers will experience visual loss during their lifetime. The conversion rate for male carriers is ~ 50% compared with only ~ 10% for female carriers. LHON is therefore characterised by both marked incomplete penetrance and a striking male bias for visual loss. The secondary factors that modulate the phenotypic expression of the underlying pathogenic mtDNA mutation have been the subject of intense research over the past two decades. Although we do not yet have the full picture of what is proving to be a relatively complex disease, a number of genetic, hormonal, and environmental factors have been identified, some of which are particularly relevant to patient counselling and the development of drug treatments for LHON.

Heteroplasmy is thought to influence disease penetrance based on the observation that affected LHON carriers have mutation levels greater than 60% in peripheral blood leucocytes. However, incomplete penetrance is still observed among heteroplasmic carriers with mutation levels exceeding this nominal threshold and the majority of LHON families (80-90%) harbour homoplasmic mtDNA mutations. Heteroplasmy is therefore not a major contributor to the incomplete penetrance pattern seen in LHON. Another factor that could be modulating the risk of visual loss in LHON is the mitochondrial genetic background.
on which the pathogenic mtDNA mutation is segregating. The mitochondrial genome is highly polymorphic and during human evolution, ancient mtDNA variants have gradually clustered together in specific combinations known as haplogroups. Mitochondrial haplogroups have a differential effect on the efficiency of the mitochondrial respiratory chain and this could possibly influence the overall deleterious impact of the LHON mutation on RGC survival.

In a large meta-analysis of Caucasian LHON pedigrees, haplogroup J was associated with a significantly increased risk of visual loss among m.11778G>A and m.14484T>C carriers, whereas m.3460G>A carriers were more likely to become affected on a haplogroup K background. LHON carriers with the m.11778G>A mutation had a lower risk for visual loss when the mutation arose on haplogroup H. Other haplogroup associations have been reported in families with LHON from mainland China, but none in those from South-East Asia. The influence of specific mtDNA polymorphisms on the risk of visual failure in LHON is therefore not entirely clear-cut and further investigation is warranted.

The predominance of affected males in LHON cannot be explained by mitochondrial inheritance. Segregation analysis of a large number of LHON families was consistent with the existence of a recessive X-linked susceptibility gene acting in synergy with the mtDNA mutation to precipitate visual loss. Three independent linkage studies have revealed overlapping candidate regions on the X-chromosome, but the actual modifier gene has still not yet been identified. The existence of autosomal nuclear modifiers in LHON remains a distinct possibility and the situation could prove even more complex if different combinations of nuclear genes are segregating in different ethnic populations.

Another obvious explanation for the striking marked male bias in LHON is a protective benefit from female sex hormones. Interestingly, treatment with 17β-oestradiol resulted in reduced reactive oxygen species (ROS) levels, increased activity of the antioxidant enzyme superoxide dismutase (SOD), and more efficient mitochondrial biogenesis in LHON cybrid cell lines. Since RGC cell bodies have a high concentration of oestrogen b receptors, supplementation with oestrogen-like compounds represents an attractive therapeutic option. Various environmental triggers have been implicated in precipitating the onset of visual loss in LHON, including head trauma, psychological stress, exposure to industrial toxins, and drugs with mitochondrial toxic effects such as antiretrovirals and ethambutol.

A recent multicentre study that enrolled 125 Northern European LHON pedigrees has provided important insight into the role of smoking and alcohol consumption on disease expression. Smoking was strongly associated with an increased risk of visual loss and this detrimental effect was more marked for heavy smokers compared with light smokers. Various toxins present in cigarette smoke are capable of depressing mitochondrial ATP synthesis either through a direct inhibitory effect on complex I activity or by reducing arterial oxygen concentration. There was also a trend towards an increased risk of visual failure with heavy binge drinking, but this effect was not as marked as for smoking.

4. DISEASE MECHANISMS
The papillomacular bundle is affected early and much more severely in LHON. The preferential involvement of the RGCs within the papillomacular bundle is likely related to their relatively small calibres and limited mitochondrial energetic reserves. Two major mechanisms have been proposed to precipitate RGC loss in LHON – a biochemical respiratory chain defect and increased levels of reactive oxygen species (ROS). There are supporting lines of evidence for both these pathological pathways and they represent obvious therapeutic targets to halt the catastrophic loss of RGCs that occurs during the acute phase of LHON. The three most common primary LHON mutations (m.3460G>A, m.11778G>A, and m.14484T>C) all affect critical complex I subunits and impaired complex I-driven ATP synthesis has been identified using both in vitro and in vivo biochemical assays. A mouse model has recently been developed that replicates some of the key histopathological features seen in the optic nerves of affected LHON patients, namely the preferential degeneration of the smallest calibre RGC fibres, marked axonal swelling and the accumulation of dysmorphic mitochondria within demyelinated segments. Increased ROS levels were observed with no reduction in ATP synthesis, strongly supporting oxidative stress as the major mechanism driving the loss of RGCs, at least in this specific mouse model.

AUTOSOMAL DOMINANT OPTIC ATROPHY

1. MOLECULAR GENETICS
Autosomal dominant optic atrophy (DOA, OMIM 605290) is the most commonly diagnosed inherited optic neuropathy and in a recent epidemiological study, the minimum prevalence was estimated at 1 in 25,000 in the North of England. The majority of families with DOA (50-60%) harbour pathogenic mutations in OPA1 (3q28-q29), which codes for a dynamin-related GTPase protein located within the inner mitochondrial membrane. It is a ubiquitous protein and abundant levels have been detected in RGCs, the inner ear and the brain. OPA1 is highly polymorphic and over 200 pathogenic mutations have been identified with hotspots in the catalytic GTPase domain (exons 8-15) and the dynamin central domain (exons 16-23).

2. CLINICAL FEATURES
DOA has an insidious onset in early childhood and it typically presents with bilateral, symmetrical, central visual loss and dyschromatopsia. There is a wide variability in disease severity with visual acuities ranging from 20/20 to the detection of hand movement. Although the rate of progression can be highly variable both between and within families, visual loss is invariably progressive.
and nearly half of all patients are eventually registered legally blind.\textsuperscript{42, 43} Similar to LHON, the pathological hallmark of DOA is the preferential early loss of RGCs within the papillomacular bundle, accounting for the distinctive temporal wedge of pallor that is frequently observed at the optic nerve head. However, pallor of the neuroretinal rim can be subtle and the demonstration of pathological thinning of the retinal nerve fibre layer (RNFL), especially in the temporal quadrant, with optical coherence tomography (OCT) imaging can be particularly helpful in equivocal cases.\textsuperscript{44, 45} Limited post mortem studies suggest the relative preservation of melanopsin-containing RGCs and this could account for the lack of an afferent pupillary defect in patients with DOA, which is another clinical feature shared with LHON.\textsuperscript{46} Although progressive central visual loss is the defining feature of DOA, up to 20% of OPA1 mutation carriers are at risk of developing a more severe neuromuscular (DOA+) phenotype complicated by sensorineural hearing loss, ataxia, myopathy, peripheral neuropathy and chronic progressive external ophthalmoplegia.\textsuperscript{46-48}

4. DISEASE MECHANISMS

OPA1 is a multifunctional protein located within the inner mitochondrial membrane. It is a critical pro-fusion protein and pathogenic OPA1 mutations result in marked mitochondrial network fragmentation.\textsuperscript{49} This physical disruption has a knock-on effect on the stability of the mitochondrial respiratory chain complexes, resulting in increased ROS levels and a reduction in overall ATP synthesis.\textsuperscript{50, 51} Pro-apoptotic cytochrome c molecules are carefully sequestered within the cristae spaces by the zipper-like action of OPA1 and mitochondria are major stores of calcium.\textsuperscript{52, 53} Mitochondrial network fragmentation results in the uncontrolled release of these potent pro-apoptotic factors, which ultimately trigger irreversible cell death. Although the mechanisms still need to be fully elucidated, OPA1 mutations result in mitochondrial genome instability and the accumulation of multiple mtDNA deletions in affected tissues.\textsuperscript{54} Patients with DOA+ phenotypes harbour significantly higher levels of these somatic mtDNA abnormalities suggestive of a contributory role in the development of the more severe neuromuscular complications.\textsuperscript{48} Although OPA1 regulates a whole host of interrelated cellular pathways, compromised OXPHOS and elevated ROS levels are two major disease mechanisms that overlap with LHON, raising the exciting prospect of generic neuroprotective strategies applicable to both these mitochondrial optic neuropathies.

PATIENT MANAGEMENT

1. GENERAL SUPPORTIVE MEASURES

The sudden onset of severe visual loss in LHON causes significant distress and anxiety for patients and their families. Although DOA has a less dramatic presentation, visual loss is progressive and in a quality of life survey, half of all the patients interviewed reported high levels of anxiety and depression.\textsuperscript{55} Clinicians therefore have an important role to play in facilitating access to rehabilitative services such as low visual aids and occupational therapy. Patient groups and information websites can also provide invaluable support, especially in the immediate period after a diagnosis has been made (https://sites.google.com/site/planetleader/lhon and http://www.lhon.org/lhon/LHON.html, accessed 28th of August 2013). In addition to visual loss, patients with LHON and DOA can also develop neurological features such as ataxia, peripheral neuropathy and hearing impairment. Clinicians need to be aware of these “plus” phenotypes to ensure their early detection and patients in this high-risk group are best served by a multidisciplinary team to aggressively manage and minimise the functional consequences of these systemic complications.

2. GENETIC COUNSELLING

The mitochondrial genome is maternally inherited and male LHON carriers can be reassured that that their children are not at risk of inheriting their genetic defect. On the other hand, all the children of a homoplasmic female carrier will harbour their mother’s mtDNA mutation. The situation is rather more complex for a heteroplasmic mother as she could transmit a higher or a lower level of her mtDNA mutation to a particular offspring, which could influence the latter’s risk of becoming clinically affected. The sometimes rapid shifts in mitochondrial allele frequencies that occur between maternally-related generations have been explained by a “mitochondrial bottleneck” operating in the female germline.\textsuperscript{56} Prenatal testing for heteroplasmic female LHON carriers is therefore unhelpful because the mutant load detected in amniocytes and chorionic villi may not correspond to that in other foetal cell populations, especially those destined to mature into RGCs.

A frustrating aspect of the management of LHON is the current inability to accurately predict whether a familial carrier will eventually experience visual loss. Despite these limitations, individuals can be counselled based on the two major identifiable risk factors in this disorder, namely age and sex.\textsuperscript{1, 2} Male carriers have about a 50% lifetime risk of visual failure compared with only 10% for female carriers, and the peak age of onset is in the second and third decades of life. As a general health measure, patients with mitochondrial disorders should be strongly advised not to smoke and to moderate their alcohol intake. This is especially the case for unaffected LHON carriers as smoking, and to a lesser extent excessive binge drinking, have been linked with an increased risk of disease conversion.\textsuperscript{57} It also seems sensible to avoid exposure to other putative environmental triggers for visual loss in LHON, in particular industrial toxins and drugs with mitochondrial-toxic effects, for example ethambutol.\textsuperscript{1, 2}

DOA is an autosomal dominant Mendelian disorder, but genetic counselling for patients and their families remains challenging for several reasons. It is not possible to
predict the rate of progression of visual loss, which can be highly variable even within families harbouring the same pathogenic OPA1 mutation.42, 43 Furthermore, although patients harbouring missense OPA1 mutations in the GTPase domain of the protein have a statistically higher risk of developing DOA+ phenotypes, not all of them will do so, and the development of neurological features only becomes manifest in mid- to late adulthood, introducing another element of uncertainty.48 OPA1 mutation carriers have a 50% chance of transmitting the pathogenic allele to each of their children and pregnant women can request prenatal testing after having been appropriately counselled. Prenatal diagnosis is possible by analysing DNA extracted from foetal cells and the method used depends on the mother’s personal choice and her gestational status, either amniocentesis (15-18 weeks) or chorionic villus sampling (10-12 weeks).

TREATMENT OPTIONS – LHON

1. MITOCHONDRIAL COCKTAILS
There is currently only limited evidence to support the use of any intervention in mitochondrial disorders.57 In a recent systematic review of the literature, only 35 out of 1,039 publications on treatments for mitochondrial diseases included more than five patients, and most of these suffered from significant methodological weaknesses, suggesting a publication bias toward positive but poorly executed studies.58 Over the years, various combinations of vitamins (B2, B3, B12, C, E, and folic acid) and other compounds with putative mitochondrial antioxidant and bioenergetic properties have been used to treat patients with mitochondrial disease, including LHON, but none with any convincing proof of efficacy.57-59 The list of supplements that are frequently promoted on the internet includes alpha-lipoic acid, carnitine, creatine, and L-arginine.

2. UBIQUINONE ANALOGUES
Ubiquinone is a fat-soluble molecule present at a very high concentration within the inner mitochondrial membrane and it plays a unique role in OXPHOS as the only carrier that can efficiently transfer electrons from complexes I and II to complex III.4, 5 Pathogenic mtDNA mutations associated with LHON destabilise complex I resulting in a reduction in ATP synthesis and increased ROS levels. An attractive strategy to restore the flow of electrons along the mitochondrial respiratory chain is to bypass the blockage occurring at the level of complex I by enabling and maximising the direct shuffling of electrons to complex II. Coenzyme Q10 (CoQ10) is a ubiquinone analogue with a long history of use for patients with a broad range of mitochondrial disorders.57-59 Although, there is a sound scientific basis based on the potential antioxidant and bioenergetic properties of CoQ10, a Cochrane review found no objective evidence of any significant patient benefit in the limited number of small studies that have been published.59 Putting these methodological issues aside, the lack of efficacy of CoQ10 could be due to its lipophilic nature, this physical property hindering its delivery to mitochondria following oral administration of the drug. There is one anecdotal report of an affected patient carrying the m.11778G>A mutation who experienced marked visual improvement after he was started on CoQ10 about eight months following the first onset of symptoms.60 This could simply have been a chance occurrence given that spontaneous visual improvement has been noted in up to 25% of patients harbouring this mtDNA mutation.

Idebenone and EPI-743 are newer generation shorter-chain analogues of ubiquinone that are reported to be more potent compared with CoQ10, at least in vitro.61, 62 The possible visual benefit of idebenone in LHON was first reported in 1992 by Mashima and colleagues who treated a ten-year-old boy harbouring the m.11778G>A with a relatively low daily dose of 90 mg/day.63 The obvious confounding factor in this case is the relatively young age of the patient since childhood-onset LHON seems to be a distinct entity associated with a much more benign clinical course and a higher rate of spontaneous visual recovery.18 In a larger case series from the same Japanese group, 14 patients with LHON were treated with a combination of idebenone (180 mg/day), vitamin B, and vitamin C.64 No significant difference in the proportion of eyes showing visual recovery was observed when this intervention group was retrospectively compared with 14 untreated patients. However, if it occurred, a faster rate of visual recovery was reported in the treated eyes compared with the untreated eyes. In contrast to these results, Barnils and colleagues found no visual benefit with the use of the same treatment cocktail in two visually affected individuals carrying the m.11778G>A mutation.65 To address the true potential of idebenone as a treatment modality in LHON, a multicentre, double-blind, randomised placebo-controlled trial was initiated. RHODOS (Rescue of Hereditary Optic Disease Outpatient Study, ClinicalTrials.gov identifier: NCT00747487) enrolled 85 patients with a confirmed primary mtDNA mutation (m.3460G>A, m.11778G>A, and m.14484T>C) and with disease duration of up to five years.66 The active arm received idebenone (900 mg/day) and no adverse drug reactions occurred over a treatment period of 24 weeks. This trial failed to meet its pre-specified primary end point (best recovery of visual acuity at week 24), but all of the secondary end points showed a positive trend towards visual improvement in the idebenone-treated group. A post hoc analysis of the trial data also indicated that patients with discordant visual acuities (LogMAR > 0.2), and hence at highest risk of further deterioration in the least affected eye, were more likely to benefit from treatment with idebenone. In the follow-up study (RHODOS-OFU), the beneficial effect of 24 weeks of treatment with idebenone seemed to persist following discontinuation of the active medication at the end of the trial.68 In a large retrospective Italian study involving 103 patients with LHON, 44 patients with visual loss of one year’s duration or less were treated with idebenone and
followed for at least five years. A greater proportion of patients receiving idebenone recovered vision and the most consistent prognostic factors associated with visual recovery were the early initiation of treatment and a more prolonged course of treatment.

A marketing authorisation application by Santhera Pharmaceuticals Ltd (Liestal, Switzerland) to the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recently received an unfavourable opinion and additional clinical evidence for the efficacy of idebenone in LHON has been requested by CHMP (http://www.santhera.com/index.hp?docid=212&vid=&lang=en&newsdate=201301&newsid=1671337&newslang=en, accessed 28th of August 2013). The Newcastle Mitochondrial Research Group is planning a second double-blind, randomised placebo-controlled trial that will investigate the benefit of treatment with a higher dose of idebenone (2,250 mg/day) given for a total duration of 48 weeks instead of 24 weeks as for RHODOS. Further work is also needed to determine the appropriate duration of the treatment of asymptomatic carriers or patients with longstanding visual loss. Although idebenone is currently not licensed for clinical use, patients with LHON frequently opt to gain access to it at their own expense from various internet sources. EPI-743 has been used in an open-labelled study of five patients with LHON who were treated within 90 days of disease conversion. Although the results need to be confirmed in a properly designed clinical trial, four out of five patients demonstrated arrest of disease progression and variable extents of visual improvement.

3. BRIMONIDINE
Brimonidine is a topical α-2 agonist that is commonly used to lower intraocular pressure in the management of glaucoma. Some studies have suggested that brimonidine can exert a synergistic RGC neuroprotective effect by upregulating a number of anti-apoptotic factors and by blocking glutamate excitotoxicity induced by mitochondrial oxidative stress. Topical brimonidine has therefore been tested as a prophylactic agent for second-eye involvement in an open-labelled study of nine patients with unilateral acute visual loss secondary to LHON. Brimonidine failed to prevent fellow eye involvement and there was no evidence of any visual benefit following the onset of visual loss. Although this study was negative, raised intraocular pressure has been linked with an increased risk of visual loss in LHON and an agent with putative neuroprotective properties such as brimonidine could represent an ideal choice of treatment for unaffected LHON carriers diagnosed with glaucoma or ocular hypertension.

4. STEROIDS AND IMMUNOSUPPRESSANTS
Patients with LHON are not infrequently treated with high-dose steroids before a molecular diagnosis has been secured to exclude the possibility of an inflammatory optic neuropathy. Steroids do not prevent the involvement of the fellow unaffected eye in LHON and there has been no reported benefit on disease progression and the final visual outcome. In an experimental paradigm involving the supplementation of the culture media with hydrogen peroxide, LHON cybrids harbouring the m.11778G>A mutation showed an increased sensitivity to oxidative stress. This increased susceptibility to undergo apoptosis was postulated to be secondary to a toxic rise in intracellular calcium and the activation of the mitochondrial transition pore (MTP). Pre-treatment with cyclosporin A blunted the deleterious consequences of hydrogen peroxide by blocking the MTP pore, indicating a possible therapeutic pathway for LHON. The anti-apoptotic effect of cyclosporine A has also been demonstrated in LHON cybrids harbouring the m.14484T>C and m.14279G>A mutations. On the basis of this in vitro data, a French study is currently underway recruiting patients with unilateral visual loss from LHON for treatment with cyclosporin A in an attempt to prevent the involvement of the fellow eye (Dr Dominique Bonneau, University of Angers, France, personal communication).

5. HYPERBARIC OXYGEN THERAPY
There is highly anecdotal “internet” evidence of patients with LHON benefiting from hyperbaric oxygen therapy (HBOT) (http://hyperbariclink.blogspot.co.uk/2012/06/in-news-hyperbaric-oxygen-therapy-for.html, Accessed 28th of August 2013). The purported rationale for this treatment is to provide increased levels of oxygen to RGCs during the acute phase of LHON with the aim of improving mitochondrial biogenesis. HBOT is a controversial treatment modality that has been applied with limited success to other optic nerve disorders such as radiation-induced optic neuropathy and anterior ischaemic optic neuropathy. Given the rather slim evidence base, the theoretical toxic effects of supraphysiological levels of oxygen in LHON should be considered in the context of a dysfunctional mitochondrial respiratory chain that is already producing increased ROS levels.

6. NEAR-INFRARED LIGHT THERAPY
Near-infrared light (NIR) therapy has been shown to improve mitochondrial function and cellular survival in various models of wound healing, neurodegeneration and methanol-induced retinal toxicity. Although these findings are not universally accepted, NIR photobiomodulation is thought to increase ATP synthesis by stimulating the activity of cytochrome c oxidase (complex IV). The application of NIR therapy to RGCs via a light-emitting diode has therefore been proposed as a possible rescue strategy for LHON. A study was initiated to investigate the visual benefit of NIR therapy in affected LHON carriers, but it has been terminated because of the inability to record reliable pattern electroretinography (pERG) measurements, which was the planned primary outcome measure, due to poor subject fixation (http://clinicaltrials.gov/ct2/show/NCT01389817?term=LHON+whelan&rank=3, accessed 28th of August 2013).
TREATMENT OPTIONS – DOA
Compared with LHON, the rate of RGC loss in DOA is relatively slow and the detection of a clinically meaningful benefit over the course of a one or two-year treatment trial is a major methodological consideration. Long-term natural history studies are therefore urgently needed to more precisely define the visual parameters that are most sensitive at detecting a significant change in optic nerve structure and function for insidiously progressive optic nerve disorders like DOA. Idebenone has recently been evaluated in a limited case series involving seven patients with DOA and confirmed pathogenic OPA1 mutations. A variable daily dose of idebenone was used (270-675 mg) and all the patients were treated and reviewed for at least one year. No adverse drug reactions were reported and some improvement in visual function was reported for five of the seven idebenone-treated patients. The results of this pilot study remain preliminary and a randomised placebo-controlled trial with an adequate duration of follow-up will be needed to prospectively evaluate the possible benefit of using idebenone in DOA. Looking into the future, an open-labelled study of EPI-743 for patients with DOA is currently under preparation (Dr Valerio Carelli, University of Bologna, Italy, personal communication), and the potential benefit of near-infrared light in rescuing RGC loss is also being tested in a mouse model of DOA harbouring a splice site mutation (c.1065+5g>a) within intron 10 of the Opa1 gene (Professor Marcela Votruba, Cardiff University, UK, personal communication).77

FUTURE PROSPECTS AND CHALLENGES

1. DRUG SCREENING AND DEVELOPMENT
With idebenone and EPI-743, we are witnessing the first tentative steps in our effort to try and modulate disease progression for mitochondrial optic neuropathies. Several research groups worldwide are actively pursuing the identification of novel neuroprotective agents for other, more prevalent, optic nerve disorders such as glaucoma and anterior ischaemic optic neuropathy, the results of which are likely to be highly relevant for LHON and DOA.59, 78 The technological revolution of the past decade has launched a new era of personalised medicine with mitochondrial optic neuropathies.58 Functional unit within the inner mitochondrial membrane.85, 86

The consolidation of the cell’s antioxidant defences could therefore prove a complementary approach to the replacement of the mutated gene product in LHON. A radically different strategy is based on the xenotopic expression of Nd1, an alternative NADH oxidase expressed in yeast (saccharomyces cerevisiae) mitochondria. Nd1 is a versatile enzyme that can bypass a malfunctioning complex promotes OXPHOS by upregulating the transcript levels of “master” genes involved in mitochondrial biogenesis, namely PGC-1α, PGC-1β, and TFAM.79, 80 A study is currently nearing completion looking at the effect of ALCAR on neuronal conduction along the visual pathways in patients with chronic LHON and disease duration of more than two years (http://apps.who.int/trialsearch/trial.aspx?trialid=EUCTR2009-016982-26-IT, accessed 28th of August 2013).

2. GENE THERAPY
Gene replacement therapy for LHON is an attractive strategy given the easy anatomical accessibility of the RGC layer for direct manipulation. However, the double-membrane nature of mitochondria presents a formidable series of technical challenges that need to be overcome. First and foremost, a highly efficient vector is needed to penetrate the relatively impermeable inner mitochondrial membrane and to allow a sufficient number of mitochondria to be transfected in order to achieve the desired gene replacement effect. A possible solution is to bypass the mitochondrial genome altogether by using an elegant alternative approach that relies on the nuclear allotropic expression of the gene of interest.81 The relevant mtDNA gene can be efficiently transfected into the nuclear compartment with an adeno-associated virus (AAV) vector after it has been reconfigured to fit the slightly different coding system operating within the nuclear genome. This hybrid nuclear-encoded protein has also been engineered with a specific targeting sequence to facilitate its efficient import into mitochondria, thereby compensating for the missing or dysfunctional mitochondrial protein. The potential of this gene therapy approach in rescuing the disease phenotype was first demonstrated in m.11778G>A LHON cybrids.82 The ability to rescue RGCs and improve visual function was subsequently confirmed in vivo by two independent research groups working on LHON rodent models expressing mutated ND4 (m.11778G>A) complex I subunits.83, 84 These groundbreaking experiments are paving the way for more advanced studies involving primates, but a note of caution is required here given the ongoing debate as to whether the imported wild-type ND4 subunit actually integrates into the native complex I to produce a stable functional unit within the inner mitochondrial membrane.85, 86 Proof-of-principle has also been demonstrated for two other forms of gene therapy based on nuclear allotropic expression. One strategy involves the transfection of the nuclear genome with the neuroprotective SOD2 gene packaged into an AAV vector.87 The over-expression of the superoxide dismutase ROS scavenger in m.11778G>A LHON cybrids suppressed apoptosis and resulted in increased cell survival.87 The consolidation of the cell’s antioxidant defences could therefore prove a complementary approach to the replacement of the mutated gene product in LHON.
I to restore downstream electron transfer whilst at the same time suppressing ROS overproduction.\textsuperscript{88} 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.\textsuperscript{88}

Despite the technical difficulties of directly introducing genetic material into mitochondria, two recent studies have suggested that this could be achieved using two very different genetic engineering approaches. In one study, whole circular mtDNA molecules isolated from healthy human donors were complexed with human recombinant TFAM and this genetic construct was able to gain direct entry into cells. When applied to m.11778G>A LHON cybrids, this novel strategy was able to restore cellular respiration and ATP synthesis by promoting mitochondrial biogenesis.\textsuperscript{89} In the other study, a mitochondrial targeting sequence was attached to the capsid element of an AAV vector carrying the replacement ND4 subunit gene.\textsuperscript{90} This additional tag allowed the direct introduction of the wild-type ND4 gene into the mitochondrial compartment, leading to the successful rescue of the pathological phenotype in both m.11778G>A LHON cybrids and a mouse model manifesting optic atrophy secondary to allotopic expression of the human ND4 mutation.\textsuperscript{90} The introduced ND4 gene construct is thought to remain episomal, which should prevent the mutagenic disruption of the endogenous genes contained within the host mitochondrial genome.\textsuperscript{91} Although direct mitochondrial gene delivery offers exciting therapeutic potential, these potentially groundbreaking findings should be viewed as preliminary until they have been independently replicated by other research groups.

Gene therapy for DOA is being contemplated for affected patients harbouring truncating OPA1 mutations that result in haploinsufficiency. The strategy being developed involves the intravitreal injection of an AAV vector to deliver the wild-type OPA1 gene to surviving RGCs in a mouse model of DOA carrying the exon 27 (c.2708-2711delTTAG) mutation.\textsuperscript{92} Although conceptually simpler than mitochondrial gene therapy, further methodological refinements are needed to achieve stable transfection in a sufficient proportion of RGCs to result in a clinically meaningful effect (Dr Guy Lenaers, University of Montpellier, France, personal communication). It is important to emphasise that all the gene therapy approaches being envisaged for LHON and DOA are still at an early experimental stage of development and further evidence of their safety and efficacy is needed before the initiation of human trials can be contemplated.

3. STEM CELLS

The therapeutic potential of stem cells is being investigated for a wide range of genetic eye disorders and patients with mitochondrial optic neuropathies will frequently enquire with their clinicians whether they are likely to benefit from this form of treatment.\textsuperscript{93} Various poorly monitored “stem cell institutes” worldwide are promoting the use of non-validated experimental protocols, and patients with LHON and DOA need to be carefully advised before embarking on multiple expensive courses of treatment with the possible associated biological risks. In sharp contrast to this unregulated parallel market, there are a number of well-established research programmes that are rigorously assessing the possible application of stem cell technology for optic nerve disorders.\textsuperscript{93, 94} Two main paradigms are being explored, namely the generation and transplantation of RGCs, or the use of specific stem cell populations to generate trophic factors that promote RGC survival.\textsuperscript{93, 94} The technique for generating and purifying mature RGCs from embryonic stem cells or induced pluripotent stem cells is still in its infancy. Another major complicating factor is how to integrate these differentiated RGCs into the retina and then force them to make the right topographical connection. At least in the short term, it is more likely that human-derived RGCs will provide the ideal tool for drug screening and understanding the basic mechanisms regulating RGC physiology in both health and disease states.\textsuperscript{68, 95}

A proportion of patients with LHON will experience partial visual recovery, mostly within one year of being affected, but sometimes several years after the onset of the disease. It is therefore highly likely that a subpopulation of RGCs that survived the initial massive wave of apoptosis remain in a state of suspended animation awaiting two possible fates: a final push towards apoptosis or a gradual recovery of cellular function. These surviving RGCs are being targeted by oral neuroprotective agents, but mesenchymal stem cells are also an interesting modality based on promising data from experimental glaucoma and optic neuritis studies.\textsuperscript{68, 95} Autologous mesenchymal stem cells can be isolated from bone marrow isolates and they secrete several diffusible neurotrophic factors that are thought to promote neuronal survival in adverse metabolic and excitotoxic environments. Rather encouragingly, the injection of mesenchymal stem cells was well tolerated in a small proof-of-concept study of ten patients with secondary progressive MS.\textsuperscript{96} Although not definitive, there was a suggestion of structural, functional, and physiological improvement in some visual endpoints suggestive of a neuroprotective effect. If confirmed, a similar strategy is entirely conceivable to halt or slow down the irreversible loss of RGCs in LHON and DOA.

4. PREVENTION OF GERMLINE TRANSMISSION

\textit{In vitro} fertilisation (IVF) techniques are currently being developed to prevent female carriers of child-bearing age from transmitting pathogenic mtDNA mutations to the next generation. Two different IVF options have been proposed, namely pronuclear transfer and metaphase II spindle transfer, to generate the so-called “three-parent embryos” devoid of mutant mtDNA molecules.\textsuperscript{97} The aim of both techniques is to transfer the parental nuclear genetic material (devoid of the mother’s mutant mtDNA molecules)
into a donor cytoplast containing a normal wild-type mtDNA population. In the pronuclear technique, the male and female pronuclei are transferred post-fertilisation into a mitochondrial donor zygote harbouring wild-type mtDNA. The alternative approach involves the transplantation of metaphase II spindles between unfertilised oocytes followed by intracytoplasmic sperm injection fertilisation. There seems to be no significant carryover of mutant mtDNA with both IVF approaches and further work is currently underway in higher primates. Preventing the germline transmission of pathogenic mtDNA mutations is an exciting development, but a stringent series of safety tests will first need to be fulfilled. A significant proportion of manipulated zygotes showed abnormal development and other iatrogenic genetic consequences must be considered, including an increased risk of aneuploidy and epigenetic abnormalities. The manipulation of human embryos also entails a number of important legal, religious and ethical ramifications that will need to be addressed. The United Kingdom has been at the forefront of this important debate and an expert panel was recently convened by the Human Fertilisation and Embryology Authority (HFEA) to review the fertilisation methods that could be used to prevent mitochondrial disease. This public consultation indicated positive support for mitochondria replacement to take place, but subject to strict safeguards and careful regulation being adhered to (https://www.gov.uk/government/news/innovative-genetic-treatment-to-prevent-mitochondrial-disease, accessed 28th of August 2013).

CONCLUSION

The pace of translational research for mitochondrial optic neuropathies is entering an exciting accelerated phase providing renewed hopes to patients and their families that the inexcorable visual loss associated with this group of disorders can at least be halted. We still need a better understanding of the pathological mechanisms underpinning the preferential vulnerability of RGCs in LHON and DOA, but these more basic studies are now proceeding in parallel with major national and transnational initiatives aimed at drug development and early phase clinical trials. The establishment of patient cohorts will provide a strong base to launch properly designed randomised placebo-controlled trials and the prospective collection of long-term natural history data will be essential to identify the best outcome measures to detect a treatment benefit. The challenges of identifying and validating treatments for relatively rare inherited optic nerve disorders remain daunting, but twenty-five years after the birth of mitochondrial genetic medicine, tractable solutions are finally emerging.

CME ANSWERS

1. True  
2. False  
3. False  
4. False  
5. True

REFERENCES


71. Wong A, Cortopassi G. MtDNA mutations confer cellular sensitivity to oxidant stress that is partially rescued by calcium depletion and cyclosporin A. Biochemical and Biophysical Research Communications 1997; 239(1): 139-145.
5:00 p.m. - 5:15 p.m. Angela M. Herro, MD
Retinal Ganglion Cell Injury Precedes RNFL loss
In Acute Optic Neuritis

5:15 p.m. - 5:30 p.m. Fiona Costello, MD, FRCP
The Impact of Vitamin D Status on Recovery from Optic Neuritis

5:30 p.m. - 5:45 p.m. Christian J Lueck, PhD, FRACP
Effects of Stimulating Melanopsin-Containing Retinal Ganglion Cells in Migraine Patients using Multifocal Objective Pupillometry

5:45 p.m. - 6:00 p.m. Robert C. Sergott, MD
Progression of Plaques in Retina with Dementia in Alzheimer’s Disease

6:00 p.m. - 6:15 p.m. Sidney M. Gospe III, MD, PhD
Anatomic and Visual Outcomes of Pediatric Idiopathic Intracranial Hypertension

6:15 p.m. - 6:30 p.m. Shaobo Lei, MD
Full-Field Chromatic Pupillometry in the Assessment of the Post-Illumination Pupil Response Driven by Melanopsin-containing Retinal Ganglion Cells

6:30 p.m. - 6:45 p.m. David E. Newman-Toker, MD, PhD
Small Posterior Fossa Strokes Causing Severe Vertigo: Anatomic Distribution and Clinical Features of the “Lacunar” Acute Vestibular Syndrome

6:45 p.m. - 7:00 p.m. Hadas Kalish, MD
Another reason for pediatricians to counsel against obesity; childhood body mass index above the 85th percentile is associated with a five-fold risk for recurrence of pediatric idiopathic intracranial hypertension
Monday, March 3, 5:00 - 5:15 p.m.

Retinal Ganglion Cell Injury Precedes RNFL loss In Acute Optic Neuritis

Angela M Herro, John Guy, Veeral Shah, Vittorio Porciatti, Byron L Lam

Bascom Palmer Eye Institute, Miami, FL, USA

Introduction:
Studies in the experimental autoimmune encephalomyelitis (EAE) animal model of MS have shown that RGC injury is an early event in the neurodegeneration of EAE and occurs before transection of axons. Here we tested for RGC injury in patients with acute ON using pattern electroretinogram (PERG) and ganglion cell layer analysis (GCL).

Methods:
After obtaining informed consent and IRB approval we prospectively measured visual acuity, visual field mean defect, RNFL and GCL thickness and RGC function using PERG in 11 patients diagnosed with acute ON within 2 weeks of visual loss.

Results:
At baseline average ETDRS acuity was 51 letters (~20/100) in affected eyes and 87 letters (~20/20) in unaffected eyes. Average RNFL was 118 µm in affected eyes and 96 µm in unaffected eyes with average GCL of 76 µm and 77 µm respectively. Baseline PERG amplitudes averaged 51% of normal in affected eyes and 75% of normal in unaffected eyes (p=0.002) and timing was significantly delayed in affected eyes compared to unaffected ones (p=0.039). In the 5 eyes with 3 month follow-up there is a strong correlation between % of age-specific normal amplitude at baseline and acuity in the affected eye at 3 months (r=0.98, p=0.004). The GCL analysis also showed a decline at 3 months with affected eyes averaging 55 µm and unaffected eyes maintaining 74 µm. Comparisons of the PERGs of ON to affected G11778A LHON subjects and fellow unaffected eyes of ON to asymptomatic LHON carriers showed similar reductions in amplitude and timing implicating mitochondrial injury in both disorders.

Conclusions:
The loss in PERG amplitude and delay in phase implicate RGC injury as an early event in acute ON. Furthermore, the GCL is a more sensitive marker of cell death and is reduced before the RNFL. The PERG may predict visual recovery, perhaps allowing early interventions to prevent neurodegeneration and disability in ON and MS.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Monday, March 3, 5:15 - 5:30 p.m.

The Impact of Vitamin D Status on Recovery from Optic Neuritis

Fiona Costello1,3,4, Jodie Burton1,2,4, Jessie Trufyn1,4

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Introduction:
Optic neuritis (ON) is a common manifestation of multiple sclerosis (MS), and serves as a model to study the effects of inflammatory and degenerative activity in this central nervous system(CNS) disorder. Vitamin D insufficiency is a risk factor for MS and ameliorates inflammation. The objective of this study is to study the relationship between vitamin D status and ON recovery, by using optical coherence tomography (OCT) measures of retinal integrity. The hypothesis is that vitamin D sufficiency (25(OH)D > 80 nmol/L) is associated with better OCT outcomes. Primary outcomes include retinal nerve fiber layer (RNFL) thickness, inter-eye differences (IED) in RNFL thickness and ganglion cell layer (GCL) thickness at 6 months and at baseline between vitamin D sufficient and insufficient groups.

Methods:
In this prospective cohort study, patients with acute ON are undergoing OCT, full field visual evoked potential (VEP), and ophthalmic testing at baseline, 3-months, 6-months, and 12-months. Serum 25(OH)D testing is performed at baseline and 6-months.

Results:
To date, 49/50 patients have been enrolled (36 females). Sixty-eight percent of patients have been vitamin D insufficient at baseline, which has been associated with more optic disc edema and increased mean RNFL thickness (131 vs 106 μm, p=0.14), macular volume (10.2 vs 9.8 mm³, p=0.04) and IED in RNFL in acute ON. At month 6, IED in GCL thickness has been greater in vitamin D insufficient patients (13 vs 8 μm). Regardless of baseline RNFL thickness or vitamin D level, men have had significantly lower 6 month RNFL values (70 vs 81 μm, p=0.03) and greater IED in RNFL and GCL measures (20 vs 8 μm for both, p=0.012 and p=0.008 respectively) versus women.

Conclusions:
Vitamin D insufficiency is associated with worse optic disc edema in acute ON. Male gender is an independent risk factor for worse recovery at 6-months. Ganglion layer measures at 6-months in sufficient patients suggests a possible neuroprotective role for vitamin D.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Monday, March 3, 5:30 - 5:45 p.m.

Effects of Stimulating Melanopsin-Containing Retinal Ganglion Cells in Migraine Patients using Multifocal Objective Pupillometry

Christian J Lueck1,2, Eman N Ali3, Ted Maddess3, Corinne F Carle3

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Introduction:
Recent evidence has linked intrinsically-photosensitive retinal ganglion cells (ipRGCs) to photosensitivity in migraine. It is possible that multifocal pupillographic objective perimetry (mfPOP) might exacerbate migraine and the response to mfPOP might be different in migraineurs. This study was designed to establish the effects of stimulating ipRGCs using mfPOP on migraine severity parameters and pupillary response characteristics

Methods:
A randomized case-control crossover study tested migraineurs and normal controls using mfPOP utilising a blue protocol (BP) to stimulate ipRGCs and a yellow protocol (YP) to stimulate cone photoreceptors. Migraine diaries were obtained a week prior to, and a week after, each testing. Responses were analysed according to response time-to-peak and standardised amplitude (AmpStd). The percentage area under the receiver operator characteristic (%AUC) was used to predict migraine status.

Results:
38 migraineurs (41.97 ± 16.02 years, 23 females) and 24 normal controls (39.17 ± 14.84 years, 14 females) were enrolled. There was no significant difference in the mean number of migraine attacks/subject in the weeks prior to, or following, testing with either protocol. The AmpStds (in dB) were lower for migraineurs than controls: 9.04 ± 11.2 (mean ± SE) vs. 9.48 ± 10.4 for BP, and 10.74 ± 4.96 vs. 11.4 ± 5.23 for YP, though these differences did not reach statistical significance. A migraine attack occurring in the 2 weeks prior to testing had a significant independent effect in lowering AmpStd while a history of triptan use increased AmpStd. Time-to-peak was shorter in YP, probably related to differences in the stimuli. The %AUC was highest for AmpStd (77.2% for YP and 84.6% for BP).

Conclusions:
Stimulating ipRGCs did not affect migraine severity. Pupillary response characteristics were influenced by recent attacks of a migraine and a history of triptan use.

Financial Disclosures: Christian Lueck, Eman Ali: None. Ted Maddess received personal compensation from EyeCo for consulting services and received share options from Seeing Machines Pty. Corinne Carle and Ted Maddess are authors on a patent application that is under license to Seeing Machines Inc., which produces the pupil perimeter used in this research.

Grant Support: None.
Monday, March 3, 5:45 - 6:00 p.m.

PROGRESSION OF PLAQUES IN RETINA WITH DEMENTIA IN ALZHEIMER’ S DISEASE

ROBERT C. SERGOTT2 UMUR A. KAYABASI1

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

Introduction:
Optical coherence tomography (OCT) and fundus autofluorescence (FAF) examinations provide us with important information about neurodegenerative diseases. Since the optic nerve and retina share similar structures with the brain, any defect detected by OCT and/or FAF may be related to a disease in the nervous system.

Methods:
We examined 10 patients with dementia due to Alzheimer's disease (AD) and 10 other patients with a family history of AD, but none of them had dementia. All the patients were given oral curcumin (100 mg/kg) one day before the second examination. The FAF examinations were performed after which OCT was done through the abnormal (hyperfluorescent or hypofluorescent) spots or regions. Results of the two groups were compared in a masked fashion by two neuro-ophthalmologists with significant experience interpreting OCT and FAF images. Important differences between the images of the two groups were examined.

Results:
The patients with dementia had significant shining dots and regions mostly in the ganglion and nerve fiber layers whereas only sporadic plaque-like lesions were detected in the second group. As the patients demonstrated more cognitive problems, the greater was the chance of discovering plaques within the retina. Hypofluorescent lesions on FAF were more likely to be detected in the first group because atrophy of the retina layers became more evident. Also, the chances to image larger plaques increased in the hypofluorescent retinal regions.

Conclusions:
We believe that detection of the plaques early in the disease, before the onset of dementia or very early in the course of the disease, is extremely important. Retina examination with FAF and OCT may be a valuable supplement to the neurological examination in neurodegenerative diseases. The difference in images between hypofluorescent and hyperfluorescent plaques may be explained by the stage of the disease.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Monday, March 3, 6:00 - 6:15 p.m.

Anatomic and Visual Outcomes of Pediatric Idiopathic Intracranial Hypertension

Sidney M. Gospe III1, M. Tariq Bhatti, Mays A. El-Dairi

Duke University Department of Ophthalmology, Durham, NC, USA

Introduction:
There is a paucity of information in the literature describing the risk factors for vision loss in pediatric idiopathic intracranial hypertension (IIH). We investigate the final vision, visual fields and optical coherence tomography (OCT) outcome in children and teenagers with papilledema caused by IIH and the risk factors associated with worse outcomes.

Methods:
This is an ongoing study of patients with IIH aged ≤21 years presenting to the pediatric neuro-ophthalmology clinic since 2010. Inclusion criteria included normal neuro-imaging, intracranial pressure >25 cm H2O, normal cerebrospinal fluid analysis, and improvement of headaches and/or optic disc swelling following lumbar puncture and treatment. Age, gender, pubertal status, and hemoglobin on presentation were noted for each patient. Disc photos on presentation and final Spectralis (Heidelberg, Germany) Spectral Domain OCT (SD-OCT) images of the optic nerve head (ONH) and macula were analyzed by a blinded reader and correlated with final visual outcomes as determined by acuity and perimetry.

Results:
Forty eyes of 19 prepubertal (13 male, 6 female, 7.4±3.1 years) and 21 pubertal (1 male, 20 female, 16.6±2.4 years) children were included. Seven eyes had visual field deficits (1 central/paracentral, 4 peripheral, and 2 with severe constriction encroaching on central vision). High grade disc edema on presentation (≥3 on Frisén scale) was the only significant predictor of adverse visual outcome (likelihood ratio (LR)=13.1, p=0.0003) and photoreceptor damage (LR=10.2, p=0.006). Photoreceptor damage on final OCT was associated with central/paracentral scotomas (LR=17.5, p=0.0002). Twenty of 33 eyes (61%) demonstrated buried ONH drusen on enhanced-depth imaging.

Conclusions:
High grade ONH edema is associated with adverse outcomes. Photoreceptor loss can be detected by SD-OCT and is associated with central/paracentral scotomas. Finally, a majority of patients also had ONH drusen. Additional longitudinal studies with a larger number of patients investigating the long term significance of these findings are warranted.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Monday, March 3, 6:15 - 6:30 p.m.

Full-Field Chromatic Pupillometry in the Assessment of the Post-Illumination Pupil Response Driven by Melanopsin-containing Retinal Ganglion Cells

Shaobo Lei¹, Mano Mano Chandrakumar, Herb Goltz, Agnes Wong

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Introduction:
Post-illumination pupil response (PIPR) is produced by the intrinsically photosensitive melanopsin-containing retinal ganglion cells (ipRGCs), and can be measured by chromatic pupillometry. While chromatic pupillometry holds promise as a new diagnostic and outcome measurement tool to assess ipRGC function, current testing protocols use central-field stimulation and require a very bright light of long duration which can be difficult for some subjects. We test the hypothesis that a more robust PIPR can be induced with full-field blue light stimuli of shorter duration and lower intensity than with existing protocols.

Methods:
Ten visually-normal adult subjects were tested. Pupil response was recorded with an infrared eye tracker. Using a Ganzfeld system, full-field red and blue stimuli were presented in a darkened room. In experiment 1 (intensity trials), PIPR was induced using 1-second full-field stimuli of increasing intensities from 0.1 to 400 cd/m² (11 steps). For comparison with a previously published protocol, a 60°×90° central-field blue stimulus of 400 cd/m² was also presented for 1 second. In experiment 2 (duration trials), PIPR was induced using 100 and 400 cd/m² full-field stimulus of increasing duration from 4 to 1000 ms (10 steps).

Results:
PIPR increased monotonically with increasing stimulus intensity. Full-field stimulation using blue light at 400 cd/m² intensity induced significantly more sustained PIPR than central-field stimulation. In addition, PIPR increased as the duration of stimulus increased from 4-200 ms; however, no further increase in PIPR was observed when the duration increased from 400-1000 ms.

Conclusions:
Compared to existing central-field protocols, robust PIPR can be induced with a full-field protocol with lower intensity and shorter duration. This study is the first to demonstrate that saturating PIPR can be induced in vivo with a strong blue flash of only a few hundred milliseconds. This refined protocol will improve the recording quality and the subjective experience of current pupillometry testing.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Small Posterior Fossa Strokes Causing Severe Vertigo: Anatomic Distribution and Clinical Features of the “Lacunar” Acute Vestibular Syndrome

David E. Newman-Toker², Ali S. Saber Tehrani¹, Georgios Mantokoudis², Jorge C. Kattah¹, John H. Pula¹, Deepak Nair¹, Ari Blitz³, Sarah Ying³, Daniel F. Hanley³, David S. Zee²

¹Illinois Neurologic Institute and the University of Illinois College of Medicine at Peoria/Department of Neurology, Peoria, IL, USA, ²Johns Hopkins University School of Medicine/Department of Neurology, Baltimore, MD, USA, ³Johns Hopkins University School of Medicine/Department of Radiology, Baltimore, MD, USA

Introduction:
Small brainstem and cerebellar strokes affecting central vestibular pathways may present clinically with acute vestibular syndrome (AVS). Careful study of acute sub-centimeter lesion locations may help elucidate structure-function relationships. We sought to describe the frequency, anatomic distribution, and clinical manifestations of small posterior fossa strokes in patients with AVS.

Methods:
Prospective cross-sectional study of consecutive AVS patients (acute vertigo or dizziness, nystagmus, nausea/vomiting, head-motion intolerance, unsteady gait) with at least one stroke risk factor from 1999-2011 at a single stroke referral center. Patients underwent HINTS examination (Head Impulse, Nystagmus, Test-of-Skew), neuroimaging to confirm diagnoses (almost all by MRI), and repeat MRI in those with initially normal imaging but clinical signs of a central lesion. We identified all patients with diffusion weighted imaging (DWI) strokes <10mm in axial diameter. We sought to identify the principal vestibular structures involved.

Results:
Of 190 high-risk AVS presentations including 105 strokes, we found sub-centimeter lesions in 15 patients (median age 64, range 41-85). Structures involved were inferior cerebellar peduncle (9), medial vestibular nucleus (1), both (2), root entry zone of 8th nerve (1), nodulus (1), and interstitial nucleus of Cajal (1). Initial MRIs were falsely negative in 53% (n=8/15) of those with sub-centimeter strokes compared to 7.8% (n=7/90) of those with larger strokes (Fisher’s exact p<0.001). In 93% (n=14/15), the HINTS exam suggested a central localization. Non-lacunar stroke mechanisms were responsible in 47% (n=7/15 cases), including 2 vertebral dissections, 4 vertebral occlusions, and 1 cardiac embolism.

Conclusions:
Small strokes involving vestibular projections within the brainstem or cerebellum can produce AVS. The HINTS battery identifies these patients with greater accuracy than early MRI with DWI, which is falsely negative in more than half. Non-lacunar mechanisms are often the cause, suggesting greater risk than might be assumed for patients with such small infarctions.

Financial Disclosures: Authors have received research support from GN Otometrics (loaned video-oculography goggles).

Grant Support: None.
Monday, March 3, 6:45 - 7:00 p.m.

Another reason for pediatricians to counsel against obesity; childhood body mass index above the 85th percentile is associated with a five-fold risk for recurrence of pediatric idiopathic intracranial hypertension

Hadas Kalish1,2,3, Irena Serov2,3, Ruti Sella2,3, Gabriel Chodick3,4, Moshe Snir2,3,5

1Rabin Medical Center/Neuro-Ophthalmology Unit, Petah Tikva, Israel, 2Rabin Medical Center/Ophthalmology, Petah Tikva, Israel, 3Tel Aviv University/Sackler School of Medicine, Tel Aviv, Israel, 4Department of Epidemiology and Preventive Medicine/Sackler School of Medicine, Tel Aviv, Israel, 5Schneider Childrens Medical Center of Israel/Pediatric Ophthalmology, Petah Tikva, Israel

Introduction:
Pediatric idiopathic intracranial hypertension (IIH) is treated by a multi-disciplinary team; neurologists, neuro-ophthalmologists and pediatricians. Obesity is an important risk factor for IIH in adults and in post-pubertal/adolescent children. In prepubertal children, however, IIH is less closely associated with obesity. Parents of children with IIH often enquire about the prognosis and recurrence rate of their child’s disease. Recurrence seems to occur in approximately 20% of children. Data examining whether childhood overweight increases the risk of IIH recurrence is lacking.

Methods:
A long-term follow-up study of children younger than 18 years with IIH was performed to investigate the correlation between overweight [body-mass-index (BMI) ≥85th percentile] and the rate of IIH recurrence and visual loss. Children with non-idiopathic and drug-induced intracranial hypertension were excluded. The rate of recurrence was determined using a Kaplan-Meier survival curve for IIH recurrence, analyzed by BMI percentile groups. Recurrence was defined as a new onset of disease symptoms or papilledema occurring after remission and remeeting the modified Dandy criteria.

Results:
Long-term neuro-ophthalmological follow-up and body weight measurements were available for 43/45 patients (96%), with an average follow-up of 6.7 years (SD 3.6 years). Mean age of the 43 patients at diagnosis was 11 years, SD 4.5 years. Fifty-six percent had a body-mass-index ≥85th percentile. After ten years, the cumulative incidence of recurrence among children with a body-mass-index of less than the 85th percentile was 11%, compared to 57% among those with body-mass-index ≥85th percentile (Log-rank test p=0.04).

Conclusions:
The overall risk for long-term IIH recurrence in children is ~20%. Following weight stratification, the risk for IIH recurrence is five-fold higher (57%) in children with a body-mass-index ≥85th percentile, compared to children with healthy weight (11%). This study calls for Pediatricians to play a crucial role in counseling families towards weight-control as a means of decreasing the risk of recurrence of IIH.

Financial Disclosures: The authors had no disclosures.

Grant Support: None
Tuesday, March 4, 2014

6:00 a.m. – 6:45 a.m.  Yoga Class  Gazebo
6:30 a.m. – 12:30 p.m.  Registration  Rio Mar Foyer
6:30 a.m. – 7:30 a.m.  Breakfast  Rio Mar 6-10/Carribbean
6:30 a.m. – 12:15 p.m.  Exhibits  Rio Mar Foyer
6:30 a.m. – 7:30 a.m.  JNO Editorial Meeting  Parrot
6:00 a.m. – 7:30 a.m.  YONO Committee Meeting  Pelican
7:00 a.m. – 7:30 a.m.  Practice Management Career Support Subcommittee Meeting  Seagull
7:00 a.m. – 7:30 a.m.  CME Committee Meeting  Board Room
7:30 a.m. – 12:00 p.m.  SCIENTIFIC PLATFORM PRESENTATIONS: SESSION II [3.75 CME]  Rio Mar 1-5
9:15 a.m. – 9:30 a.m.  Update: The Journal of Neuro-Ophthalmology  Rio Mar 6-10
  Lanning Kline, MD, Editor-in-Chief & Jason Roberts, PhD, Managing Editor
9:30 a.m. – 10:00 a.m.  Coffee Break  Rio Mar Foyer
12:15 p.m. – 5:00 p.m.  Rainforest Tour  Depart from El Yunque Foyer
12:15 p.m. – 6:00 p.m.  Old San Juan Historical Tour  Depart from El Yunque Foyer
6:00 p.m. – 9:30 p.m.  POSTER SESSION [3.5 CME]  Rio Mar 6-10/Carribbean

Guests are welcome.
Event is complimentary for attendees but guests must purchase tickets.
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<tr>
<th>Time</th>
<th>Speaker</th>
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<tr>
<td>7:30 a.m. - 7:45 a.m.</td>
<td>Byron L. Lam, MD</td>
<td>Leber Hereditary Optic Neuropathy G11778A</td>
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<td>Gene Therapy Clinical Trial: Stability of Clinical Parameters of Carriers in Preparatory Phase</td>
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<td>7:45 a.m. - 8:00 a.m.</td>
<td>Kenneth S Shindler, MD, PhD</td>
<td>HE3286 Suppression of Experimental Optic Neuritis</td>
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<td>8:00 a.m. - 8:15 a.m.</td>
<td>Y. Joyce Liao, MD, PhD</td>
<td>In Vivo and In Vitro Imaging of RGC Axonal Transport and Degeneration Following Experimental Anterior Ischemic Optic Neuropathy</td>
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<td>8:15 a.m. - 8:30 a.m.</td>
<td>Ajay E. Kuriyan, MD, MS</td>
<td>Orbital Fibroblasts From Thyroid Eye Disease Patients Differ In Proliferative And Adipogenic Responses Depending On Disease Sub-type</td>
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<td>8:30 a.m. - 8:45 a.m.</td>
<td>Robert A. Avery, DO</td>
<td>Immunologic Biomarkers of Ocular Myasthenia Gravis in Children</td>
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<td>8:45 a.m. - 9:00 a.m.</td>
<td>Audrey Fel, MD</td>
<td>Minocycline as a Neuroprotective Agent in a Rodent Model of NAION</td>
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<td>9:15 a.m. - 9:30 a.m.</td>
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(Platform Session II Continued)

10:00 a.m. - 10:15 a.m.  Thomas Meier, PhD  
Clinical experience with Idebenone (Raxone®) in the treatment of patients with Leber’s Hereditary Optic Neuropathy (LHON)

10:15 a.m. - 10:30 a.m.  Patrick Sibony, MD  
Peripapillary RPE-layer shape in Idiopathic Intracranial Hypertension: before and after treatment

10:30 a.m. - 10:45 a.m.  Gena Heidary, MD, PhD  
Non-invasive Assessment of Intracranial Pressure Using Otoacoustic Emissions in Pediatric Patients with Idiopathic Intracranial Hypertension (IIH)

10:45 a.m. - 11:00 a.m.  Scott L. Stafford, MD  
Gamma Knife Radiosurgery for Pituitary Adenomas <2mm From The Anterior Visual Pathway(AVP)

11:00 a.m. - 11:15 a.m.  Mark Kupersmith, MD  
Retinal Ganglion Cell Layer Thinning within One Month of Presentation for Non-arteritic Anterior Ischemic Optic Neuropathy and Optic Neuritis

11:15 a.m. - 11:30 a.m.  Norah S. Lincoff, MD  
Investigating Regional Grey Matter as Well as White Matter Atrophy in MS—Retinal Nerve Fiber Layer Thickness and Thalamus Pathology in Multiple Sclerosis Patients

11:30 a.m. - 11:45 a.m.  Randy H. Kardon, MD, PhD  
A New Automated 20 Second Pupillographic Test to Quantify the Log Unit Relative Afferent Pupillary Defect and its Relationship to Retinal Ganglion Cell Thickness

11:45 a.m. - 12:00 p.m.  Sashank Prasad, MD  
Peduncular Hallucinosis: A lesion-based network analysis
Leber Hereditary Optic Neuropathy G11778A Gene Therapy Clinical Trial: Stability of Clinical Parameters of Carriers in Preparatory Phase

Byron L. Lam1, William J. Feuer, Vittorio Porciatti, Ruth Vandenbroucke, Joyce Schiffman, Fawzi Abukhalil, Potyra R. Rosa, Sophia Cuprill-Nilson, John Guy

Bascom Palmer Eye Institute, University of Miami, Miami, FL, USA

Introduction:
The preparatory phase of the LHON gene therapy trial aims to characterize affected G11778A patients and carriers for the planned trial that will utilize “allotopic expression” via an adeno-associated virus vector. This report focuses on the natural history of visual outcome measures in asymptomatic G11778A carriers.

Methods:
Forty-five asymptomatic carriers underwent ocular examination every 6 months for one or more follow-up visits (6 to 36 months) between September 2008 and March 2012. Tests included visual acuity, automated visual fields (HVF 24-2), pattern electroretinogram (PERG) and spectral-domain OCT (Cirrus) to evaluate peripapillary retinal nerve fiber layer (RNFL) thickness and macular Ganglion Cell Layer (GCL) thickness. All measurements were averaged for the two eyes of each carrier. The strength of correlation was assessed with Pearson’s r.

Results:
Baseline visual acuity and visual field were normal. Visual acuity, visual fields, RNFL thickness, and GCL thickness were stable over time. In contrast, mean PERG amplitudes dropped progressively by ~34% from baseline to 36 months (p<0.001). Baseline macular GCL thickness correlated with PERG amplitudes at baseline and during follow up from 6 to 18 months with r ranging from 0.38 to 0.65 (all p<0.05), but not significantly from 24 to 36 months which may be related to reduced sample size. Baseline RNFL showed weaker correlations with PERG amplitude at each time point with r ranging from 0.21 (p=0.27) to 0.45 (p=0.025). At each time point, correlations with GCL were stronger than correlations with RNFL. Correlations between RNFL and GCL were strong (r>0.65) and highly significant (p<0.001) at all time points.

Conclusions:
The correlation between PERG and baseline GCL thickness suggests abnormal structure and function of macular retinal ganglion cells in LHON carriers. If these findings are potential predictors of conversion to the affected state, they may have important implications to isolate a subset of carriers as candidates for therapy.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: Supported by National Eye Institute grant R24EY018600.
Introduction:
Optic nerve inflammation, demyelination and axonal loss are all prominent features of optic neuritis. While corticosteroids can hasten visual recovery in optic neuritis, no treatment is available to improve visual outcomes. HE3286 (17α-ethynyl-5-androstene-3β, 7β, 17β-triol), a synthetic derivative of a natural steroid, β-AET (5-androstene-3β, 7β, 17β-triol), exerts anti-inflammatory effects in several disease models, and has purported direct neuroprotective effects as well. The ability of HE3286 to suppress optic neuritis in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis was examined.

Methods:
EAE was induced in C57/Bl6 mice by immunization with myelin oligodendroglial glycoprotein peptide. Mice were treated daily with vehicle or 40 mg/kg HE3286 i.p. Visual function was assessed by optokinetic responses (OKR) at baseline and every 10 days until sacrifice 6 weeks post-immunization. Retinas and optic nerves were isolated. Inflammation was assessed by H&E staining, and demyelination was assessed by luxol fast blue staining of optic nerve sections. Retinal ganglion cells (RGCs) were immunolabeled with Brn3a antibodies to quantify RGC survival.

Results:
Progressive decreases in OKR occurred in vehicle-treated EAE mice, and HE3286 treatment significantly reduced the level of this vision loss. HE3286 also significantly attenuated the degree of inflammation and level of demyelination in EAE optic nerves as compared to nerves from vehicle-treated EAE mice. RGC loss was observed in eyes from both vehicle- and HE3286-treated EAE mice, with a trend toward increased RGC survival in the HE3286-treated mice.

Conclusions:
HE3286 suppresses inflammation and reduces demyelination during experimental optic neuritis, although neuroprotective effects of this treatment may be limited. Importantly, HE3286 treatment also preserves some RGC function. Results suggest HE3286 is a potential novel treatment for optic neuritis and MS that warrants further study.

Financial Disclosures: Co-author Clarence Ahlem is a full-time employee of Harbor Therapeutics, Inc., the company that produces the HE3286 compound that was tested in the preclinical animal studies in this abstract.

Grant Support: None.
Introduction:
Optic nerve and retinal ganglion cells (RGCs) degenerate following anterior ischemic optic neuropathy (AION), the most common acute optic neuropathy in those over 50-years-old. We previously reported on the acute thickening and chronic thinning of the inner retinal layers using spectral-domain optical coherence tomography analyses, which reflect progressive and irreversible loss of RGC axons after experimental AION. In this study, we further investigated the impact of ischemia on RGC axonal transport and degeneration.

Methods:
We induced experimental AION using photochemical thrombosis in adult mice (rose bengal 1.25 mM, frequency-doubled Nd:YAG laser, 400 μm, 50 mW power, 1 s, 15 spots). To measure axonal transport, we performed intravitreal injections of cholera toxin-B-A488 or MnCl₂ and tracked transport using histology or 7-Tesla magnetic resonance imaging (MRI), respectively. We analyzed RGC axonal degeneration using confocal scanning laser ophthalmoscopy, annexin-V-A488 labeling, optical coherence tomography, and retinal whole mount preparations. Statistical significance was measured using Wilcoxon signed-rank test.

Results:
One day after AION, there was severe impairment of anterograde axonal transport of cholera-toxin-B-A488 to the contralateral superior colliculus (N = 19 mice, P <0.0001) and the lateral geniculate nucleus (N = 10, P <0.01). This was confirmed in serial activity-dependent manganese-enhanced MRI of the optic nerve, superior colliculus, and lateral geniculate nucleus (N = 4, P <0.05). At three-to-five days after AION, confocal scanning ophthalmoscopy and histologic analyses showed a decrease in Thy1-YFP expression in the RGC axons. One week after AION, the degenerating RGC axons exhibited dramatic axonal labelling of annexin-V-A488, a marker of apoptosis (N = 14, P = 0.003), with a punctate pattern of distribution (5.8 ± 0.4 segments/100 μm or inter-segment interval of 20.1 ± 1.4 μm).

Conclusions:
Optic nerve head ischemia led to acute, severe impairment of anterograde axonal transport and progressive axonopathy associated with prominent annexin-V labelling of degenerating axons within one week. Dysfunctional axonal transport and subsequent axonal degeneration are important milestones following AION and may serve as potential targets of future therapies.

Financial Disclosures: The authors had no disclosures.

Grant Support: Career Award in Biomedical Sciences from the Burroughs Wellcome Foundation, the Weston Havens Foundation Grant, the Center for Biomedical Imaging at Stanford grant, the Medical Scholars Program and the Vice Provost Undergraduate Education Grant from Stanford University.
Tuesday, March 4, 8:15 - 8:30 a.m.

**Orbital Fibroblasts From Thyroid Eye Disease Patients Differ In Proliferative And Adipogenic Responses Depending On Disease Sub-type**

Ajay E. Kuriyan\(^1\), Collynn F. Woeller\(^3\), Charles W. O'Loughlin\(^1\), Richard P. Phipps\(^1,3,4\), Steven E. Feldon\(^1\)

\(^1\)University of Rochester School of Medicine and Dentistry/Flaum Eye Institute, Rochester, NY, USA, \(^2\)University of Miami/Bascom Palmer Eye Institute, Miami, FL, USA, \(^3\)University of Rochester School of Medicine and Dentistry/Department of Environmental Medicine, Rochester, NY, USA, \(^4\)University of Rochester School of Medicine and Dentistry/Lung Biology and Disease Program, Rochester, NY, USA

**Introduction:**

Thyroid Eye Disease (TED), an autoimmune process most frequently associated with Graves’ Disease, is the most common orbital disease. Orbital imaging can be used to classify TED patients as Type I (predominantly fat compartment enlargement) or Type II (predominantly extraocular muscle enlargement). In vitro, orbital fibroblasts (OFs) can be driven to differentiate into adipocytes or proliferate. We investigated whether Type I OFs undergo adipogenesis to a greater degree than Type II OFs, whereas Type II OFs undergo proliferation more than Type I OFs. We also studied the ability of cyclooxygenase (COX)-inhibitors to inhibit OF adipogenesis and proliferation.

**Methods:**

Type I, Type II, and control OFs were treated in vitro with an endogenous PPAR\(\gamma\) ligand to induce adipogenesis and transforming growth factor beta (TGF\(\beta\)) to induce proliferation. The AdipoRed assay, OilRedO staining, and flow cytometry were used to measure adipogenesis and the \([^{3}\text{H}]\)thymidine assay was used to measure proliferation. The ability of COX inhibition to inhibit OF adipogenesis and proliferation was assessed using the AdipoRed and \([^{3}\text{H}]\)thymidine assays, respectively.

**Results:**

Type I OFs accumulated approximately 5-times more lipid than Type II OFs (\(p<0.05\)) and 15-times more lipid than non-TED OFs (\(p<0.05\)). OilRedO staining and flow cytometry also showed increased adipogenesis in Type I OFs compared to Type II and non-TED OFs. Type II OFs incorporated approximately 2-times more \([^{3}\text{H}]\)thymidine than Type I OFs (\(p<0.05\)). COX inhibition significantly inhibited proliferation and adipogenesis in Type II OFs, but not Type I OFs.

**Conclusions:**

Our study demonstrated that OFs from TED patients have heterogeneous responses to pro-proliferative and pro-adipogenic stimulators in vitro corresponding to their different clinical manifestations. Additionally, we demonstrated a varying effect of COX-inhibition on Type I and Type II OF proliferation and adipogenesis.

**Financial Disclosures:** The authors had no disclosures.

**Grant Support:** TL1 RR024135, R01 EY023239, ES023032, Research to Prevent Blindness Unrestricted Grant, a research grant from the Rochester/Finger Lakes Eye & Tissue Bank
Tuesday, March 4, 8:30 - 8:45 a.m.

**Immunologic Biomarkers of Ocular Myasthenia Gravis in Children**

Robert A. Avery¹, Henry J. Kaminski², Yanchen Xie³, Natalie C. Glaug¹, Linda L. Kusner²

¹Children's National Medical Center, Washington, DC, USA, ²George Washington University, Washington, DC, USA, ³Capital Medical University, Beijing, China

**Introduction:**
Pediatric onset myasthenia gravis (MG) is profoundly understudied and development of novel therapeutics is compromised by the lack of biomarkers. The immunologic profile of children with ocular (OMG) has not been investigated. The purpose of this study was to determine the IgG subclass and cytokine profiles of pediatric patients with OMG and compare them to generalized (GMG) forms of MG and controls.

**Methods:**
Eleven children with MG (9 OMG, 2 GMG) and 4 control subjects provided serum samples. MG subjects had a mean age of 9.1 years (range 3.9 – 15.6) and a mean duration of symptoms of 3.2 years (range 0.16 – 6.3 years). Two subjects were on prednisone for less than 6 months. Acetylcholine receptor (AChR) specific IgG and subclass titers were determined by ELISA. Cytokine profiles were analyzed by Human Cytokine Array Panel A from R&D Systems.

**Results:**
All symptomatic OMG subjects (8 of 9) and GMG subjects demonstrated elevated AChR-IgG and AChR-IgG subclasses compared to control sera. GMG subjects had higher IgG titers and higher levels of granulocyte macrophage colony-stimulating factor (GM-CSF), chemokine (C-C motif) ligand 1 (CCL1), IL-1ra, CXCL10 and IL-17E compared to OMG subjects. All OMG and 1 GMG subject demonstrated reduction in C5/C5a complement levels. Total complement activity (CH50) was markedly reduced in all cases of symptomatic OMG.

**Conclusions:**
Pediatric OMG subjects have a unique immunologic profile whose cytokine levels suggest several potential points of immune system deregulation. Preferential involvement of extraocular muscles in OMG indicates a reduction of intrinsic complement inhibitors (Kaminski, 2004). Our findings suggest that future therapeutics for pediatric OMG could potentially include complement inhibitors.

**References:**


**Financial Disclosures:** The authors had no disclosures.

**Grant Support:** NIH CTSI (UL1TR000075)
Minocycline as a Neuroprotective Agent in a Rodent Model of NAION

Audrey Fel1,2, Nicolas Froger2, Manuel Simonutti2, Steven L. Bernstein3, Neil R. Miller4, Phuc LeHoang1, José-A Sahel2, Serge Picaud2, Michel Paques2, Valérie Touitou1,2

1Ophthalmology Pitié Salpêtrière Hospital, Paris, France, 2Institut de la vision, Paris, France, 3University of Maryland, Baltimore, MD, USA, 4Johns Hopkins University, Baltimore, MD, USA

Introduction:
Minocycline has demonstrated neuroprotective effects in animal models of glaucoma and optic nerve crush. We have investigated the neuroprotective properties of minocycline in a rodent model of NAION (rAION).

Methods:
Two groups of 6-week-old Long Evans male rats (n=8/group) had rAION induction in the right eye following intravenous rose bengal injection and laser-induced photothrombosis of the optic nerve head. The contralateral eye was used as an untreated control. Treated animals were intraperitoneally injected with minocycline 22mg/kg/day, beginning 3 days before induction and continued until euthanasia 30 days after induction. Control animals were treated with intraperitoneal injection of PBS for the same time period. Scanning laser ophthalmoscopy (SLO), fluorescein angiography (FA), and optical coherence tomography (OCT) were performed at 1, 8, 15 and 30 days to assess peripapillary retinal nerve fiber layer (PRNFL) thickness. After euthanasia, retinae were flat mounted and immunostained with Brn3a. Retinal ganglion cells (RGCs) were counted by stereology using an automatic method.

Results:
PRNFL thinning was observed in the PBS-treated group by SLO beginning day 8 post-induction of NAION. The PBS-injected group exhibited a 47.9% average RGC loss in induced right eyes compared with control left eyes (p<0.05). In contrast, RGC loss was not observed by SLO at 8 days in the minocyclin-treated group, and stereology in this group revealed a 9.58% loss of RGCs compared with a 47.9% loss in control animals (PBS-injected group). This difference in loss was statistically significant. (p<0.05).

Conclusions:
Minocycline appears to be an effective neuroprotective agent in a rodent model of NAION when administered before and after rAION induction. The mechanisms involved in this neuroprotective effect are still being evaluated. Nevertheless, minocycline could thus be a promising candidate, in the treatment of NAION.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Evolution of Macular Findings on Optical Coherence Tomography (OCT) in Papilledema

Mark J Morrow, Farah Villanueva, Fawzi Abukhalil

Harbor-UCLA Department of Neurology, Torrance, CA, USA

Introduction:
In eyes affected by papilledema, optical coherence tomography (OCT) quantifies retinal nerve fiber layer (RNFL) and optic nerve head (ONH) swelling. These improve over time with the underlying condition, sometimes revealing residual axonal loss. Parallel changes in the macula have not been well described. We used serial OCT to assess the evolution of macular anatomy in papilledema patients.

Methods:
We analyzed 40 eyes in 20 patients with optic disc edema associated with increased intracranial pressure (70% with idiopathic intracranial hypertension), using spectral-domain OCT. Serial testing was conducted over 3-28 months (mean, 11 months). We measured the thickness and volume of the 6mm-diameter central retina and its individual layers and of the peripapillary RNFL and ONH. We excluded eyes with peripapillary intraretinal fluid or unrelated retinal pathology.

Results:
Mean total macular volume (TMV) fell non-significantly from 8.38 to 8.23 mm³ in the group, usually in parallel with improvement of ONH and RNFL swelling. TMV fell by >0.08 mm³ in 25 eyes, but only rose by this value in 2 eyes. Macular change was chiefly attributable to thinning of the RNFL, retinal ganglion cell (RGC) and inner plexiform layers. Four eyes from 2 patients with severe peripapillary RNFL loss showed gradual thickening of the inner nuclear layer (INL) associated with the formation of perifoveal microcysts.

Conclusions:
Mild macular thinning often accompanies the resolution of ONH and RNFL swelling in papilledema. This pattern suggests a transition from distended to normal or atrophic RCC axons and cell bodies. Microcystic macular edema originating in the INL in 2 patients was similar to that seen in multiple sclerosis and neuromyelitis optica. We conclude that this finding may sometimes be caused by neuronal loss rather than inflammation.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Tuesday, March 4, 10:00 - 10:15 a.m.

Clinical experience with Idebenone (Raxone®) in the treatment of patients with Leber’s Hereditary Optic Neuropathy (LHON)

Thomas Meier², Constanze Gallenmüller¹, Günther Metz², Nick Coppard², Thomas Klopstock¹

¹Friedrich-Baur-Institute, Ludwig-Maximilians-University, Munich, Germany, ²: Santhera Pharmaceuticals, Liestal, Switzerland

Introduction:
An increasing body of evidence indicates that idebenone has therapeutic potential for the treatment of LHON. Data from a randomized placebo-controlled study (RHODOS) and from case reports and retrospective cohort studies demonstrate that patients with established vision loss may benefit from idebenone treatment and recover visual acuity (VA). This study reports VA outcomes for LHON patients with recent onset of vision loss who received idebenone (Raxone®) treatment under an ongoing Expanded Access Program (EAP).

Methods:
LHON patients with recent onset of vision loss were enrolled in a global EAP. Treating physicians who wished to enrol patients were provided with Raxone® (idebenone 150 mg tablets). Physicians were requested to report any safety issues and were encouraged to report VA outcomes in 3-monthly intervals for all patients under treatment. Clinically meaningful recovery of VA was defined as (i) improvement in VA from nadir by at least 10 letters on the ETDRS chart or (ii) improvement from “off-chart” VA at nadir to being able to read at least 5 letters on-chart.

Results:
Here we report on 50 LHON patients currently enrolled in the EAP of which 42 patients had provided post-treatment VA data. Average time from onset of symptoms to treatment start was 7 months. Patients had disease-typical demographics with respect to age at symptom onset (mean: 32 years), gender (72 % male), and mtDNA mutations (G11778A: 54%, G3460A: 20%, T14484C: 14%, other: 12%). Across all mutations, 19 of 42 (45 %) of patients experienced clinically meaningful VA recovery from nadir with the majority (74%) of these patients showing VA recovery within 6 months of treatment. Treatment with idebenone was safe and well tolerated.

Conclusions:
A high proportion of LHON patients treated with idebenone under a global EAP experienced a rapid, clinically meaningful recovery of vision, further demonstrating the therapeutic potential of idebenone in the treatment of LHON.

Financial Disclosures: G. Metz, N. Coppard, T. Meier are regular employees of Santhera Pharmaceuticals, the sponsor of the Expanded Access Program.

Grant Support: None.
Peripapillary RPE-layer shape in Idiopathic Intracranial Hypertension: before and after treatment

Patrick Sibony¹, Robert Honkanen¹, Mark J. Kupersmith², F. James Rohlf⁴

¹SUNY Stony Brook, Stony Brook, NY, USA, ²INN @ Roosevelt Hospital and New York Eye and Ear Infirmary, NY, NY, USA

Introduction:
We previously reported that the shape of the peripapillary-RPE(ppRPE) layer in papilledema has an inverted U-shape indentation to mild flattening of the globe compared normals who exhibit a V-shape. This study attempts to determine the magnitude and type of shape changes that occur with a decrease in CSF-pressure that follows lumbar puncture and after successful treatment.

Methods:
We studied 30 patients with idiopathic intracranial hypertension; 27 female, mean age 25.6. We used the SD-OCT to evaluate three groups with respect to 1. shape of the RPE layer (using Geometric Morphometrics ¹⁻²), 2. anterior-posterior displacement of the RPE layer at its margin and 3. RNFL thickness. We compared eyes with: A. papilledema before(Pre) and after lumbar puncture(P-lp), B. before(Pre) and after treatment with resolution(P-r); C. resolved papilledema(P-r) to normal controls.

Results:
There was a statistically significant difference in the shape of the RPE-layer after LP (p=.004) and after resolution(p=.001) compared to the Pre. The inverted-U indentation of the globe decreased slightly after LP and decreased further in the P-r group. Despite “resolution”, the P-r shape was statistically different(p=.001) from normals. The average posterior displacement after spinal tap was -78um and -215um after resolution. The mean RNFL at presentation was 278um, and decreased to 94u with resolution. There was a statistically significant (p=0.000) decrease of the mean RNFL(56um) after LP(before treatment). Displacement correlated with shape changes (r=.87, p=0.000). There was a statistically significant but mild correlation between displacement and RNFL change (r=.37, p=.01), shape and average RNFL (r =.44, p=.002).

Conclusions:
The changes in the ppRPE-shape are dynamic and presumably reflect a decrease in the intracranial pressure after LP and treatment. There is a complex relationship between the translaminar pressure, scleral compliance and structural geometry of the neural canal that affects the shape of the peripapillary eye wall. Peripapillary deformations may be useful in the diagnosis and management of intracranial hypertension.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Tuesday, March 4, 10:30 - 10:45 a.m.

Non-invasive Assessment of Intracranial Pressure Using Otoacoustic Emissions in Pediatric Patients with Idiopathic Intracranial Hypertension (IIH)

Gena Heidary¹, Jeffrey Hollander¹, Regina Laine², Margarett Marlatt², Michelle Souris², Carly E. Milliren³, Guang-Wei Zhou⁴, Michel Fayad², Susan E. Voss⁵

¹Boston Children's Hospital, Department of Ophthalmology, Boston, MA, USA, ²Boston Children's Hospital, Department of Neurology, Boston, MA, USA, ³Boston Children's Hospital, Clinical Research Center, Boston, MA, USA, ⁴Boston Children's Hospital, Department of Audiology, Boston, MA, USA, ⁵Smith College, Picker Engineering Program, Northampton, MA, USA

Introduction:
The ability to follow response to treatment with elevated intracranial pressure (ICP) and papilledema are crucial factors in the preservation of visual function in IIH. Current methods of ICP monitoring are invasive. Distortion-product otoacoustic emissions (DPOAEs), measured non-invasively through the ear canal, appear to be sensitive to ICP changes in healthy subjects.¹ We evaluated whether changes in DPOAEs correlate with changes in ICP in pediatric patients.

Methods:
Prospective study of pediatric patients undergoing a medically necessary lumbar puncture (LP). DPOAE magnitudes for 13 frequencies (range 516-3984 Hz) were measured. Normal middle-ear function was confirmed by otoscopy and a tympanogram. Measurements were obtained using software from Mimosa Acoustics (HearID v3.1). Data including age, opening and closing ICPs were recorded.

Results:
Eighteen subjects were evaluated (14 female patients) with a median age of 13.0 years (4.0 interquartile range, IQR). Among the five patients with elevated ICP, median opening pressure was 32.6 cm H₂O (2.2 IQR) compared with 18.0 cm H₂O (3.4 IQR) for control patients. Cases and controls differed significantly on change in ICP (P=0.01). Strong negative correlations were found between the change in ICP and resulting change in DPOAE magnitude at two frequencies, 703 Hz and 984 Hz. Spearman correlation coefficients were -0.68 and -0.62, respectively.

Conclusions:
Changes in DPOAEs appear to reflect elevation in ICP. More extensive work is needed to determine the utility of DPOAE measurements in longitudinal monitoring of patients with IIH. DPOAEs may offer a promising non-invasive alternative for monitoring ICP in normal hearing patients.

References:


Financial Disclosures: Gena Heidary, Knights Templar Eye Foundation Grant

Grant Support: Knights Templar Eye Foundation Grant (GH)
Gamma Knife Radiosurgery for Pituitary Adenomas <2mm From The Anterior Visual Pathway (AVP)

Scott L Stafford1, Jacqueline A Leavitt2, Bruce E Pollock3

1Mayo/Radiation Oncology, Rochester, MN, USA, 2Mayo/Ophthalmology, Rochester, MN, USA, 3Mayo/Neurosurgery, Rochester, MN, USA

Introduction:
Various data exist with respect to the tolerance of the Anterior Visual Pathway (AVP) for single fraction radiosurgery. Conventional wisdom has historically been that tumors 2mm or closer to a part of the AVP can not be successfully treated with single fraction radiosurgery due to the tolerance of the optic nerve(s). This work adds to recent literature that disproves early assumptions published, that 8Gy is the maximum tolerated dose to the AVP from radiosurgery, and contradicts the dogma of not treating select tumors that are very close to a portion of the AVP with radiosurgery.

Methods:
Twenty seven patients without prior radiation with pituitary adenomas <2mm from either the optic nerve or chiasm of the AVP were identified treated with the Leksell Perfexion Gamma Unit, between 2007-July 2012 inclusive. Of these tumors, n=17 were non-functioning tumors and n= 10 had hormone secretion. A median of 14 isocenters were utilized to treat a median tumor volume of 3.0cm³(range, 0.8-15.9). Median tumor marginal dose was 15Gy(range,12-25) and median optic nerve/chiasm maximum dose was 11.7Gy(range,8.4-14.5). Median dose to 1% of the AVP (volume,2-5mm³) was 10.2Gy.

Results:
All patients had imaging and clinical follow-up, median follow-up was 24mo(range,12-65). One tumor had tumor growth 54 months after radiosurgery. New pituitary deficits occurred in 4/23 evaluable patients(17%), with a median time of onset of 18 months. No patient developed either visual loss or other cranial nerve deficits.

Conclusions:
Small volumes of the AVP in patients that have not had prior radiation exposures, can safely tolerate a maximal point dose to a portion of the AVP of 10-12Gy. Adherence to older data (maximum of 8Gy to the AVP) limits the applicability and effectiveness of single-fraction radiosurgery for patients with parasellar tumors.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Retinal Ganglion Cell Layer Thinning within One Month of Presentation for Non-arteritic Anterior Ischemic Optic Neuropathy and Optic Neuritis

Mark Kupersmith¹, Mona Garvin², Jui-Kai Wang², Mary Durbin³

¹INN/Roosevelt Hospital and NYEEI, New York, NY, USA, ²Department of Electrical and Computer Engineering, The University of Iowa, Iowa City, IA, USA, ³Zeiss-Meditec, Inc, Dublin, CA, USA, ⁴Department of Ophthalmology, Iowa University School of Medicine and Center for Prevention and Treatment of Visual Loss, Veterans Administration, Iowa City, IA, USA

Introduction:
High definition optical coherence tomography (HD-OCT) reveals retinal ganglion cell layer (GCL) and retinal nerve fiber layer (RNFL) thinning in chronic optic nerve injury. However, in acute optic nerve injury, the optic disc and axons are often swollen, preventing RNFL thickness evaluation of early neuron loss. Identifying early signs of nerve loss is essential for prompting treatment and testing therapies. We investigated whether GCL thinning occurs before RNFL loss in eyes with acute optic neuropathy, and if early GCL loss correlates with permanent deficits.

Methods:
We prospectively studied eyes with non-arteritic anterior ischemic optic neuropathy (NAION; n=38) and optic neuritis (ON; n=29), acutely and at 1 month, using standard automated perimetry and HD-OCT. Using 2 methods, 3-D layer segmentation (method 1) and by HD-OCT proprietary (method 2), we computed the thickness of macula combined GCL and inner-plexiform-layer (GCL+IPL) and peripapillary RNFL.

Results:
At presentation, the mean macula GCL+IPL values, 80 μm ± 8.1 for NAION and 83 μm ± 8.9 for ON eyes, did not differ from unaffected fellow eyes (83 μm ± 6.4 and 82 μm ± 7.0), using method 1 while method 2 failed in 30% of eyes. At 1month, only 4 NAION eyes and 3 ON eyes had RNFL loss, while 29 NAION eyes and 20 ON eyes had GCL+IPL thinning, with on average losses of -17.2 μm and -9.0 μm (p= 0.001) respectively. The amount of GCL+ thinning correlated with the visual field mean deviation (r=0.61, p=0.001) for NAION eyes.

Conclusions:
Conclusion: GGL thinning develops rapidly, prior to RNFL loss, and appears to be a biomarker of early structural loss in NAION and ON.

Financial Disclosures: Mary Durbin is an employee of Zeiss-Meditec, Inc.Randy Kardon has been a consultant to Novartis steering committee member for OCTiMS multi center study

Grant Support: None.
Tuesday, March 4, 11:15 - 11:30 a.m.

Investigating Regional Grey Matter as Well as White Matter Atrophy in MS - Retinal Nerve Fiber Layer Thickness and Thalamus Pathology in Multiple Sclerosis Patients

Norah S Lincoff1, Zivadinov Robert, Weinstock-Guttman Bianca, Ramanathan Murali

Department of Neurology, State University of New York at Buffalo, Buffalo, NY, USA

Introduction:
Multiple Sclerosis is commonly categorized as an inflammatory disease of the brain’s white matter. Studies have been conducted measuring RNFL loss in MS, but newer studies are relating levels of RNFL loss to regional brain atrophy of the white as well as the grey matter of the CNS. Our research indicates early grey matter involvement in MS. This is important to ascertain since it is known that grey matter damage is a critical factor leading to permanent disability in this disease.

Methods:
RNFLT was measured using OCT in 96 relapsing-remitting MS (RR-MS) patients (41% had history of optic neuritis), 25 secondary-progressive MS (SP-MS) patients (40% had a history of optic neuritis) and 46 controls. MRI was obtained within ± 3 months of OCT testing. RNFLT associations with MRI by diffusion tensor imaging were assessed in regression analyses.

Results:
In RR-MS, lower RNFLT was associated with lower white matter (WM) volume and lower whole brain volume. In RR-MS, lower RNFLT was associated with lower total deep gray matter (GM) volume and lower thalamus volume. In RR-MS, lower RNFLT was associated with greater mean diffusivity (MD) in normal appearing brain tissue (NABT) and NAGM. Trends were found for lower RNFLT with greater MD in NAWM and thalamus. RNFLT in controls and SP-MS was not associated with MD in NABT, NAGM, NAWM and in the deep gray matter, thalamus or pulvinar regions.

Conclusions:
Lower RNFLT is associated with MRI metrics of microscopic tissue injury in normal appearing (NA) regions of the brain. RNFLT is associated with, and could potentially be an imaging biomarker for, neurodegeneration of the deep gray matter and thalamus in RR-MS.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Tuesday, March 4, 11:30 - 11:45 a.m.

A New Automated 20 Second Pupillographic Test to Quantify the Log Unit Relative Afferent Pupillary Defect and its Relationship to Retinal Ganglion Cell Thickness

Randy H Kardon1,2, Pieter Poolman1,2, John Pienta1,2

1University of Iowa, Department of Ophthalmology and Visual Sciences, Iowa City, IA, USA, 2Iowa City VA Medical Center and the Center of Excellence for the Prevention and Treatment of Visual Loss, Iowa City, IA, USA

Introduction:
This study was designed to automate the measurement of the relative afferent pupillary defect (RAPD) with a compact computerized pupillometer utilizing a novel stimulus and analysis paradigm designed for high volume clinical use. The structure-function relationship of the RAPD to the inter-ocular asymmetry of the inner retinal layer thickness was also studied.

Methods:
A 20 second protocol spanning seven intensities for each eye (0.0 to 2.6 log lux) was implemented using a commercial binocular pupillometer (Neuroptics DP2000, Irvine, CA). The protocol was administered and analyzed in 37 consecutive patients tested prospectively in the setting of a neuro-ophthalmology clinic. Clinical RAPDs were obtained independently by neuro-ophthalmologists evaluating patients during their clinic visit and were quantified with neutral density filters. A software program was created to compare and match the waveform pupil light reflexes elicited from the right eye stimuli with those elicited from the left eye stimuli from the array of waveform reflexes derived as a function of light intensity. The inter-ocular difference in the OCT measured retinal ganglion cell-inner plexiform layer (RGC-IPL) thickness was also correlated with the computerized RAPD in a subset of patients.

Results:
There was a highly significant correlation between the automated and clinical RAPD (r = 0.86 p <0.01). Additionally, the relationship between RAPD as a function of light intensity revealed novel effects of damage. The automated RAPD also correlated significantly with the inter-ocular asymmetry of RCG-IPL thickness (r=.71, p<0.01).

Conclusions:
The use of a short, automated protocol to assess the log unit RAPD is feasible, returns results similar to clinical measurements, and correlates with structural loss. This allows for fast, objective screening. There may be diagnostic utility in introducing an intensity range over which the RAPD is measured as a new method of further characterizing damage.

Financial Disclosures: Department of Veterans Affairs grant funding (Division of Rehabilitation, Research and Development)Department of Defense (TATRC) grant funding (Vision Research Program)

Grant Support: Department of Veterans Affairs, Rehabilitation, Research and Development Division, The Iowa City VA Center of Excellence for the Prevention and Treatment of Visual Loss Department of Defense (TATRC), Vision Research Program
Tuesday, March 4, 11:45 a.m. - 12:00 p.m.

Peduncular Hallucinosis: A lesion-based network analysis

Sashank Prasad1, Aaron D Boes2, Alvaro Pascual Leone3, Verne S Caviness2, Michael D Fox1,2,3

1Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, 2Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, 3Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Introduction:
Lhermitte’s peduncular hallucinosis refers to complex visual hallucinations following a lesion of the caudal brainstem or thalamus.1 It is hypothesized that these lesions give rise to hallucinations by engendering increased, disinhibited extrastriate visual cortex activity.2

Methods:
In order to elucidate the neural correlates of these hallucinations, we collected a series of peduncular hallucinosis cases (N=23, including twenty descriptions in the literature and three new cases) and conducted several imaging analyses. First, we employed a traditional lesion-overlap analysis to identify common lesion sites. The most common area of overlap was in the central thalamus (N=6/23), but this site did not account for a majority of cases. Next, we developed a method termed lesion-based network analysis, in which we identified the resting state functional network associated with each lesion site by querying a large resting fMRI dataset acquired from normal subjects.3 This method determines areas within a network that show functional correlation or anticorrelation during the resting state.

Results:
By identifying regions of overlap in the resting functional networks associated with each case, we demonstrated that 96% of lesions (22/23) associated with peduncular hallucinosis showed functional anticorrelation with extrastriate visual cortex.

Conclusions:
These findings demonstrate that lesion-based network analysis may represent a substantial advance in lesion-based clinical-pathologic research; in this application, the method yielded results consistent with the hypothesis that peduncular hallucinosis stems from a pathologic ‘release’ of cortical activity in visual association areas.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: ADB was supported by NIH/NINDS grant 5R25NS065743-05. MDF was supported by NIH grants R25NS065743, K23NS083741, and the American Brain Foundation. Work on this study was also supported by grants from the National Institutes of Health and National Center for Research Resources: Harvard Clinical and Translational Science Center (UL1 RR025758).
## POSTER PRESENTATIONS

Tuesday, March 4, 2014 • 6:00 p.m. – 9:30 p.m.

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

- Odd-Numbered Posters: 6:45 p.m. – 7:30 p.m.
- Even-Numbered Posters: 7:30 p.m. – 8:15 p.m.

Posters will be segregated by category. Poster #’s 1-191 will be located in Rio Mar 6-10. Poster #’s 192-245 will be located in Caribbean 1 (adjacent to Rio Mar 6-10).

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Poster 2

**Horner’s Syndrome in patients admitted to the Intensive Care Unit that have undergone central venous catheterization: a prospective study**

Jasmine Gopwani¹, Edward Margolin

*University of Toronto, Toronto, ON, Canada*

**Introduction:**
Isolated case studies of patients with Horner’s Syndrome post Central Venous Catheterization (CVC) have been well documented in the past [5-8], however the frequency of Horner’s Syndrome to the authors knowledge has not been documented since the introduction of ultrasonography-assisted insertion which has been documented to decrease the prevalence of the more common complications of CVC such as pneuemothorax [3][4]. This study aims to determine the frequency of Horner’s Syndrome and to determine whether these practices have decreased its frequency in patients who have undergone CVC placement.

**Methods:**
Over four consecutive months we enrolled subjects who had a central venous line placed for monitoring in the Intensive Care Unit of one hospital within the past 5 days. All operators who inserted the central lines filled out a short questionnaire which included the operators' experience, number of attempts made to insert the line, whether ultrasonography-assisted insertion was used and whether the carotid artery was punctured. Patients were screened for anisocoria and/or ptosis. If the screening examination was suspicious for Horner's Syndrome, pharmacological testing was done after obtaining an informed consent from patient/family member. Apraclonidine 0.5% drops was instilled into both eyes after initial pupillary measurement and then re-examined in 60 minutes, looking for a reversal in anisocoria.

**Results:**
Of the 39 patients enrolled in the study to date, 1 patient not known to have Horner’s syndrome prior to admission was found to have a positive pharmacological test for Horner’s Syndrome.

**Conclusions:**
Our study highlights an even higher incidence of Horner's syndrome than that documented in previous literature post CVC insertion despite the now routine use of ultrasonic guidance, pointing to CVC insertion as a fairly common cause of Horner's syndrome. Our study is continuing with the goal of recruiting 100 subjects.

**References:**

4. Gann Marcus Jr, Szudi Armando. Improved results using ultrasound guidance for central venous access

**Financial Disclosures:** The authors had no disclosures.

**Grant Support:** None.
Pupil Cycle Time in optic neuritis.

Cédric Lamirel, Tristan Himpens, Antoine Moulignier, Catherine Vignal, Laurence Salomon, Isabelle Cochereau, Jean Lorencan

Introduction:
Pupil Cycle Time (PCT), induced by a slit-lamp, has previously been used to quantify optic nerve conduction time in patients with optic neuritis (ON). We tested a new way of inducing PCT by adjusting the intensity of a standard computer screen according to the pupil size measured in-real time by infrared oculography. We tested the hypothesis that, in patients with a history of unilateral ON, the pupillary oscillations frequency (POF) would be lower in the affected eye than in the fellow eye.

Methods:
We recorded PCT in 22 patients (mean age 37 years [24-60]; 15 women) with a history of unilateral ON within a 5 year-period. PCT was induced for 30 seconds in the affected eye, in the fellow eye and in binocular condition. Eight trials were collected for each condition. POF was obtained by selecting the frequency of the maximum power of a Fast-Fourier-Transform and analyzed using factorial ANOVA. We performed a Time-Frequency analysis to test the variability of the POF during each 30 seconds recording.

Results:
On the 508 recordings obtained, 54 (11%) were discarded from analysis for technical failures. The mean POF (standard-error) for the affected eye, the fellow eye and in binocular condition was respectively 1.05 Hz (0.01); 1.11 Hz (0.01) and 1.18 Hz (0.01) with a significant difference (p<10^-3). The variability of the POF during the 30 seconds of recording measured by Time-Frequency analysis in the affected eye (0.29Hz), the fellow eye (0.25Hz) and in binocular condition (0.17Hz) were significantly different (p<10^-3).

Conclusions:
Infrared oculography can be used to induce and record PCT easily and with good reliability. Pupillary oscillations frequency is lower and more variable in eyes affected by ON compared to the fellow eyes and to the binocular condition.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Afferent Pupillary Defect Assessment In Optic Nerve Pathology

Haydée S. Martinez¹, María M. Clementi Gordon¹, Mirta Arana¹, María L. Braccia Gancedo¹², Mariana de Virgiliis²

¹Hospital Clínicas José de San Martín, Buenos Aires, Argentina, ²Hospital Oftalmológico Pedro Lagleyze, Buenos Aires, Argentina

Introduction:
The objectives of the study were to explore the association between the Visual Acuity (VA)- Visual Field (VF) and Afferent Pupillary Defect (APD) - in visual pathway pathology and if there are any differences in the behavior of this variables in groups according to etiology.

Methods:
Prospective exploratory study. 18 months duration: Unilateral AV commitment, visual pathway pathology and consequently APD or relative afferent RAPD measured on a logarithmic scale using the toolbar of NEUTRAL DENSITY FILTERS (NDF). Evaluation : Baseline, Month, two months. Excluded patients: bilateral involvement, iris pathology, history of previous VA reduction, incomplete controls and informed consent refusal. Data was classified according to: etiology,(inflammatory, tumoral or compressive, ischemic) VA compromise, VF, age and sex, DPA (logarthimic).

Results:
Thirty two (32) patients were included. 50% men. Mean age: 47,8 ± 17. Ischemic: 59,38%; Inflammatory: 31,25%; Compressive/tumoral: 9,8%. Visual Acuity significantly improved over the controls, except in compressive/tumoral group meanwhile there were no statistically significant differences in APD changes related with AV, except in inflammatory disease group where the APD was good correlated with visual improvement. Visual field defect (VFD) persistance was not related with VA improvement, but with APD persistanec

Conclusions:
To date there’s no study that determine the degree of severity of the DPA for etiologic cause, nor in specific scales or visual acuity commitment. This study showed an association between VA and APD in reverse, noticing an improvement in VA and APD notorious decrease until disappearing in inflammatory optic pathway lesion, the opposite findings in the compressive or tumoral etiology, and no remarkable changes with respect to these two items in ischemic diseases We can also conclude that in the latter group respecting to inflammatory etiology with the same VA, APD continued to be altered. Further analysis is required to correlate APD with VFD evolution.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Poster 5

Localizing Value of Ipsilateral Horner’s Syndrome and Fourth Nerve Palsy.

Roberto Ebner1, Dolores Ribero Ayerza

British Hospital, Buenos Aires, Argentina

Introduction:
To describe the association of ipsilateral Horner’s Syndrome and IVth nerve palsy in a patient with a right cavernous sinus tumor.

Methods:
Single case report

Results:
A 54-year-old female presented with vertical diplopia and neck pain. Mild ptosis and miosis were observed in the right eye. Her examination was normal except for 2mm blepharoptosis and miosis OD with anisocoria greater in the dark. An ice-pack-test was negative. Topical Apraclonidine 0.5% test demonstrated midriasis and lid retraction OD after 20 minutes confirming the presence of Horner’s syndrome. Parks three-step-test was suggestive of right superior oblique muscle paresis with right hypertropia of 6 prism diopters most consistent with IVth nerve paresis. MRI of the brain and orbits with and without contrast revealed a mass in the right cavernous sinus most consistent with meningioma.

Conclusions:
The presence of contralateral IVth nerve palsy with ipsilateral Horner’s syndrome has been previously documented in ventral midbrain lesions. However, our case suggests that clinicians should be aware that cavernous sinus lesions may also lead to a similar clinical presentation when ipsilateral IVth nerve palsy and Horner’s Syndrome are present.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Poster 6

Sixth Nerve Palsy + Ipsilateral Horner’s Syndrome = Parkinson’s Syndrome.

Roberto Ebner, Dolores Ribero Ayerza

British Hospital, Buenos Aires, Argentina

Introduction:
We present five patients with VI th nerve palsy and ipsilateral Horner’s Syndrome (HS), an association orienting diagnosis towards the carvernous sinus.

Methods:
Consecutive case series of five patients with horizontal diplopia due to VIth nerve paresis and HS with ipsilateral cavernous sinus lesion.

Results:
All 5 patients had abducens palsy with horizontal diplopia in primary postion (3 patients) or evident in lateral gaze only (2 patients) and ipsilateral HS. Apraclonidine 0.5% evidenced sympathetic denervation in all patients in this series. All 5 cases had neuroimages (MRI in 3 cases, Computarized Tomography-CT in one case and Cerebral Angiography-CA in one case) demonstrating cavernous sinus lesions; 2 meningiomas, 1 carotido-cavernous aneurism, 1 forcing body (bullet) and 1 scamous cell carcinoma.

Conclusions:
The association of VI th nerve palsy with ipsilateral HS was described by D. Parkinson and named after him (PS). It has a great localizing value being the site of the lesion; the cavernous siuns. The use of Apraclonidine 0.5% has great diagnostic value for HS but does not provide information about the level of the sympathetic pathway lesion. In our series helped to demonstrated the presence of sympathetic denervation. The isolated VI th nerve palsy has no localizing value and neither for the HS alone. The association of ipsilateral HS and abducens palsy (PS) in our series was accompanied by neuroimages (MRI, CT and CA) showing cavernous sinus lesions of different origin in all cases. Neuroimaging of the cavernous sinus is recommended in the evaluation of Parkinson’s Syndrome, selecting the adequate image according to the nature of the suspected causing factor.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Benign (May Be Malignant) Episodic Unilateral Mydriasis In A Patient With Hodgkin's Disease!

Ahmara G. Ross¹, Tarek A Shazly, Gabrielle R Bonhomme

Dept. of Ophthalmology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Introduction:
Benign episodic unilateral mydriasis (BEUM) is an isolated benign cause of intermittent anisocoria. The underlying physiopathology is not clear and may involve either parasympathetic paralysis or sympathetic hyperactivity affecting the iris musculature. Other life threatening causes of anisocoria should be ruled out.

Methods:
Case report and review of the literature.

Results:
A 26-year-old woman with stage IIA nodular sclerosing Hodgkin’s disease presented for urgent evaluation of anisocoria noted by co-workers. She denied headaches or other neurological symptoms. Her left pupil was 1 millimeter larger than her right in bright light while in dim light the right was larger. The rest of her ophthalmic and neurological examination was normal. Ocular motility was full with normal alignment. She underwent Magnetic resonance imaging of her brain and orbit as well as magnetic resonance angiography of her head and neck to rule out compressive lesions, vascular malformations or dissecion. No intracranial pathology was evident. Her anisocoria resolved in 24 hours, suggesting a pharmacologic inoculation related to her occupation as a veterinarian technician. Eight weeks later the patient came back for an urgent evaluation of recurrent anisocoria. This time, she reported a migraine headache with blurriness, seeing sparkling peripheral lights in both eyes. At that time her pupils were check by a nurse to be equal and then an hour later her left pupil became larger than the right pupil. On exam, her pupils were 6.5 mm in dim light. In bright light, her right pupil was 3.5mm and the left was 5.5mm with no afferent pupillary defect or light near dissociation. The rest of her examination was unremarkable.

Conclusions:
BEUM is an uncommon cause of anisocoria. Careful history taking, comprehensive examination and neurological imaging are required to rule out life threatening causes of anisocoria especially in high risk patients or patient with know malignancies.

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A Simple Infrared-Augmented Digital Photography Technique

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Introduction:
Infrared photography is a useful tool for detection and documentation of pupillary size and reactivity. Infrared photographs and videos provide documentation and contribute to medical education of students and house-staff. However the dedicated equipment may not be widely available. Infrared cameras are sensitive only to infrared light by blocking visible light. Charge-coupled device (CCD) camera sensors are inherently sensitive to both visible and infrared light. Commercially available point and shoot cameras are typically equipped with infrared attenuating filters. These filters don’t completely block near infrared light in the 800nm-900nm range. Utilizing a regular digital camera for documentation of pupillary abnormalities becomes challenging under dim light conditions and in patients with dark colored irides. This problem can be solved by utilizing infrared illumination.

Methods:
An unmodified 12 megapixel point and shoot digital camera was used to obtain binocular still photos and videos under different light conditions with near-infrared illumination. A commercially available infrared light emitting diode irradiating near-infrared light of 850 nm was used to illuminate the eyes, since this wavelength minimally stimulates pupillary light reaction while remaining visible to the camera. The infrared illumination allows the capture of clear pupil images in both dim and bright light conditions and allows easy visualization of the pupil despite pigmented irides, by increasing the contrast.

Results:
Photos and videos were obtained using the aforementioned technique demonstrating a variety of pupillary abnormalities, including afferent pupillary defects, light-near dissociation, and anisocoria due to Horner syndrome, tonic pupil, and third nerve palsy. This technique also allowed easy, rapid, and accurate measurement and documentation of the pupil sizes under dim and bright conditions.

Conclusions:
This infrared-augmented photography technique supplements medical education, and aids in the more rapid detection, diagnosis and documentation of a wide spectrum of pupillary abnormalities. Its portability and ease of use with minimal training.

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Grant Support: None.
**Unusual Neuro-Ophthalmic Manifestations Of Herpes Zoster Ophthalmicus**

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**Introduction:**
Cranial nerve palsies and pupillary changes after herpes zoster ophthalmicus (HZO) are rare but have important therapeutic implications.

**Methods:**
Case-series

**Results:**

**Case 1: HZO with presumed vasculitic cavernous sinus involvement:** A 28 year old immunocompetent male presented with pain and left sided Horner's pupil, limited abduction, periorbital erythema and swelling. MRI showed preseptal and lacrimal gland and cavernous sinus enhancement. A week later, he developed HZV forehead skin lesions and anterior uveitis. Treatment with IV antivirals and topical steroids led to relief. Anisocoria persisted.

**Case 2: HZO with orbital involvement of the lateral rectus and ciliary ganglion:** A 54 year old immunocompetent female with HZO- conjunctivitis, keratouveitis and forehead/scalp lesions was treated with oral antivirals. One month later she developed diplopia (left eye abduction limitation) and anisocoria (tonic pupil and light-near dissociation). MRI showed enhancement of left lateral rectus close to superior orbital fissure. Diplopia resolved in 1 week with oral antivirals. The tonic pupil persisted with supersensitivity to dilute cholinergics at follow-up.

**Case 3: HZO with 3rd nerve palsy and stroke:** A 76 year old immunocompetent male presented with HZO (keratouveitis and V1 skin lesions) treated with 10 days of oral antivirals. 2 weeks later he developed altered mental status which was treated with IV antivirals for 3 days until a negative CSF HSV PCR. Three weeks later he developed a right pupil involving oculomotor nerve palsy. MRI revealed a small acute infarct in the ipsilateral centrum semiovale. CSF showed lymphocytic pleocytosis with positive HZV DNA. Treatment included intravenous antivirals followed by long-term prophylaxis. A year later he had full eye movements with residual upper lid ptosis.

**Conclusions:**
HZO with pupil changes or cranial nerve palsies warrants emergent imaging of the orbit and brain for possible disseminated HZV, which may need intravenous and long-term antiviral therapy

**Financial Disclosures:** The authors had no disclosures.

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**Poster 10**

**Damping of Monocular Pendular Nystagmus with Vibration**

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**Introduction:**

Acquired pendular nystagmus (APN) may be monocular or binocular, vary in trajectory, and consists of pseudo-sinusoidal oscillations, that are transiently-abolished by saccades and blinks. APN results in highly-disabling oscillopsia that impairs visual acuity and postural stability, and affects cosmetic appearance. We present two patients with monocular APN that was attenuated by application of vibration to the skull.

**Methods:**

Patient 1 was a 32-year-old woman with multiple sclerosis (characterized by prior left optic neuritis, internuclear ophthalmoplegia and ataxia) with small amplitude, left monocular pendular horizontal nystagmus. Patient 2 was a 62-year-old man who developed an acute eight-and-a-half syndrome (one-and-a-half syndrome plus facial palsy) following a pontine-tegmentum hemorrhage, and later developed a small amplitude, right monocular vertical pendular nystagmus. In both, the nystagmus was temporarily-damped following blinks and saccades albeit unaffected by convergence, covering either eye, head-shaking, hyperventilation, body position. We applied vibration to the vertex, both mastoids, chin, dorsal neck muscles, and elbow and assessed its effects on the nystagmus.

**Results:**

The nystagmus amplitude (and oscillopsia) was strikingly-diminished with vibration over the vertex, mastoids, and chin; the effect of dorsal neck muscle vibration was less evident. The nystagmus immediately resumed unabated when vibration ceased. It was unaffected by elbow vibration, or exposure to only the noise or pressure of the vibrator.

**Conclusions:**

Both patients demonstrated marked damping of APN, and associated improvement in oscillopsia, with vibration. While the pathophysiologic underpinnings remain unclear, one possible mechanism is vibration-induced vestibular afferent stimulation, an explanation that has been posited for the nystagmus-dampening effects of head-shaking in spasmus nutans. Alternatively, vibration may modulate brainstem proprioceptive input, a mechanism that has been proposed for the damping-effect of vibration and acupuncture on congenital nystagmus. If our preliminary observations can be replicated in a larger cohort, a technology development plan to fabricate an effective, convenient, user-friendly, vibration-stimulus delivery device, would be justified.

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Poster 11

Neuro-ophthalmological Features in Children and Adolescents with Chronic Ataxia in Manitoba, Canada

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Introduction:
Chronic ataxia is a challenging problem in pediatric neurology. It is caused by a multitude of disorders that at least initially have similar or non-specific phenotype. Some of these disorders have associated neuro-ophthalmological signs (N-OS). The aims of this study are to describe the N-OS and their frequencies in general and by disease etiology in pediatric patients with chronic ataxia in Manitoba.

Methods:
Previously we identified 184 patients (M=F) <17y with chronic ataxia (>2 months duration or recurrent) during 1991-2008 from multiple sources. Patients with tumors, isolated vestibular or peripheral nerves diseases were excluded. Diagnoses (known in 128) and N-OS were ascertained following charts review.

Results:
Mean age (SD) was 15 (7.7)y. Median duration of follow-up was 6.4y. There were 214 N-OS in 115 patients (median=2, range=1-5 N-OS/ patient). Strabismus was present in 29.3% of patients, nystagmus 27.7%, impaired smooth pursuit (SP) 23.4%, hypometric saccades 10.3%, decreased visual acuity 9.2%, abnormal optic discs 8.7%, abnormal pupillary exam 2.7%, hypermetric saccades 2.2%, impaired ductions 1.6%, and abnormal visual fields in 1.1% of patients. N-OS were reported most commonly among patients with the following disorders (number of patients with N-OS/ total number of patients with a specific disease, commonest N-OS and its frequency): Hypoxic-ischemic encephalopathy (N=5/5, strabismus: 4), episodic ataxia (N=6/7, nystagmus: 5), neuronal ceroid lipofuscinosis (N=5/6, abnormal optic discs: 5), neuronal migration disorder (N=4/5, strabismus: 4), ischemic stroke (N=7/9, nystagmus: 6), Joubert syndrome (N=3/4, strabismus: 3), leukodystrophy (N=3/4, nystagmus: 3), Friedreich’s ataxia (N=5/7, hypometric saccades/impaired SP/nystagmus: 2 each sign), mitochondrial disease (N=6/9, strabismus/nystagmus: 2 each sign), epilepsy (N=3/5, impaired visual acuity: 2), ataxia telangiectasia (N=6/13, impaired SP: 4), and Angelman syndrome (N=5/16, strabismus: 3).

Conclusions:
N-OS occur commonly in children with chronic ataxia. Although non-specific, they vary with disease etiology thus potentially prioritizing the list of differential diagnosis.

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Do Clinical Features in Infantile-onset Saccade Initiation Delay (congenital ocular motor apraxia) Correlate with Brain MRI Findings?

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Introduction:
Infantile-onset saccade initiation delay (ISID) is a defect in initiating saccades. Other features include impaired smooth pursuit, developmental delay, hypotonia, and ataxia. Brain MRI can be normal or show supra- or infratentorial abnormalities. Our aim was to determine if there are correlations between the clinical features of ISID and MRI findings.

Methods:
Detailed review of the English medical literature between 1952 and 2012 revealed 383 patients (67 studies) with possible ISID. Patients without a brain MRI, inadequate information, Joubert syndrome, neurodegenerative disorders or acquired SID were excluded (N=292). The remaining 91 patients (age range: 3 months-45 years) were divided into three groups according to their brain MRI findings: Normal (N=55), supratentorial abnormalities (N=17) and infratentorial abnormalities (N=19). The patients’ clinical features (e.g. impaired smooth pursuit or optokinetic response (OKR), abnormal tone, developmental or cognitive delay, language or motor delay, and ataxia) were compared and analyzed among the groups using Chi-Square tests.

Results:
Horizontal head thrusts were significantly more common in patients with infratentorial abnormalities or normal brain MRI while vertical head thrusts were more common among patients with supratentorial abnormalities (p<0.0001). The slow phases of the OKR were significantly more likely to be impaired in patients with supratentorial abnormalities than in patients with a normal MRI (p=0.011). Other neuro-ophthalmological, neurological and developmental features were similar among patients in the three neuroimaging groups.

Conclusions:
The direction of head thrust and the integrity of the smooth phases of the OKR are useful clinical indicators of possible sites of abnormality on brain MRI in patients with ISID.

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Risk of Fractures and Musculoskeletal Injuries in Medicare Beneficiaries with Disorders of Binocular Vision

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Introduction:
Disorders of binocular vision (DBVs) are increasingly prevalent among aged fee-for-service Medicare beneficiaries. Visual impairment is a known risk factor for fractures, a significant cause of morbidity and mortality in the elderly population. Despite the known association of visual impairment and fall risk, no studies have examined the association of DBV (strabismus, nystagmus, amblyopia) with musculoskeletal injury and falls in the elderly.

Methods:
A 5% random sample of Medicare Part B physician claims was used to identify beneficiaries ≥65 years in age with ten-year-follow-up data available. Incidence of fractures and musculoskeletal injuries was evaluated in the same population. A multivariable logistic regression analysis was used to estimate the association between the diagnoses of a disorder DBV and injury. Analyses were adjusted for age, sex, race/ethnicity, region of residence, systemic health, and ocular comorbidities.

Results:
There were 1,280,543 Medicare beneficiaries in the 5% sample in 2002, and 509,905 of them had 10 years of follow-up until 2011. Of these, 41,733 (8.2%) had a DBV (6.2% strabismus, 1.2% amblyopia, 1.5% diplopia, 0.16% nystagmus). There were 403,453 (79%) patients who had fracture, musculoskeletal injury or fall. The adjusted odds ratio was 1.26 (95% confidence interval 1.23-1.30, p<0.0001).

Conclusions:
In a cohort of aged Medicare beneficiaries, patients with DBV had a higher chance of sustaining a fall, fracture, or musculoskeletal injury. This finding adds to our understanding of risk factors for falls and ultimately designing measures to prevent these injuries.

References:

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**Poster 14**

**Isolated Horizontal EOM deficits in a patient with Platybasia**

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**Introduction:**
Anomalies of the hindbrain, posterior fossa, and skull base can cause visual symptoms due to their effects on oculomotor pathways in the brainstem and cerebellum. Anomalies at the craniocervical junction, such as Chiari malformations, often cause downbeating nystagmus. We have not found a previous report of isolated horizontal gaze deficits in the setting of anatomic variants affecting the craniocervical junction.

**Methods:**
A 67 year old man was referred to our clinic for evaluation of horizontal nystagmus, found during Neurology consultation for blurred vision, gait problems, and “head pressure” in the occiput. He had problems following fast-moving objects even as a young man, but this worsened over the years. He had worsening gait imbalance over the years, resulting in frequent falls. He had history of hypertension and hyperlipidemia. He was not diabetic, did not abuse alcohol or smoke. On exam, his mentation and speech were normal. He had normal acuity, color vision, and visual fields. Pupils were 7 mm and briskly reactive. He had normal optic discs, vessels, and maculae. He had normal vertical saccades and pursuits. No eye deviations were found on cover-uncover or cross-cover tests. Horizontal pursuit movements were absent, only saccades were seen. He had normal horizontal VOR responses, but no VOR cancellation. No horizontal optokinetic responses were elicited. Gaze-paretic horizontal nystagmus was present on extremes of gaze. On neurologic exam, he had positive Romberg, wide-based gait, and poor postural stability. MRI brain imaging a year earlier had revealed variant cranio-vertebral junction anatomy suggesting platybasia, resulting in increased angulation at the cervico-medullary junction. A relatively small posterior fossa was seen, and mildly low lying peg-shaped tonsils were noted.

**Results:**
Eye movement recordings to further characterize the oculomotor deficits are planned for the near future.

**Conclusions:**
Posterior fossa anomalies affecting the craniocervical junction can result in isolated horizontal EOM dysfunction.

**References:**


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Strabismus Caused by Infantile Orbital Myofibromatosis Originating From An Extraocular Muscle

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Introduction:
Myofibromatosis is the most common fibrous tumor of infancy. Of the two forms, solitary and multicentric, the solitary form is the more common. Skin, bone, viscera, and soft tissue involvement is typical, but lesions rarely involve the orbit. Spontaneous regression can occur within two years and recurrence is rare in multicentric disease.

Methods:
We present an atypical case of a child with orbital myofibroma resulting in strabismus requiring surgical intervention despite spontaneous regression.

Results:
A 2-year-old girl with systemic myofibromatosis and a history of excision of multiple non-ocular myofibromas presented with right upper lid ptosis, 20 prism diopters (∆) of right hypertropia, and unilateral downgaze restriction of the right eye. Echography and magnetic resonance imaging confirmed a lesion of the right superior/levator complex, with characteristics favoring a diagnosis of right orbital myofibroma. Serial echography demonstrated spontaneous regression of the lesion with normalization of the involved extraocular muscles. However, the right hypertropia persisted and increased in magnitude to 35Δ. The patient subsequently underwent right superior rectus recession with no residual hypertropia in primary gaze one year after surgery.

Conclusions:
Notably, this patient had a remnant motility deficit requiring strabismus surgery despite the spontaneous regression of the myofibroma. To our knowledge, there are no reported cases of spontaneously regressing orbital myofibromas in a person with systemic myofibromatosis. Of the cases of orbital myofibroma, most originated from the inferior orbit whereas our patient’s lesion originated from the superior orbit. Furthermore, we were unable to find any other published cases of an infantile myofibroma originating from the extraocular muscles.

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Congenital Ocular Motor Apraxia with Wheel-Rolling Ocular Torsion—A Diagnostic Sign of Joubert

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Introduction:
Joubert syndrome is a multisystem disorder that is associated with a constellation of cyclic ocular motor disturbances.¹,² We describe the association of congenital ocular motor apraxia with tonic alternating torsional deviations of the eyes as a diagnostic sign of Joubert syndrome.

Methods:
Retrospective review of clinical, neuroimaging, video-oculography and genetic studies in two children with congenital ocular motor apraxia and Joubert syndrome.

Results:
In both children, retinal examination showed a tonic alternating cyclo deviation with a periodicity of 10 to 15 seconds. Heidelberg infrared videoimaging documented tonic conjugate wheel-rolling torsional rotations of both eyes (ranging in amplitude from 30 to 45 degrees in each direction). Video-oculography showed a periodic alternating skew deviation. Magnetic resonance imaging showed a pathognomonic “molar tooth” sign with hypoplasia of the cerebellar vermis and elongated non-decussating superior cerebellar peduncles. Genetic testing confirmed sequence variants in the CC2D2A gene in our first patient, and in the C5orf42 gene in our second patient.

Conclusions:
In patients with congenital ocular motor apraxia, the unique finding of tonic alternating ocular torsional deviations on retinal examination establishes the diagnosis of Joubert syndrome. It is unclear whether the tonic wheel-rolling torsional eye movements resulted from cerebellar malformations of Joubert syndrome or from the non-decussation of brainstem pathways that are known to accompany this condition. This finding does not appear to be mutation specific.

References:


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Ocular Neuromyotonia 23 Years after Stereotactic Radiosurgery

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Introduction:
Ocular neuromyotonia is a relatively rare clinical entity resulting in spasm of extraocular muscles. The pathophysiology may be related to spontaneous firing of axons, and it has been associated with compressive lesions or previous radiation to the sellar region. Stereotactic radiosurgery is a relatively modern form of radiation therapy, and fewer cases have been described as a consequence.1 We found the longest duration between radiation treatment of any kind and the onset of neuromyotonia previously reported was 18 years.2

Methods:
We submit a case report, including video. A review of the literature is also presented, describing published reports of ocular neuromyotonia related to sellar radiation, with duration from treatment to symptoms.

Results:
In 2013, an 82 year old man presented with episodic binocular diplopia. In 1990, he had developed peripheral vision loss and was found to have a sellar tumor. He underwent Gamma Knife radiotherapy with subsequent stabilization of his field loss. At initial consultation in October 2013 he described one month of brief diplopia (<10 seconds) numerous times per day, worse in the morning. On exam, his eye movements were initially normal. After sustained down and leftward gaze, he developed right eyelid retraction, followed by transient loss of abduction, supraduction, and infraduction of the right eye, lasting about 5 seconds. A diagnosis of ocular neuromyotonia was made. He was offered treatment with carbamazapine or clonazepam, but declined.

Conclusions:
Ocular neuromyotonia is a rare cause of episodic diplopia. We present a patient who developed ocular neuromyotonia 23 years after gamma knife radiosurgery to the sella.

References:


Financial Disclosures: The authors had no disclosures.

Grant Support: N/A
Introduction:
Estimates of the sensitivity of diagnostic testing in ocular myasthenia gravis vary. We describe how diagnoses were reached in a large, multi-center cohort of ocular myasthenia patients.

Methods:
A retrospective chart review was performed in two university-based ophthalmology departments to identify patients presenting with ocular myasthenia gravis between 7/1/1986 and 5/23/2013 with at least two years of follow-up. Results of testing used to reach the diagnosis – including acetylcholine (Ach) receptor antibody assays, single-fiber electromyography (SFEMG), edrophonium challenge, and evidence of response to therapy – were compiled for each patient.

Results:
We identified 162 patients with ocular myasthenia gravis – 54 (33.3%) women and 108 (66.7%) men with an average age at diagnosis of 58.9 years (range 18 to 87 years). One hundred and seventeen (72.2%) of the 162 patients had positive Ach receptor antibody testing. Of the 45 with negative Ach receptor testing, 36 underwent SFEMG with 34 (94.4%) having a positive result. The remaining 11 patients (6.8%) in the cohort where Ach-receptor testing was negative and SFEMG was either negative or not performed were diagnosed via edrophonium challenge or by demonstrating a response to treatment.

Conclusions:
Previous estimates of the rate of Ach receptor antibody positivity in isolated ocular myasthenia gravis – 50% or less – are significantly lower than those seen in generalized disease (85-95%)\(^1\). We report a higher diagnostic sensitivity of antibody testing in a large cohort of ocular myasthenia patients with long-term follow up.

References:


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TREATMENT OF PENDULAR NYSTAGMUS WITH GABAPENTIN AND MEMANTINE IN PATIENTS WITH MULTIPLE SCLEROSIS: FUNCTIONAL ASPECTS

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Introduction:
Pendular nystagmus (PN) observed in multiple sclerosis (MS) leads both to oscillopsia and poor visual acuity that are reported to be disabling and distressing by patients. Different treatment trials have shown interesting effects of gabapentin or memantine on PN in MS. While the effects of treatments were evaluated on nystagmus parameters and visual acuity, none of the trials took in consideration the oscillopsia perception and visual quality of life. In this monocentric opened cross-over treatment trial in patients with MS, we aim at evaluating the effect of either gabapentin or memantine on PN, visual acuity as well as oscillopsia and functional score.

Methods:
Ten MS patients with PN were included in the study (5 mens and 5 womens with a mean age of 36 years). Patients were evaluated prior to and following 1 week of full dosage of each drug, with far and near visual acuity and estimation of oscillopsia, binocular eye movement recording and functional visual questionnaire (NEIVFQ25).

Results:
For the group, both drugs reduced significantly far and near visual acuity (rmANOVA, pre-post effect, respectively p=0.04 and p=0.02), nystagmus velocity (non parametric Wilcoxon test, p=0.05 for memantine and p=0.01 for gabapentin) and composite score of NEIVFQ25 (rmANOVA, pre-post effect, p=0.006). Although we could not demonstrate different effects of both drugs, three patients showed nystagmus resolution under memantine. We could not demonstrate oscillopsia change neither correlation with nystagmus parameters.

Conclusions:
This study confirms the efficacy of memantine or gabapentin in PN in MS patients, but also emphasize that functional consequence of acquired pendular nystagmus is complex but still need to be taken into consideration in therapeutic trials.

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Vestibular Signs of Thiamine Deficiency during the Early Phase of Suspected Wernicke’s Encephalopathy

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Introduction:
Non-encephalopathic presentations of central nervous system thiamine deficiency may be difficult to diagnose. Vestibular findings in the pre-encephalopathy phase, despite their potential value to assist early diagnosis and enable early treatment before severe neurologic morbidity occurs, are not widely known. We describe neuro-otologic findings of Wernicke’s syndrome in five patients with vestibular manifestations.

Methods:
We conducted a retrospective chart review of five cases of thiamine deficiency presenting with vestibular findings to a single center (07/2008-10/2011). All patients underwent clinical neurologic, neuro-ophthalmologic, and neuro-vestibular evaluation. Vestibulo-ocular reflex (VOR) testing was performed by clinical head impulse testing in all five, video-nystagmography in two, and by video head impulse testing in one. Diagnosis was confirmed by low serum levels of thiamine, response to replacement, and brain MRI to exclude other causes.

Results:
One of the patients presented with an acute vestibular syndrome characterized by acute, persistent, vertigo, with severe vomiting and gait ataxia for 48 hours, mimicking vestibular neuritis or stroke. The others presented with subacute, progressive imbalance, unsteadiness, falls and oscillopsia. All 5 patients had bilaterally abnormal horizontal head impulse VOR responses and pathologic gaze-evoked nystagmus, without encephalopathy. In three where vertical-VOR responses were tested, two had dissociated loss of horizontal-VOR function with spared vertical -VOR function. After thiamine replacement, four had total resolution of vestibular and oculomotor findings. Novel findings included two patients whose VOR function improved within minutes of intravenous repletion and one whose recovery was documented by serial quantitative recordings.

Conclusions:
Patients with thiamine-deficiency may present with predominantly vestibular symptoms and signs without encephalopathy. Head impulse VOR responses in these patients could be an important bedside marker for diagnosis, response to therapy, or prognosis. Early diagnosis of Wernicke’s by examining vestibular reflexes and prompt intravenous treatment might prevent encephalopathy and other neurologic or systemic complications of thiamine depletion.

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Differentiating Vertical Misalignment Using Different Head Positions

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Introduction:
To evaluate whether testing ocular vertical alignment in the seated position vs. supine position aids in diagnosis of vertical diplopia.

Methods:
Prospective patients with binocular vertical diplopia, over the age of 18 were recruited. Subjects with childhood strabismus, extraocular muscle surgery, neuromuscular junction disease, intraorbital disease or visual acuity worse than 20/70 were excluded. Ocular alignment in the seated position was measured using alternate cover and/or red Maddox rod in the nine positions of gaze in addition to head tilt; subjective torsion in primary position was recorded using double Maddox rod. These measurements were then repeated in the supine position (only primary position, head tilt and torsion). In this ongoing study, 8 patients were recruited so far; 5 had skew deviation while 3 had other causes. Over 30 patients are planned for recruitment prior to data analysis and presentation.

Results:
To be presented at the NANOS meeting.

Conclusions:
It is anticipated that our findings will help determine the usefulness of measuring ocular alignment in different head positions.

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Low Conversion Rate Of Ocular To Generalized Myasthenia Gravis In An Asian Population

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Introduction:
Ocular myasthenia gravis (OMG) is a common, localized form of myasthenia gravis limited to the extraocular, levator palpebrae superioris, and orbicularis oculi muscles. Generalization of OMG is believed to occur in 50-80% of patients, usually within 2 years.1 The prevalence of OMG generalization in Asian populations is unclear, although previous studies have suggested that conversion to generalized myasthenia gravis (GMG) may be lower in this part of the world.2

Methods:
We conducted a retrospective review of all patients with OMG seen at our Ophthalmology and Neurology departments between 2008 and 2012. Inclusion criteria were: patients aged 18 or older with clinical signs suggestive of isolated OMG (variable, fatigable ptosis and/or double vision) associated with at least one of the following positive findings: ice test, acetylcholine receptor antibodies, single fibre EMG, repetitive nerve stimulation, Tensilon or Prostigmin test, response to treatment. GMG was defined as the development of generalized motor weakness including symptoms and signs of proximal limb and bulbar weakness.

Results:
Among the 155 patients diagnosed with OMG (74 female; 81 male patients), 99 had a follow-up duration of more than 2 years. Isolated variable ptosis was the presenting symptom in 48% (75/155 patients), diplopia with ptosis in 42% (65/155 patients) and diplopia without ptosis in 10% (15/155 patients) of patients. Acetylcholine receptor antibodies were found in 36 (53%) of the 67 tested patients. Among patients who had at least 2 years follow-up, the overall generalization rate was 15%. Administration of corticosteroids did not appear to modify conversion of OMG to GMG in a subgroup analysis.

Conclusions:
The conversion rate to GMG in our study is lower than in other reported series performed in Caucasians populations. This may be due to genetic or other yet unknown factors. Our novel findings have relevant implications in the management of MG patients.

References:

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David Bardenstein

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Introduction:
Diplopia assessment is critical in evaluating conditions including: thyroid associated orbitopathy (TAO), orbital trauma, and idiopathic orbital inflammation (IOI) among others. Currently diplopia is assessed using: qualitative clinical assessment, prism quantitation of deviation, and techniques like Goldmann perimeters which though accurate, require specialized unavailable instruments. We developed a simple hand-held instrument (diplopometer) that allows reproducible quantitative assessment of the diplopic field. It has the resolution and reproducibility of the most sophisticated instruments.

Methods:
The diplopometer was developed to assess the point of onset of diplopia with gradations of 1 degree. An orientation component of the device allowed for alignment along the vertical and horizontal meridia and the 4 oblique meridia. 3 measurements were taken for each gaze direction using a white linear target 1.5 mm in diameter. Intrapatient measurement reproducibility was analyzed by noting the difference between the greatest and smallest measurement for each direction, Δ. The ranges and standard deviations for Δ were calculated. Patients included those with TAO, IOI, fracture, and orbital abscess.

Results:
In >90% of patients reproducible measurements were obtained and Δ was less than 3 degrees. Patients denying diplopia with gross acute misalignment of the eyes were assumed to be suppressing and excluded. Rare patients showed inconsistent measurements with Δ of 10-20 degrees. If this occurred repeatedly, they were excluded. The diplopometer identified unsuspected diplopia in some patients not felt to have diplopia qualitatively.

Conclusions:
The diplopometer can identify unsuspected diplopia and patients who are suppressing. It can reproducibly quantitate diplopic fields and allow for serial assessment of diplopia to quantitatively follow the resolution or worsening of active conditions. It also allows assessment of a patient's perceived diplopia which can help guide their functional assessment as well as that of ability/disability. Its reproducibility equals those of the most sophisticated instruments, while requiring less time, space and technical help.

Financial Disclosures: David Bardenstein co-inventor of diplopometer (No financial support to date)

Grant Support: Jean Schroeder Foundation
Unstable Strabismus Secondary to Amyloid Infiltration of the Extraocular Muscles Preceding a Diagnosis of Primary Amyloidosis

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Introduction:
Amyloid infiltration of the extraocular muscles is a rarely reported finding in the literature with eleven total cases reported in the last twenty-five years. In approximately half of the reported cases, patients had an associated systemic hematologic abnormality. We present a patient with a history of unstable strabismus, found to have biopsy-proven amyloid infiltration of the extraocular muscles as an initial presentation of systemic amyloidosis with extraocular involvement. We discuss the appropriate systemic evaluation for patients with extraocular muscle amyloid infiltration, as well as the pathology and prognosis for amyloidosis.

Methods:
A 66 year-old Hispanic female with a history of hypertension presented with approximately 1.5 years of horizontal, binocular, constant diplopia. Examination revealed limited ductions in all directions of gaze. An MRI of the brain and orbits with and without gadolinium was consistent with enlargement of multiple extraocular muscles of the right eye. Further diagnostic studies revealed thyroid nodules, although laboratory testing indicated she was euthyroid and lacked Grave's antibodies. She continued to have progressively worsening diplopia and ophthalmoplegia despite euthyroid status over the subsequent year, so the decision was made to proceed with extraocular muscle biopsy.

Results:
Histologic specimens revealed Congo-red staining and apple-green birefringence consistent with amyloid infiltration of the rectus muscles. The patient had no systemic manifestations of amyloidosis at the time; however, hematologic work-up demonstrated an M-spike as well as multiple other biopsies positive for amyloid. She is currently undergoing chemotherapy treatment for primary amyloidosis.

Conclusions:
A diagnosis of extraocular muscle amyloid infiltration necessitates a full systemic work-up as untreated primary amyloidosis has poor overall survival rates. This case demonstrates the need for pursuing additional systemic diagnostic testing when the clinical progression does not match the expected course of a particular diagnosis, as well as the role of the ophthalmologist in detecting potentially fatal systemic conditions.

References:


Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Torsional Nystagmus in Syringobulbia: An association often listed, but rarely described

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Introduction:
Syringobulbia is characterized by a syrinx in the brainstem, typically the medulla. Torsional nystagmus is a common sign in syringobulbia [1]. It tops the list of causes of torsional nystagmus in two works on Neuro-ophthalmology, yet the association receives little attention [2,3]. It is characterized by rhythmical slow followed by fast corrective movements about the visual axis [4]. Initially it may be present in extreme lateral gaze, but over time it may present in all directions [1]. Primarily torsional nystagmus is usually due to diseases affecting the central vestibular connections [3] such as brainstem stroke, tumor, vascular malformations, multiple sclerosis and trauma [4]. We report a patient whose oscillopsia from torsional nystagmus led to discovery of syringobulbia.

Methods:
A clinical case presentation includes a video and MRI

Results:
A 50 year-old female treated for herpetic keratitis complained of oscillopsia. She had a car accident 10 years prior with injury to her neck and back. On exam she had torsional nystagmus in all fields of gaze. The torsional nystagmus was characterized by the upper poles of the patient’s eyes beating toward her left shoulder. The frequency and amplitude of the nystagmus, as well as the oscillopsia, increased with levoversion. The patient had paresthesias and decreased sensation on the left arm. Imaging revealed a syrinx extending from the T8 level to the cervicomedullary junction and obex. T2 prolongation extended into the posterior aspect of left medulla.

Conclusions:
This case demonstrates torsional nystagmus in syringobulbia. This confirms the finding that torsional nystagmus beats toward the affected side of the medulla [1, 5] and contradicts opposing findings[4]. The patient suffered from hypoesthesia, but ultimately it was nystagmus that led to imaging and the diagnosis of syringobulbia. This case correlates nystagmus with abnormalities in the brainstem and demonstrates how an ophthalmic exam can uncover systemic disease.

References:

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Grant Support: None.
A 4-Generation Family Case Series of Spinocerebellar Ataxia Type 7

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Introduction:
Spinocerebellar Ataxia Type 7 (SCA7) is an autosomal dominant disorder associated with progressive vision loss. SCA7 exhibits marked genetic anticipation, caused by expansion of CAG trinucleotide repeat within the ATXN7 gene during parent-to-child transmission. Neurologic defects include ataxia, dysarthria, dysphagia, and pyramidal signs. Visual symptoms include progressive central vision loss, photosensitivity, dyschromatopsia, optic atrophy, nystagmus, and difficulties with saccades and pursuits.

Methods:
The fourth generation patient is a 12 year-old girl presenting with reduced vision of 20/250 OU, upbeat nystagmus in upgaze, and a decreased supraduction capacity OU; neurologic symptoms are limited to mild ataxia. Her brother died at age 2½ from complications related to SCA7. Her mother experienced an onset of vision loss in her 20s and within 15 years progressed to complete blindness; she is confined to a wheelchair. The second generation, grandmother, had an onset of symptoms at age 48, characterized by mobility issues and vision of 20/120. The first generation great-grandfather, exhibited primarily mobility and speech issues at age 60.

Results:
This case series presents four generations of a family affected by SCA7, where the diagnosis was not identified until the 3rd generation. Early generations were initially thought to have multiple sclerosis. Each successive generation has an earlier age of onset and stronger phenotypic expression. Typical of SCA7, earlier generations with a later age of onset present with neurologic symptoms, as compared with later generations with an earlier age of onset, who present with visual symptoms.

Conclusions:
SCA7 is a debilitating neurodegenerative disease that can be devastating within families due to its marked genetic anticipation. Early generations may present primarily with neurologic symptoms and only mild vision impairment, whereas later generations may present initially with visual symptoms. Identification of this disease in early generations is essential for patient education and referral for genetic counseling.

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Ocular Motor Deficits Induced by Deep Brain Stimulation

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Introduction:
Deep brain stimulation (DBS) has been used to successfully treat a variety of movement disorders, particularly Parkinson’s disease (PD). Rare reports exist in the literature of complaints of vision changes of patients with DBS. We report a subject who enjoyed improvement of Parkinsonian symptoms but complained of blurry vision with his stimulators turned on. Eye movements were analyzed using scleral search coil technology.

Methods:
Data was observed through a single case study.

Results:
A 48 year old man with Parkinson’s disease underwent bilateral subthalamic nucleus quadripolar electrode implantation which improved his PD symptoms and reduced his medication requirements. However, when stimulators were turned on, he noted that his visual environment would tilt counter clockwise and his vision would blur. Examination revealed square wave jerks, a prolonged latency of saccades, mild slowing of vertical saccades, profound gaze impersistence, eyelid retraction, and he could not generate optokinetic nystagmus or suppress his vestibulo-ocular reflex. He developed a right head tilt and convergence holding was poor. Almost all ocular motor abnormalities abated when stimulators were turned off. The abnormal ocular motor findings could be duplicated with only the right stimulator on and neuroimaging revealed that the right stimulator tip was placed just past the subthalamic nucleus into the right substantia nigra near the red nucleus.

Conclusions:
This patient displayed an array of ocular motor abnormalities that accompanied his subjective symptoms. Our patient had such good relief of his Parkinsonian features that he did not desire a modification of his deep brain stimulator settings. Practitioners should be aware that patients may suffer from significant ocular motor deficits after placement of subthalamic nucleus deep brain stimulators. Depending on the severity, adjustments to deep brain stimulator settings and alternating contact electrodes may help alleviate the visual complaint and concurrently diminish adventitious motor movements.

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Quantifying the Natural History of Postinfectious Ocular Flutter

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Introduction:
Ocular flutter is a rare ocular oscillation which consists of bursts of involuntary conjugate rapid horizontal eye movements without an intersaccadic interval and is frequently associated with truncal ataxia. It is proposed to be caused by lesions in omnipause neurons or cerebellar vermal pause neurons [1]. Etiologies are varied and include vascular, inherited disorders, paraneoplastic, demyelinating, auto-immune, and postinfectious. In the postinfectious case, resolution is spontaneous though various treatments may speed up recovery [2]. Because a quantified natural history of ocular flutter has not been presented in detail, we present a time series data of postinfectious ocular flutter to aid in clinical management.

Methods:
We studied two patients (3rd and 5th decades) that presented simultaneously to the hospital service with ocular flutter and debilitating truncal ataxia. Both patients were admitted to the hospital for workup and in both the etiology was determined to be postinfectious. Treatments included levetiracetam and IVIG. Eye movement recordings were obtained on consecutive days during admission as well as one month post discharge. Equipment included a video based SMI iView eye tracker synchronized to custom visual display software (PEECS). Data was analyzed offline in MATLAB.

Results:
During admission of the two patients, one did not improve significantly while the second patient improved significantly. Eye movement recordings aided in management for one patient to prevent a month course of antibiotics. One month post discharge follow up in both patients noted decreased ocular flutter associated with the decreased ataxia and overall functional improvement in all ADLs.

Conclusions:
In patients with postinfectious ocular flutter and truncal ataxia, symptom severity peak within a 1-2 week period of initial symptoms. However immediate improvement can be variable with a significant gain of function occurring 6 weeks after initial presentation. Quantitative eye movement recordings are helpful to clinically manage and follow these patients.

References:

Financial Disclosures: The authors had no disclosures.

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Nutritional Optic Neuropathy and Wernicke's Encephalopathy After Bariatric Surgery As a Result of Micronutrient Malnutrition

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Introduction:
Bariatric surgery has become increasingly popular as the prevalence of the obesity epidemic steadily increases. The long term neurologic and ocular complications of bariatric surgery can result in disabling ocular sequelae. Most of these neurologic and ocular sequelae are related to nutritional deficiencies secondary to starvation injury. We report a case of nutritional optic neuropathy and Wernicke's encephalopathy after starvation injury from bariatric surgery resulting in vision loss, ophthalmoplegia and ataxia.

Methods:
A 40-year-old woman presented with decreased vision, intermittent diplopia, headache and ataxia. She had a recent 100 pound weight loss within a 3 month period after having bariatric surgery and had a recent hospitalization for dehydration. She was found to have bilateral horizontal gaze restriction, gaze evoked nystagmus, vision loss to 20/200 OU with scotomas bilaterally, bilateral optic disc edema and truncal ataxia. Additional testing revealed normal magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), lumbar puncture (LP) with confirmation of optic disc edema on optical coherence tomography (OCT). She was found to have vitamin B2, B6 and B12 deficiency, elevated anion gap metabolic acidosis and anemia.

Results:
The patient was admitted and treated with IV hydration, adequate nutrition, vitamin supplementation and IV thiamine. This led to rapid improvement of her visual acuity to 20/25 OU, and almost complete resolution of her ophthalmoplegia, nystagmus and ataxia. The patient was then discharged to a rehabilitation unit for physical therapy, continued thiamine use, hydration, vitamin supplementation and adequate nutrition.

Conclusions:
This case highlights the ocular complications that can occur after bariatric surgery and starvation injury. With the incidence of bariatric surgery rising, ophthalmologists should realize the potential multifactorial ocular sequelae. Understanding micronutrient deficiencies, fat and protein malabsorption and starvation injuries in patients such as this, is important in obtaining prompt treatment and follow up for prevention of potential long term and disabling sequelae.

References:

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Poster 30

Idiopathic Unilateral Enlargement of the Extraocular Muscles in an Infant

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Introduction:
The differential diagnosis for enlargement of the extraocular muscles (EOMs) generally includes infiltrative, inflammatory, and vascular processes. Herein, we report the unusual case of an infant who presented with unilateral restrictive strabismus secondary to idiopathic enlargement of the EOMs.

Methods:
A 6-month-old boy, with an uneventful birth history and normal development, presented with a unilateral motility deficit of the right eye first noticed by the pediatrician 2 months prior. External exam revealed 2 mm of right-sided ptosis and 1 mm of enophthalmos. Motility exam demonstrated a marked elevation and abduction deficit in the right eye. By Krimsky testing, there was a 15-prism diopter (PD) right hypotropia and 25-PD esotropia. Examination under anesthesia revealed restriction of elevation and abduction. Anterior and posterior segment examinations were normal bilaterally. Neuroimaging showed unilateral enlargement of the medial, lateral, and inferior rectus muscles with sparing of the tendons and no soft tissue involvement. MRA was normal. Urine catecholamines and MRI of the chest and abdomen were negative. Thyroid function tests were normal in the infant. The mother has a history of hypothyroidism, but labs conducted before and during the pregnancy were normal.

Results:
The patient underwent inferior rectus recession and biopsy. The pathology demonstrated normal muscle architecture with no evidence of inflammation or fibrosis. Repeat MRI 3.5 months later demonstrated no change in the size and appearance of the muscles. There was a residual 10 PD right hypotropia. Compliance with alternating occlusion has been excellent.

Conclusions:
While TED and unilateral congenital fibrosis of the EOMs are plausible diagnoses, this constellation of findings including ptosis, enophthalmos, and unilateral enlargement of the EOMs in the setting of a euthyroid mother and infant is unique. A review of the literature reveals the rare nature of this presentation, which we propose is congenital enlargement of the extraocular muscles.

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Grant Support: None.
Atrophy and Fibrosis of Extraocular Muscles in Anti-Acetylcholine Receptor Antibody Myasthenia Gravis: A Clinicopathologic Case Report

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Introduction:
Myasthenia gravis (MG) is an autoimmune disorder involving the neuromuscular junction. It frequently involves the extraocular muscles (EOMs) resulting in diplopia.

Methods:
A 66-year-old man presented with two months of right eyelid drooping and vertical diplopia. Examination showed almost complete ophthalmoplegia of the right eye. The left eye also had difficulty with abduction and depression. He had complete right ptosis and no levator function. Digital forced ductions were normal. His pupils were 4.5 mm and equally reactive. The remainder of his exam was normal.

Results:
MRI showed uniformly small extraocular muscles in both eyes suggesting CPEO. An intravenous edrophonium test was deferred due to elevated blood pressure (194/107). Serum AChR-binding antibodies were ordered and found to be elevated. A diagnosis of myasthenia gravis was made. He was treated with oral corticosteroids and pyridostigmine, followed by the addition of azathioprine. While his ptosis improved, he continued to have constant vertical diplopia. One year later he opted for surgical correction of the diplopia. The resected superior rectus muscle specimen was sent for histopathological analysis. H&E staining appeared to be consistent with EOM, but modified trichrome stains revealed near-complete replacement of muscle by connective tissue. This finding was later confirmed using desmin and other special histochemical stains.

Conclusions:
In a search of the medical literature we were unable to find another case with small EOMs on MRI or histopathology with marked atrophy and fibrosis of an extraocular muscle in a patient with MG and AChR antibodies. While denervation atrophy in MG has been shown in other striated muscles and the diplopia of MG typically responds to medical management, our case suggests that the presence of atrophic EOMs on MRI likely portends a poor response to medical management alone.

References:

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Grant Support: None.
Poster 32

Sphenoid Sinus Mucocele: The Next Great Mimicker

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Introduction:
Neuro-ophthalmic emergencies require early recognition and prompt diagnosis. We report three cases of sphenoid sinus mucocele each presenting as a neuro-ophthalmic emergency. Expeditious recognition and treatment of this disorder may prevent permanent visual loss.

Methods:
Three consecutive cases of sphenoid sinus mucocele presenting as acute cranial nerve palsies were retrospectively reviewed.

Results:
All 3 cases mimicked a distinctive characteristic of an acute neuro-ophthalmic disorder: (1) Posterior ischemic optic neuropathy of giant cell arteritis, (2) retrobulbar optic neuropathy of optic neuritis, (3) third cranial nerve palsy.

Conclusions:
Conclusion: Sphenoid sinus mucocele can create a diagnostic dilemma in that it may mimic classic neuro-ophthalmic disorders and should be kept in the differential diagnosis of neuro-ophthalmic emergencies.

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Successful Outcomes in Surgical Treatment of Third Nerve Palsy

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Introduction:
Strabismus from third nerve palsy (3NP) is difficult to treat. Our goal was to explore factors associated with successful surgical outcomes in 3NP.

Methods:
Institutional records of all adult patients (≥18 years) from 1988-2012 with 3NP who underwent strabismus surgery or botulinum toxin injections were retrospectively reviewed. Success was defined as absence of diplopia, vertical deviation ≤2PD, and horizontal deviation ≤10PD.

Results:
56 patients from four surgeons were included. 30 (53.6%) were female; mean age was 47 (range 20-80). 44 (79%) had unilateral 3NP; 9 (16%) had other ocular motor nerve palsies. 3NP were complete in 24 (43%). Underlying etiology was idiopathic/microvascular in 5 (9%), traumatic in 13 (23%), neoplastic in 12 (21%), aneurysmal in 10 (18%), and other central nervous system related in 16 (29%). Trauma was associated with more frequent aberrant regeneration than other etiologies: 9/13 (69%) vs. 4/43 (9%) (p<0.01). 10 patients (18%) had >1 surgery. Surgical success was achieved in 28/56 (50%). Success rate was unaffected by etiology, degree of palsy, pupillary involvement, presence of aberrant regeneration, or number of other cranial nerves involved. However, adjustable sutures were used in 27 patients (48%), and there was a trend toward higher success rates when adjustable vs. nonadjustable sutures were used (63% vs. 38%, p=0.06).

Conclusions:
Unlike with 6th nerve palsies, the etiology and degree of 3NP does not appear to affect the ultimate success rates or number of procedures performed. Strabismus surgeries for 3NP with adjustable sutures may be associated with better outcomes.

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Introduction:
Patients who develop acute problems with ocular misalignment often present urgently to resident-run ophthalmology clinics with complaints of diplopia. Correct diagnosis of the etiology of ocular misalignment is essential to select appropriate subsequent investigations and interventions. Classic neuro-ophthalmic teaching for identifying cranial nerve palsies uses a picture of a patient’s eye positions in nine fields of gaze to teach the trainee to identify the presence of an eye misalignment and which nerve is involved. In the pictures the deviated eye is evident, the presentation is classical and clear cut and identification of the affected cranial nerve relies on simple pattern recognition. In clinical practice, patients’ presentation can be less than classical and orthoptic measurements are helpful to make the diagnosis. To use these measurements appropriately, the trainee must have the knowledge required to interpret them. Currently there are few resources commonly available and used by ophthalmology residents.

Methods:
All current Canadian ophthalmology residents years PGY3-5 will be sent an anonymous survey with a series of orthoptic measurements representing cases of acute cranial nerve palsies. They will be asked to identify the paralytic eye, the muscles and cranial nerve(s) implicated and to draw the corresponding ocular motility diagram. Based on common errors and sources of confusion, a learning tool is being developed.

Results:
At the time of submission this study is ongoing. Preliminary data indicates trainees have difficulty isolating which muscles are involved and producing the expected ocular motility diagram.

Conclusions:
We hope from this study to define the learning needs for cranial nerve palsy recognition and then create a useful self-learning tool that can be used by ophthalmology trainees to help them read and interpret orthoptic measurements.

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Grant Support: None.
The Effect of 4-aminopyridine on the Velocity Versional Dysconjugacy Index (VDI), an Objective Ocular Motor Metric of Dysconjugacy Associated with INO in MS Patients, During High Precision Escalation in Core Body Temperature

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Introduction:
The primary goal of the study was to test the hypothesis that the potassium channel blocker, 4-aminopyridine (4-AP), could mitigate a precisely defined heat stress-induced worsening in the ocular motor dysconjugacy associated with internuclear ophthalmoparesis (INO), in patients with Multiple Sclerosis. A substantial portion of the day-to-day disability in living with MS is related to a number of factors that influence conduction slowing and conduction block in demyelinated axonal segments, which correspondingly produce stereotyped, recurrent, and reversible changes in neurologic functional capabilities (Uhthoff's phenomenon). These include thermal stressors, infection, psychological stress, exercise, the menstrual cycle, and metabolic abnormalities. What is germane to all of these provocative factors, is their ability to increase core body temperature in MS patients

Methods:
Utilizing infrared oculography, we have previously reported that MS patients with INO, exhibit a significant worsening of interocular dysconjugacy, secondary to elevations in core body temperature. Electrophysiologic studies of demyelinated axons have shown that abnormal potassium currents decrease action potential duration and amplitude, contributing to action potential failure or conduction block. Alternately, 4-AP, prolongs action potential duration. Fifteen patients diagnosed with Multiple Sclerosis and chronic unilateral or bilateral INO (confirmed by established infrared oculographic criteria, as previously established by our group) participated in a double-blind, randomized, prospective, placebo-controlled, crossover study of 4-AP, and its effect on core-body temperature elevation-induced worsening of INO, defined by an increase in the velocity versional dysconjugacy index (VDI), the ratio of the velocities of the abducting to adducting eye movements during horizontal saccades (the primary outcome).

Results:
We will present the final safety, tolerability, clinical, and infrared oculography data on the effects of 4-AP versus placebo, on patients with MS and an INO during a well-defined, high precision, escalation in core body temperature, induced by a thermal heat stress.

References:


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Poster 36

Aberrant Regeneration of the Abducens Nerve to the Medial Rectus Muscle

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Introduction:
Following traumatic cranial nerve injury, aberrant regeneration involving the extraocular muscles is almost invariably confined within the distribution of the injured nerve. In this report, we describe a patient who developed synkinesis from the abducens nerve to the territory of the oculomotor nerve.

Methods:
Observational case report

Results:
A 21-year-old male was referred for evaluation of ocular misalignment following trauma. Medical history was significant for a motor vehicle accident 6 months prior. Injuries included left sided frontal and tripod fractures and a hemorrhagic contusion within the left frontal lobe. Immediately following the accident the patient was hospitalized where he spent six weeks prior to regaining consciousness. Upon awakening the patient noted that his left eye was “turned in”. During the following three months, the eye drifted to its present position. No formal ophthalmic evaluation was performed during this period. On examination best corrected visual acuity was 20/20 OD and NLP OS, with a dense afferent pupillary defect. The only notable finding on funduscopic evaluation was a pale left optic nerve. The globes were in normal position with no enophthalmos. Extraocular motility was consistent with a left partial oculomotor and near complete abducens nerve palsy, with synkinesis. Right eye motility was normal. In primary gaze, the left eye was less than 10 degrees esotropic. With attempted left gaze, the left eye turned inwards (to the right) roughly 50% past midline. With attempted right gaze, adduction was markedly reduced. Supraduction and infraduction were moderately reduced. Eyelid elevation was observed in downgaze. No pupillary changes were observed with movement in any direction.

Conclusions:
We describe a patient with aberrant regeneration of the left abducens nerve to the ipsilateral medial rectus muscle following traumatic abducens nerve palsy. To our knowledge this is the third such report. (1,2)

References:


Financial Disclosures: The authors had no disclosures.

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Introduction:
Patients with peripheral neuropathy or trigeminal nerve injury are at risk for developing neurotrophic cornea, which may lead to corneal epithelial erosions, corneal ulcers and permanent visual loss. New methods of quantifying corneal innervation in vivo using confocal microscopy may aid in the diagnosis and evaluation of new treatments for peripheral neuropathy.

Methods:
Corneal confocal microscopy (Heidelberg HRT, Heidelberg, GE) was used to collect a stack 40 images every 2 microns (400x400x80 micron volume) from the central cornea of each eye of 10 normal subjects, 9 subjects with diabetes, and 2 subjects with unilateral trigeminal damage seen in our neuro-ophthalmology clinic. Corneal confocal microscopy was repeated 5 times in each eye on 5 different days in the normal and diabetic subjects to determine measurement variability of the summed nerve branches using an automated 3D software analysis.

Results:
The total micron nerve length in the central corneal including all branches (mean±SD) for normal subjects was 2064±489 (OD), 2019±477 (OS), and 66±727 (OD-OS). For diabetic subjects, 1993±533 (OD), 2038±481 (OS) and 44±733 (OD-OS), not significantly different from normal. Patient 1 with a neurotrophic cornea after optic nerve sheath fenestration had no nerves that could be visualized in that eye. Patient 2 with a prior Wallenberg syndrome showed significantly reduced ipsilateral nerve length. Anterior segment SD-OCT of the corneas in these two patients revealed no significant inter-ocular asymmetry in the measured epithelial or stromal thickness compared to the normal subjects.

Conclusions:
Neurotrophic cornea from damage to the proximal or distal trigeminal nerve results in a dramatic loss of corneal nerves in the sub-epithelial basal plexus. Confocal microscopy can easily identify such differences, but subtle changes over time in progressive peripheral neuropathy (i.e. diabetic neuropathy) would not be detectable until at least half of the total nerve length is lost, as visualized by confocal microscopy.

References:


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An Alternative Surgical Treatment of Torsional Diplopia Secondary to Bilateral Superior Oblique Palsy

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Introduction:
Torsional diplopia causes significant visual disturbance for patients with bilateral superior oblique palsies and often poses a surgical challenge. The Harada-Ito procedure may address the excyclotorsion by inducing an intorsion effect from transposition of the anterior superior oblique tendon fibers, however this procedure may be technically challenging, may induce a Brown syndrome and may not address the associated V-pattern esotropia. We present a case of a patient with severe torsional diplopia secondary to a bilateral superior oblique palsy that resolved with a bilateral inferior rectus recession with nasal transposition.

Methods:
A 25 year old female with a pineal Schwannoma underwent resection via a right occipital craniotomy and post-operatively developed constant diplopia with 15 degrees of excyclotorsion in primary position and 14 prism diopters of esotropia in down gaze, requiring her to occlude one eye. We performed a bilateral inferior rectus recession of four millimeters with nasal transposition. Two months after surgery she had no diplopia or torsion, except in extreme downgaze, where she demonstrated 5 degrees of excyclotorsion and 4 prism diopters of esotropia. Binocular diplopia fields did not reveal diplopia.

Results:
This case was unique in that the Harada-Ito procedure was not attempted as the first line for torsional diplopia. Bilateral inferior rectus recessions in combination with nasal transposition decreases excyclotorsion and adduction in downgaze, making it an ideal procedure of choice when excyclotorsion and esotropia are worse in downgaze. In addition, it has the advantage of being a less technically challenging surgery with a more predictable outcome.

Conclusions:
Vertical rectus muscle recession and transposition may be an alternative to consider as first line in the presence of significant excyclotorsion and V-pattern esotropia. Future studies should replicate this procedure to further quantify the results and support the successful outcome.

References:


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Grant Support: None.
Ocular neuromyotonia noted after Recent Botulinum Toxin Injection for Sixth Nerve Palsy following Resection of a Posterior Fossa Skull Based Meningioma

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Introduction:
Ocular neuromyotonia (ONM) is a rare paroxysmal neuromuscular disorder characterized by involuntary contraction of one or more ocular muscles resulting in episodic diplopia and strabismus. Reported etiologies include radiation, chronic nerve palsy, Graves’ disease, compressive lesions, stroke or idiopathic. The disorder is thought to be secondary to axonal instability; therefore membrane-stabilizing agents such as carbamazepine and gabapentin have been utilized. Sparse literature exists describing the role of radiation, the onset of prior nerve palsies in causing ONM, or the association with botulinum toxin. We present a case of ONM following botulinum toxin for a recent postoperative 6th nerve palsy with a prior history of radiation.

Methods:
A 56 year old female, with a history of a left skull base tuberculum meningioma treated fifteen years prior with resection and stereotactic radiation, now presents with a left 6th nerve palsy after a second operation for tumor recurrence on neuroimaging. There was no prior history of a 6th nerve palsy. The patient measured 70 prism diopters of esotropia and a complete left abduction deficit. She was treated with 7.5 units of botulinum toxin to the left medial rectus muscle. Three months after the injection, the patient had significant improvement of the left sixth nerve palsy; however was noted to have a strabismus characterized by an esotropia in primary gaze converting to an exotropia after prolonged lateral gaze, suggestive of ONM.

Results:
Unique features of this case include whether the ONM was related to the recent use of botulinum or to the radiation treatment 15 years prior. The simultaneous development of ONM at the time of the partial recovery of the 6th nerve palsy is also of interest.

Conclusions:
Further studies must be conducted to decipher the timing of onset of ONM as related to cranial nerve palsies, radiation and whether botulinum toxin had any role in this case.

References:

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Poster 40

A Squirmy Situation?

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Introduction:
In this case report, a 14-year old girl presented with a three month history of binocular vertical diplopia and left upper eyelid ptosis. Visual acuity was 20/15-2 in the right eye and 20/20 in the left eye. Pupils measured 8 mm in dark and constricted to 3 mm in bright light, with no relative afferent pupillary defect. Palpebral fissures measured 10 mm in the right eye and 8 mm in the left eye. Lid crease measurements were 4 mm in the right eye and 6 mm in the left eye. Marginal reflex distance was 3.5 in the right eye and 2 mm in the left eye. Ocular ductions showed -1 limitation of abduction in the right eye, with normal elevation, adduction and depression. In the left eye, she had -2 adduction, -1 elevation, -1 abduction and full range depression. Alignment showed a 12-prism-diopter (PD) exotropia (XT) and 3-PD right hypertropia (RHT) in primary position, a 35-PD XT and 8-PD right hyperphoria in left gaze, and a 2-PD esophoria in left gaze.

Methods:
Diagnostic tests were performed.

Results:
Cranial MRI showed a T2 hyperintense lesion with surrounding vasogenic edema located in the left frontal lobe [1.9 x 1.8 x 1.9 cm with associated midline shift (7 mm)], a left medial occipital lesion with vasogenic edema and peripheral rim enhancement (0.4 x 0.4 x 0.4 cm.), and a left frontal lobe lesion (0.5 x 0.5 x 0.5 cm). There was enhancement and thickening of the left lateral rectus muscle. Brain biopsy revealed a membranous structure adherent to brain tissue. Although it appeared to be of helminth origin, there were insufficient morphological details for a specific diagnosis. Serum immunoblot assay was positive for Taenia solium.

Conclusions:
The patient presented with a partial left third nerve palsy and bilateral abduction deficits secondary to neurocysticercosis. Potential mechanisms included cranial nerve and extraocular muscle infiltration, and raised intracranial pressure.

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Introduction:
An isolated abducence nerve palsy is a rare presenting sign of nasopharyngeal carcinoma in the skull base and cavernous sinus. The authors report a case of nasopharyngeal cancer (adenoid cystic carcinoma) with intracranial extension in a patient of chronic unresolved abducens nerve palsy.

Methods:
A 52 year-old male without underlying disease was referred with abducence nerve palsy in left eye and glaucoma suspect on both eyes, which diagnosed 2 years ago with normal brain MRI. The BCVA was 20/20 on both eyes. The cup to disc ratio were 0.7 in both eyes and visual field showed inferior area defect in left eye. The fluorescein angiography demonstrated delayed arterial filling in left eye. The carotid Doppler test was normal. Patient had 25 prism diopter esotropia and wearing prism glasses. The patient wanted to take off prism glasses. We performed left medial rectus recession with adjustable suture.

Results:
After 3 months, the patient complained discomfort on left eye with 20/20 visual acuity. The visual field in his left eye showed aggravation of visual field defects involving central area. The MRI and MRA showed diffusely enhancing mass like lesion extent to skull involving orbital apex, nasopharynx and diffuse narrowing in the distal internal carotid artery. He had endoscopic transnasal approach biopsy and diagnosed with primary adenoid cystic carcinoma (ACC). He received radiation therapy for 9 months, and made recovery of visual field defect.

Conclusions:
Abducence nerve palsy may not always be due to a benign process that permits full return of function within months. Nasopharyngeal ACC must be considered in the differential diagnosis of isolated chronic sixth nerve palsy or suspicious nongranulomatous optic disc. In adults, it is essential that the nasopharynx be examined carefully in case of unexplained abducence nerve palsy.

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Poster 42

Associated Injuries and Prognosis in Traumatic Isolated 3\textsuperscript{rd}, 4\textsuperscript{th}, and 6\textsuperscript{th} Cranial Nerve Palsies

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Introduction:
To analyze the relationship between prognosis and the severity of associated injuries in traumatic isolated 3\textsuperscript{rd}, 4\textsuperscript{th}, and 6\textsuperscript{th} cranial nerve palsies.

Methods:
The records of 39 patients (39 eyes) who were diagnosed with isolated 3\textsuperscript{rd}, 4\textsuperscript{th}, or 6\textsuperscript{th} cranial nerve palsy following trauma were reviewed retrospectively to analyze the etiology of trauma, the degree of associated injuries, the degree of paralysis, and the prognosis.

Results:
The 4\textsuperscript{th} cranial nerve was affected most frequently (19 patients, 48.7%), followed by the 6\textsuperscript{th} nerve (12 patients, 30.8%) and the 3\textsuperscript{rd} nerve (8 patients, 20.5%). Traffic accidents were the most frequent etiology of traumatic cranial nerve palsies. Loss of consciousness, intracranial hemorrhage, craniofacial fracture, c-spine injury, and optic nerve injury were among the most common accompanying conditions. The 3\textsuperscript{rd} cranial nerve was the most severely paralyzed and showed the highest number of associated injuries. The recovery rate of all cranial nerve palsies was 46.2%. By nerve, the 3\textsuperscript{rd} cranial nerve palsy showed the lowest recovery rate of 25%, followed by the 4\textsuperscript{th} nerve at 47.4%, and the 6\textsuperscript{th} nerve at 58.3%.

Conclusions:
The prognosis was worse in patients with intracranial hemorrhage compared with those without intracranial hemorrhage. There was a higher average number of associated injuries and the degree of paralysis was more severe in 3\textsuperscript{rd} nerve palsies.

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Risk Factors and Clinical Features of Isolated Ischemic 3rd, 4th, and 6th Cranial Nerve Palsies in Korean

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Introduction:
To investigate the clinical features and risk factors of ischemic third, fourth, and sixth cranial nerve palsies in Korean.

Methods:
A case-control study of 46 Korean patients who were diagnosed with ischemic third, fourth, and sixth nerve palsies was done to evaluate the risk factors. The mean number of risk factors in each nerve group, recovery rate and recovery time were examined retrospectively.

Results:
The mean age of onset was 64.9 years. Of the 46 patients, 15 patients (32.6%) in third cranial nerve palsy group, 15 patients (32.6%) in fourth cranial nerve palsy group, 16 patients (34.8%) in sixth cranial nerve palsy group. Diabetes mellitus and Hypertension were significantly more prevalent than other risk factors such as hyperlipidemia, ischemic heart disease, left ventricular hypertrophy, smoking, elevated blood hematocrit level in the patients group. The mean number of risk factors was 2.3 ± 0.5 in third cranial nerve palsy group, 1.6 ± 1.1 in sixth cranial nerve palsy group, 1.4 ± 1.1 in fourth cranial nerve palsy group. Of the 46 patients, 42 patients (91.3%) were recovered. There was no significant difference in recovery rate by each nerve group. Patients with intracranial abnormalities in brain imaging showed long recovery time (10.5±2.9 weeks) than that of no intracranial abnormalities (7.5±5.1 weeks).

Conclusions:
Ischemic ocular motor cranial nerve palsy is closely related to diabetes mellitus and hypertension in Korean patients. Third nerve palsy group showed tendency to combine multiple risk factors than fourth or sixth nerve palsy group. If there were intracranial abnormalities in brain imaging, it took a long time to recover.

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Clinical Presentations of Perineural Invasion from Squamous Cell Carcinoma

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Introduction:
Perineural invasion in squamous cell carcinoma of the head and neck has been associated with locoregional recurrence and decreased survival in various studies. Periocular squamous cell carcinoma spreads intraorbitally along the supraorbital and infraorbital nerves into the cavernous sinus. Patients with perineural invasion can present with clinical signs and symptoms of cranial nerve involvement, with or without magnetic resonance imaging (MRI) evidence. The recognition of perineural spread is crucial in that the treatment approach will often be altered.

Methods:
A retrospective chart review was performed at a single institution on all patients presenting with cranial nerve palsies due to perineural invasion of squamous cell carcinoma to the brain. Patient demographics, clinical presentations, neuroimaging, treatment, and follow-up were recorded and described.

Results:
A total of four patients were identified with squamous cell carcinoma of the head and neck with perineural invasion into the brainstem. Patients ranged in age from 56-68. The time from initial diagnosis of squamous cell carcinoma to presentation of perineural invasion was up to three years. All patients’ presenting symptoms, leading to the detection of perineural spread of squamous cell carcinoma, were caused by cranial nerve palsies. MRI evidence of perineural spread was not clear in all cases, but biopsy proved the presence of squamous cell carcinoma in these cases.

Conclusions:
In patients presenting with multiple cranial nerve palsies without a known etiology, perineural spread from periocular squamous cell carcinoma should be considered. While neuroimaging can be helpful in the diagnosis, perineural invasion can still be present without neuroimaging evidence. The diagnosis of perineural invasion is key in that the treatment is often adjusted and can have significant prognostic influence.

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Bilateral Third Nerve Palsy as a Manifestation of Multiple Intracranial Aneurysms in Klippel-Trenaunay Syndrome.

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Introduction:
The Klippel-Trenaunay-syndrome (KTS) is a mixed congenital angioosteohyperthrophy dysplasia of blood or lymph vessels characterized by three main symptoms: cutaneous vascular naevi, hypertrophy of a limb and varicose or venous malformations. Arterial system compromise is extremely rare. In this report, we present a 32-year-old woman with Klippel-Trenaunay- (Weber) syndrome who developed bilateral III nerve palsy by intracranial aneurysm

Methods:
A 32-year-old developed loss consciousness, bilateral III palsy and right hemiparesis. The personal history was remarkable by two intracranial aneurysm treated with endovascular methods, asymmetric overgrowth of a right superior limb with hemangiomas in this limb and in the right hemi-thorax and varicose.

Results:
Neuroradiology studies demonstrated multiples intracranial aneurysm in the posterior circulation and the internal carotid artery. The patient was observed. The third nerve improved in the left eye and also she developed third nerve regeneration signs

Conclusions:
Simultaneous occurrence of multiple intracranial aneurysm and syndrome of Klippel-Trenaunay has rarely been described. We emphasize that intracranial, aneurysm should be routinely excluded in Klippel-Trenaunay-Weber syndrome

References:

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A Case of Aneurysmal Bone Cyst associated with Fibrous Dysplasia

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Introduction:
15 year old girl, complained of sudden onset of headache and vomiting for 3 weeks; drooping of the left eye upper lid and associated binocular vertical diplopia on upgaze for 4 days. She was seen at a regional hospital, where she was told that the computerized tomography (CT) scan of her brain and blood work was normal.

Methods:
Examination revealed a pupil sparing left superior division of third nerve palsy, with ptosis and limitation of upgaze in the left eye. In view of the progressive ptosis and left hypotropia, an urgent CT scan and magnetic resonance imaging (MRI) was ordered.

Results:
CT scan showed an expansile lesion of the central skull base involving the sphenoid sinus on the left side with diffuse ground glass attenuation and focal cystic changes with a fluid-fluid level within it. The MRI showed the lesion bulging into the left cavernous sinus and in close proximity of the left internal carotid artery. The patient was admitted to Otolaryngology, where she underwent a functional endoscopic sinus surgery (FESS) on the same day for drainage of the cyst. Post-operatively, the ptosis and ocular motility gradually improved.

Conclusions:
The presence of fibrous dysplasia with aneurysmal bone cyst in the skull base is extremely rare 1, but may expand rapidly after puberty 2. There have been a few case reports 3-6, but this is the first case presenting with a partial cranial nerve palsy that we are aware of. Some patients present with pain 5,7, proptosis or loss of vision 1,8,9. Endonasal endoscopic procedures are increasingly used in pediatric patients with skull base pathologies 10,11, and may leave to improvement of visual acuity. However, recurrence after excision and locally aggressive behavior tends to occur 1.

References:

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Isolated Third Nerve Palsy: When More Meets the Eye

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Introduction:
The etiology of most isolated cranial nerve palsies is classically taught to have a micovascular origin. Given age and additional comorbidities such as diabetes, hypertension, and hyperlipidemia the need for immediate neuroimaging in these patient remains controversial. This case presentation highlights the importance of early imaging even in a population with clear vascular risk factors.

Methods:
A case study of a patient with severe vascular risk factors presenting with pupil sparing-isolated oculomotor cranial nerve palsy will be examined for the necessity to image based upon history and clinical examination. Pupil measurements, extraocular movements, alignment, color vision, and fundoscopic findings pre- and post treatment will be revealed. MRI imaging before and after chemotherapy, bone scan, biopsy, and resolution of symptoms after treatment will be presented.

Results:
Visual acuity was 20/60 OD and 20/30 OS, color vision was intact, visual fields were normal and pupils were normal with a right near-complete ptosis with severely depressed Levator excursion testing. Alignment and motility revealed profound defects in adduction, elevation, and depression. Thin sliced MRI of the brain and orbits with and without contrast showed an enhancing lesion in the right parietal bone, anterior clinoid process with soft tissue changes extending into the right orbital apex. CT of the chest, abdomen, and pelvis revealed multiple well-circumscribed nodules suspicious for metastatic disease. Bone scan showed evidence of multiple areas of involvement in skull, right humerus and left tibia. Lung and parietal bone biopsy revealed CD10 positive atypical lymphoid cells consistent with a diagnosis Post-transplant Lymphoproliferative Disorder (PTLD). After treatment with chemotherapy and prism therapy resolution of motility as well as complaints of diplopia resolved.

Conclusions:
This presentation highlights the importance of early and reliable neuro-imaging during initial evaluation. While the decision to image is often balanced with cost-effectiveness and diagnostic yield, the decision to delay is often predicated on a detailed history and clinic examination.

References:


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Grant Support: None.
Peripheral Cone Dystrophy: An Unusual and Rare Form of Cone Dystrophy

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Introduction:
Cone dystrophy refers to a group of disorders characterized by cone dysfunction and can subdivided into central and peripheral forms. Both are regional cone dystrophies where the cone system is predominately impaired with preservation of the rod system and lack of fundus changes on ophthalmoscopy.

Methods:
Case report.

Results:
A healthy 19 year-old man presented with an 8 month history of progressive peripheral field loss OU, photophobia, and hemeralopia. Visual acuity, color vision and pupillary examination was normal. Automated fields showed generalized constriction OD and temporal constriction OS. Fundoscopic exam was normal. Visual evoked potentials were normal. Full field electroretinogram (ERG) showed diminished photopic amplitudes in the right eye. Macular OCT with autofluorescence shows slight thinning of the fovea and abnormal subretinal pigmentation in both eyes. Genetic testing for Stargardt’s disease was negative. The patient was diagnosed with peripheral cone dystrophy.

Conclusions:
Our case is a rare type of cone dystrophy called peripheral cone dystrophy. This disorder may mimic early Stargardt’s. Multifocal ERG can distinguish which area of cones are affected and monitor for progression. With awareness of this disorder and advances in technology this entity may be more readily diagnosed.

References:


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Iatrogenic Ophthalmic Artery Occlusion Caused by Collagen Injection During Cosmetic Procedure

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Introduction:
We presented an acute ophthalmic artery occlusion caused by facial filter injection during comic procedure in a small beauty salon near Shanghai city, China.

Methods:
case report

Results:
A 37-year-old woman presented with blindness and painful ophthalmoplegia in the right eye after collagen injection on her right nasolabial while doing rhinoplasty. The neuro-ophthalmology examination 28 hours later revealed the patient to be alert and oriented. Best corrected visual acuities were no light perception OD and 20/20 OS. Pupils were 5mm OD and 3mm OS and showed no direct or consensual light response OD, whereas a reversed relative afferent pupillary defect in the left eye. The lid showed 3 mm ptosis on the right. Examination of extraocular motility revealed ophthalmoplegia in all directions OD (Fig 1). Slit lamp examination revealed normal conjunctiva, cornea, anterior chamber. The crystalline lenses were normal. Applanation tonometry revealed pressures of 8 mm Hg OD; 12 mm Hg OS. Funduscopic examination revealed severe diffuse edema of the retina, as well as the optic nerve OD without a cherry red spot in macular (Fig 2). Spectral-domain optical coherence tomography (SD-OCT) showed decreased vascularity in the choriocapillaris and large choroidal vessels with edema of the macular and peripheral retina. Orbital MRI showed the acute ischemic of the right optic nerve, the ocular muscles and lacuna lesions in brain (Fig 3). Color Doppler ultrasound detected no flow of right central retinal artery, posterior ciliary artery and ophthalmic artery.

Conclusions:
Facial cosmetic injections caused acute ophthalmic artery and/or retina artery embolism had been reported mostly in Korea and the vision loss is profound when emboli retrograde to the more proximal artery—ophthalmic artery¹. Although some precautions may minimize the risk of embolization², plastic surgeons and patients should be aware of the dangerous of blindness while injecting filter for facial cosmetic procedure.

References:

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Poster 49

The Injury Response Factor JUN is Expressed in Multiple Retinal Cell Types After Excitotoxic Insult

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Introduction:
Excitotoxicity has been suggested to contribute to retinal ganglion cell (RGC) death in many diseases. The transcription factor JUN plays a major role in regulating RGC death after a variety of insults and has been shown to control excitotoxic neuronal death in other systems. Also, a recent study suggested that TNF released from Muller glial cells mediates excitotoxicity induced RGC death. Interestingly, JUN can control injury induced TNF expression. Therefore, JUN may play a central role in excitotoxicity induced RGC death.

Methods:
Intravitreal NMDA injections were used to induce excitotoxic insult. Eyes subjected to intravitreal PBS injections were used as control. Retinas were harvested seven days post insult to determine the level of neuronal loss and six hours post insult to determine the pattern of JUN expression. Immunohistochemical analysis of the following markers were used to identify and count cell types: RGCs, TUJ1 and POU4F2; amacrine cells, AP2a; and Muller glia, SOX2.

Results:
NMDA injections significantly reduced RGC number (% PBS injected eyes; 21.9%; P<0.001). No significant loss of amacrine cells was observed. Six hours after PBS injection, JUN expression was not detected in control eyes. In NMDA injected eyes, JUN\textsuperscript{+} cells were detected throughout the inner retina. In the RGC layer, JUN colocalized with the RGC marker POU4F2. In the inner nuclear layer, JUN colocalized with the Muller glia marker SOX2. Small, elongated JUN\textsuperscript{+} cells were also observed along retinal vessels, suggesting that either some retinal pericytes or vascular endothelial cells express JUN after excitotoxic insult.

Conclusions:
The pattern of JUN expression supports both an intrinsic and extrinsic role for JUN in regulating RGC viability after excitotoxic insult. Ultimately, using \textit{Jun} deficient mice subjected to excitotoxic insult, we will critically test the requirement of JUN in controlling TNF expression in Muller glial cells and mediating RGC death.

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Poster 50

A Case of Hemi-central Retinal Artery Occlusion in 12 year-old girl

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Introduction:
Central retinal artery usually divides into two branches at the disc, each of which further bifurcates into temporal and nasal divisions. We report a case hemi-central retinal artery occlusion presumably due to bifurcation of central retinal artery behind the lamina cribrosa.

Methods:
A 12-year-old girl with 6 months of history of decreased visual acuity visited our clinic. She was taking medication for vitamin D deficiency. She had a history of syncope and spinning sensation. Her tests performed by otolaryngologist were normal. On examinations her corrected visual acuity was 20/50 in each eye. Both anterior segments were normal. On fundus examinations superior and inferior hemi-trunks of central retinal artery were emerging separately in both eyes. We performed multifocal-ERG, visual field test, macular OCT and FAG.

Results:
Both eyes showed decreased amplitude in multifocal-ERG, macular thinning in OCT and visual field constriction in Humphrey visual field (central 30-2). In FAG, inferior branch of retinal artery of right eye showed delayed filling as 20/50 in each eye. Both anterior segments were normal. On fundus examinations superior and inferior hemi-trunks of central retinal artery were emerging separately in both eyes. We performed multifocal-ERG, visual field test, macular OCT and FAG.

Conclusions:
On entering the eye, central retinal artery loses the elastic lamina and has a prominent muscularis as it bifurcates at the optic disc. Unusual bifurcation of central retinal artery behind the lamina cribrosa coupled with the unique histological features of the retinal arterioles (hemi-trunks) may predispose to the development of ‘hemi-central retinal artery occlusion’ in young patients.

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Bilateral Central Retinal Vein Occlusion In A Patient With Multiple Myeloma

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**Introduction:**
Central retinal vein occlusion (CRVO) in one eye is common in diabetic and hypertensive patients, often from atherosclerosis of the central retinal artery. CRVO is rarely bilateral, and suggests a broad differential diagnosis including elevated blood viscosity, infection, thrombosis, or compression, calling for hematologic and radiologic evaluation.

**Methods:**
A 45-year-old hypertensive woman diagnosed with multiple myeloma three years previously was referred for reduced vision OD and glare OS. She described sudden onset of a “green circle” occluding her vision in the right eye upon waking about six weeks earlier, with only light perception OD for several days, improving since.

**Results:**
Multiple myeloma was confirmed by elevated IgG Lambda and Beta 2 monoclonal protein, lytic skeletal lesions, and plasma cells found on biopsy of her collapsed L3 vertebra. MRI showed fluid in the optic nerve sheath bilaterally with no associated mass, sinus thrombosis, or abnormal enhancement. Best corrected visual acuity was 20/50- OD and 20/25- OS. AOHRR color plates were seen 6 of 6 in each eye. Pupils were reactive without relative afferent pupillary defect. Visual fields were severely constricted OD, and the blind spot was enlarged OS. Ocular motility was normal. Optic discs were swollen, with intra-retinal hemorrhages, dilated veins and attenuated arterioles OU. Fluorescein angiography showed delayed venous filling in early frames OD, and extensive perivascular leakage and capillary dropout in late frames in both eyes.

**Conclusions:**
Our patient had bilateral CRVOs from venous stasis in the setting of multiple myeloma, exacerbated by anemia. Dilated veins and attenuated arterioles are typical of hyperviscosity. Hydration was considered as a least invasive treatment option, but not pursued because of the risk of ischemia since her hematocrit was already low. Plasmapheresis was recommended to reduce viscosity. A PubMed search found only 5 prior cases of CRVOs in patients with multiple myeloma.

**References:**

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A Case Of Rapidly Progressive Carcinoma-Associated Retinopathy Secondary To Metastatic Neuroblastoma In The Adult

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Introduction:
Carcinoma-Associated Retinopathy (CAR) is one of the least common causes of visual dysfunction in patients with neoplasms. Patients with CAR develop anti-retinal antibodies that cause concomitant loss of vision with rod and cone dysfunction. These antibodies are stimulated by systemic, non-ocular tumors from lung and breast carcinomas. To the best of our knowledge, CAR has not been associated with neuroblastoma in the adult.

Methods:
Case Report

Results:
The authors report a 58-year-old male who presents with rapid progressive loss of central vision OU. Fundus examination demonstrated decreased pigmentation within the perimacular region and posterior pole. A full-field ERG demonstrated severely reduced rod and cone retinal function. The patient has a history of stage IIIB adult neuroblastoma involving the sigmoid colon diagnosed in 2009. A CT scan in December 2012 demonstrated a 9.6 cm pelvic mass with extensive adenopathy compatible with recurrent disease. The tumor involved the paraortic and left pelvic regions extending to the left iliopectineus muscle. A biopsy of an external iliac lymph node was performed and immunohistological studies suggested recurrent neuroblastoma. Our findings were consistent with a paraneoplastic retinopathy secondary to metastatic neuroblastoma. The patient was given a short course of steroids and Intravenous Immunoglobulin (IVIG) and his vision slightly improved.

Conclusions:
The authors report a case of carcinoma-associated retinopathy secondary to neuroblastoma in an adult.

References:

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Gap Junctions Propagate Melanopsin-like Responses Among Retinal Ganglion Cells in a Mouse Model of a Macular Degeneration

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Introduction:
A missense mutation, R345W, in the extracellular matrix protein Efemp1 (or Fibulin-3) causes the autosomal dominant macular degenerative disease Malattia Leventinese (Stone et al. 1999). In mice with the same mutation, we previously discovered that about twice as many retinal ganglion cells as normal display melanopsin-like responses to light: long latency, sustained duration, and persistence when rod and cone photoreceptor input has been blocked pharmacologically (wild type: 45/354 [12.7%, SD = 7.0%; Efemp1R345W: 109/449 [24.5%, SD = 4.3%] This study was designed to determine the origin of this physiological phenotype.

Methods:
We counted melanopsin-positive retinal ganglion cells in whole mount retinas of wild type (wt) and Efemp1R345W mice, and recorded ganglion cell responses to light in vitro, using multielectrode arrays. Pharmacologic blockade of synaptic transmission revealed cells whose responses were independent of rod and cone inputs. Additional blockade of gap junctions with 18B-glycyrrhetinic acid and/or meclofenamic acid showed whether responding cells were intrinsically photosensitive (ipRGCs, containing melanopsin), or propagated from ipRGCs to other cell types via electrotonic synapses.

Results:
There was no difference in the number of melanopsin-positive ganglion cells between wild type (wt) and Efemp1R345W mice. Under pharmacologic blockade of synaptic transmission, Efemp1R345W retinas had 15 to 25 light-responsive cells per array, compared with 2-4 cells per array in control (wt) retinas. Gap junction blockade reduced the number of cells in Efemp1R345W retinas with melanopsin-like responses to that of wt.

Conclusions:
We discovered that in a model of the macular degeneration Malattia Leventinese, mice with the causative mutation (Efemp1R345W) have a higher than normal number of ganglion cells with light responses not originating in rods and cones. There are no more melanopsin-containing ganglion cells; rather, signals appear to propagate abnormally from melanopsin-containing ganglion cells to other classes of ganglion cells, via gap junctions.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: Stephen A. Wynn Institute for Vision Research
Introduction:
Activation of the trigeminal system is involved in migraine. Corneal nociceptive sensation is mediated by trigeminal axons that synapse in the Gasserian ganglion, brainstem, and serve sensory, protective, and trophic functions. In vivo Corneal Confocal Microscopy (ICCM) enables non-invasive imaging of the corneal sub-basal nerve plexus. We sought to determine if there are structural differences in the sub-basal corneal nerve plexus between chronic migraine patients and normal control participants using ICCM.

Methods:
We recruited chronic migraine patients and decade-matched control participants. Patients with peripheral neuropathy or prior corneal or intraocular surgery were excluded. Subjects underwent ICCM using a Heidelberg HRTIII with a Comstock module. Nerve fiber length (NFL) and density (NFD) were measured using established methodologies. Subjects underwent testing of basal tear production with proparacaine, corneal sensitivity assessment with cotton-tip applicator, measurement of tear break-up time, and completion of validated symptom questionnaires.

Results:
Nineteen chronic migraine patients and 30 control participants were enrolled. There were no significant differences in age or gender. NFD and NFL were significantly lower in migraine patients compared to controls (21.5 +/- 11.8 vs. 26.8 +/- 5.9 mm/mm² p<0.04 and 48.4 +/- 23.5 vs. 71.0 +/- 15.0 fibers/mm² p<0.001). NFD was also significantly lower in participants with dry eye compared to those without (51.4 +/- 25.0 vs. 66.1 +/- 19.1, p<0.03). NFD was negatively correlated with basal tear production (Pearson correlation coefficient -0.470, p<0.04, R².22).

Conclusions:
NFD and NFL were lower in migraine patients compared to non-migraine controls and NFD is lower in those with dry eye syndrome. Increased severity of dry eye is correlated with lower NFD. The presence of structural changes in nociceptive corneal axons supports the role of the trigeminal system in the pathogenesis of migraine and dry eye syndrome. ICCM holds promise as a biomarker for future migraine and dry eye studies.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Rare Primary Central Nervous System Melanoma

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Introduction:
Melanocytes arise from neural crest cells and are prevalent in the skin. However, melanocytes are also present in other neural crest derivatives, including heart, bowel, bone marrow, mucous membranes, uveal tract, and leptomeninges. Although melanoma usually originates in the skin, it is possible to have a melanoma originate from these other locations.

Methods:
A 59 year-old man reports blurry vision, reduced peripheral vision, and difficulty reading for the past 3 months. He has a 2-year history of ocular migraines with aura, which occur after exercise. He has been having worsening headaches over the past month, one of which awoke him from sleep. Examination is remarkable for a congruous right inferior homonymous hemianopia.

Results:
MRI reveals a mixed cystic and solid mass in the left occipital lobe, most consistent with a glioblastoma, for which the patient undergoes prompt neuro-surgical removal. Unexpectedly, biopsy shows that this is not a glioblastoma, but rather a melanoma. Thorough work-up shows no other primary site of involvement to indicate a metastatic melanoma. Therefore, a diagnosis of primary CNS melanoma is made.

Conclusions:
Primary CNS melanoma is a rare malignant tumor arising from the melanocytes in the leptomeninges of brain or spinal cord, and accounting for only 1% of all melanomas. Primary CNS melanoma can appear similar to astrocytoma and glioblastoma on imaging, as demonstrated in this case. It is not possible to distinguish a primary CNS melanoma from a secondary metastatic melanoma based on either imaging or histopathology.

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Grant Support: None.
Homonymous Visual Field Defect Showing Negative MRI: Crossed Cerebellar Diaschisis

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Introduction:
Homonymous hemianopia (HH) arises from a lesion interrupting the retrochiasmal visual pathways anywhere from the optic tract to the visual cortex. These lesions can usually be seen by structural imaging studies. Crossed cerebellar diaschisis (CCD) is a cerebellar suppression of the cerebral blood flow due to contralateral supratentorial lesions. CCD has usually been reported in patients with frontal or parietal lobe lesions, but rarely reported in the occipital visual cortex.

Methods:
We describe a 35-year-old man suffering from homonymous hemianopia after head trauma with negative magnetic resonance imaging (MRI) findings.

Results:
We report a young man who presented with homonymous hemianopia and mild ataxia after head trauma but without lesions on brain magnetic resonance imaging (MRI). Diffuse tensor tractography showed a symmetric optic tract and radiation. However, brain 18FDG-PET (fluorodeoxyglucose-positron emission tomography) revealed crossed hypometabolism of the occipital cortex and cerebellum, suggestive of CCD.

Conclusions:
These findings suggest that CCD can cause HH after brain injury and that HH associated with CCD is more related to cortical hypometabolism of the visual cortex rather than prominent structural lesions or fiber tract dysfunction on the visual pathway.

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Grant Support: None.
Oculomotor Nerve Palsy In a Patient With Pancreatic Neoplasm

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Introduction:
Intraductal Papillary Mucinous Neoplasm (IPMN) are potentially malignant neoplasms of the pancreas. They are managed with surgical resection versus close radiological monitoring in select cases.

Methods:
Case report and review of the literature.

Results:
We present a case of a 59-year-old male with past medical history significant for hypertension, non-insulin dependent diabetes, hyperlipidemia and prior transient ischemic attack who sustained progressive double vision, right ptosis, and severe retrobulbar pain for 3 weeks. Physical examination revealed near total, pupil-involving third nerve palsy with intact 2nd, 4th, 5th and 6th cranial nerve function. CT scan of the head and MRI of the brain obtained at an outside hospital were initially read as normal. The diagnosis of right microvascular 3rd cranial nerve palsy was made, which historically may be monitor expectantly for several months without neuroimaging. Given the patient's conjunctival chemosis and asymmetric IOP, cerebral angiography was conducted to exclude dural arteriovenous malformation, and was negative. Upon careful review of fat-suppressed orbital MRI, an intracanal, avidly enhancing, linear lesion along the inferior division of 3rd nerve as well as the labyrinthine segment of the left facial nerve can be seen. Right maxillary and ethmoidal sinusitis is also evident. Cerebrospinal fluid analysis revealed slightly elevated glucose and protein with normal cytology and negative cultures. CT scanning of his chest abdomen and pelvis ordered to rule out lymphoma revealed a 5 mm hypodensity in the body of the pancreas that likely represent an IPMN. Magnetic Resonance Cholangiopancreatography revealed 2 lobulated cystic lesions measuring 8 x 4 mm and 4 x 3 mm in the body of the pancreas. Periportal and portacaval lymph nodes were also detectable.

Conclusions:
Careful review of orbital imaging may be necessary in seemingly classic microvascular cranial neuropathy. Failure to recognize subtle MRI findings of this patient could have missed his life-threatening pancreatic pathology.

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Grant Support: None
Optical Treatment in the Balint Syndrome

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Introduction:
Simultagnosia, optic ataxia and gaze apraxia constitute the clinical triad of Balint syndrome that is typically caused by pathology affecting the parietal-occipital regions bilaterally. Because there are not treatment or therapeutic visual aids for these patients, we introduced prism and filter in order to help in the rehabilitation.

Methods:
A 22-year-old woman with encephalitis developed simultagnosia, optic ataxia, ocular apraxia, visual agnosia and achromatopsia. Prism and ChromaGen filters were tried. Prism lens and ChromaGen filter was calculated subjective until the patient improved the symptoms. The total power of the prism was 4 DP vertically and 2 DP horizontally. The filter selected was blue. The prism power decreased progressive over the time. The average period of prism and filter wearing was 4 years.

Results:
With the prism lens correction the patient was able to identified object, persons, parts of the any picture and also she can read the letter of the Snellen chart together and not isolated. The blue filter results useful in identified color and also the Ishihara test.

Conclusions:
We conclude that prism can fusion the image and ChromaGen lenses may enhance subjective color vision. Prism and color filter can be used in patients with any of the clinical manifestations of the Balint syndrome in order to improved the visual quality and to help in the rehabilitation.

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Grant Support: None.
Poster 59

Neurosurgical Cases with Cortical Vision Loss followed by Improvement

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Introduction:
Cortical vision loss (CVL) is commonly caused by cerebral infarction from arterial occlusion. Usually, the vision loss is permanent. We describe three neurosurgical cases involving CVL with improvement in visual function.

Methods:
Case Reports.

Results:
Case 1: 76-year-old man presented with papilledema due to thrombosis of the torcular herophili. One year later, he became acutely encephalopathic. Neuroimaging showed small bilateral occipital infarcts and a torcular dural arterial venous fistula. He underwent embolization of the feeding arteries followed by resection of the torcula. Post-operatively, he developed cortical blindness. Within two weeks, his vision improved but he had dyslexia. One month later, his visual acuity improved to 20/20 OU. Perimetry testing showed a residual homonymous quadrantopia. Case 2: 27-year-old man was hit in the back of head. He had a posterior skull fracture and bilateral epidural hematomas. During evacuation of hematomas it was noted that there was increased pressure on the superior sagittal sinus (SSS). Post-operatively his vision was light perception only. MRI showed weak diffusion restriction in the occipital lobes. PET scan showed marked decrease in occipital lobe glycolytic activity. Continuous EEG did not show seizures. Two months post-operatively his vision improved to 20/400 OU. Case 3: 65-year-old man was found to have incidental bi-parietal, parasagittal mass. A resection of the mass and the posterior SSS was performed. The diagnosis was meningioma invasion of the inferior part of the SSS. Post-operatively, he was unable to see inferiorly and was having constant positive visual phenomena. Perimetry testing showed bilateral inferior altitudinal visual field defects. EEG demonstrated focal occipital status. After treatment with anti-epileptics his visual fields improved markedly.

Conclusions:
In cases of CVL attributed to transient increased pressure of the SSS there may be marked improvement of visual function over time. It is important to rule out a concurrent ictal etiology.

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Poster 60

Topiramate Induced Palinopsia: Case Series Report and Review of Literature

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Introduction:
We report four cases of topiramate induced-palinopsia and compare their features with those cases previously reported.

Methods:
Retrospective review of case series and literature review

Results:
Four cases of topiramate induced-palinopsia in addition to previously reported four cases1-3 are reviewed. All were female (100%) with diagnoses of migraine (62.5%), idiopathic intracranial hypertension (25%), and bulimia nervosa (12.5%). Lowest dose of topiramate that caused palinopsia was 50 mg daily. Six patients’ symptoms resolved after stopping the drug while one patient’s palinopsia ceased despite continuing topiramate 110mg daily for several years. 50% of patients reported exacerbation of visual disturbance in early morning or late evening.

Conclusions:
Palinopsia from topiramate may be under-diagnosed because patients do not complain or the examiner does not ask.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: None
Introduction:
Although classically defined as a developmental disorder characterized by a loss of visual acuity, the impact of amblyopia on multisensory integration has not been investigated previously. The McGurk effect is a perceptual phenomenon resulting from an interaction between hearing and vision in speech perception. The purpose of this study was to assess visual-auditory integration in adults with amblyopia using the McGurk effect.

Methods:
This is a prospective, single-blinded comparative study. Adults with a history of amblyopia and visually normal controls were given a background questionnaire and baseline assessment of visual acuity, stereoacuity and eye alignment. Participants were then shown a standard video of congruent (control) and incongruent (McGurk) trials consisting of various combinations of visual and auditory phonemes and asked to report what they heard.

Results:
Twenty-two adult subjects with amblyopia (19 female, mean age 32.8 years) and 25 visually normal controls (16 female, mean age 31.8 years) participated in the study. All participants performed at ceiling for congruent trials, with mean accuracy for all groups and viewing conditions exceeding 98%. With incongruent trials, people with amblyopia were significantly less likely to report hearing a fused phoneme (i.e., demonstrate the McGurk effect) compared to controls (p = 0.01). While this difference was greatest during amblyopic eye viewing, it was also present during fellow eye and binocular viewing. No correlations were found between accuracy and visual acuity or stereoacuity.

Conclusions:
This study is the first to show that adults with amblyopia have an impairment of their ability to integrate visual and auditory signals, independent of visual acuity. Visual-auditory integration is an important perceptual ability and a key component of speech perception. The results of this study add to the growing body of evidence that amblyopia causes an array of deficits beyond the visual system.

References:


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Poster 62

Binocular Inhibition (BI) in Strabismic Patients is Associated with Diminished Quality of Life (QoL)

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Introduction:
Binocular summation (BiS) is defined as the superiority of visual function for binocular over monocular viewing, and is decreased in patients with strabismus.1 This study aimed to determine if BiS is related to quality of life (QoL) in strabismus.

Methods:
BiS was measured using ETDRS and Sloan low contrast acuity (LCA) protocols at 2.5% and 1.25% contrast in 108 prospectively enrolled strabismic patients. BiS score was calculated as the difference between the binocular score and monocular score of the better-seeing eye. Patients were categorized as having BiS (BiS score ≥ 5 letters), binocular inhibition (BI) (BiS score ≤ -5 letters) or otherwise indeterminate. QoL was evaluated by questionnaires.

Results:
There was no significant BiS or BI for high-contrast-ETDRS or 2.5% LCA tests in strabismic patients. However, mean BiS score of -2.14±7.0 letters for 1.25% demonstrated significant BI (p=0.004). Mean composite NEI-VFQ-25 score was significantly lower in subjects with BI on ETDRS (80±19 vs. 57±7 for subjects with BiS and BI, respectively, p=0.03), 2.5% LCA (81±14 vs. 66±16 for subjects with BiS and BI, respectively, p=0.01), and 1.25% LCA tests (91±9 vs. 72±14 for subjects with BiS and BI, respectively, p=0.005). After accounting for potential covariates, significant association persisted for BI demonstrated by 1.25% LCA (p=0.01). With BI demonstrable at 2.5%, Adult-Strabismus-20-QoL scores were significantly lower (p=0.04).

Conclusions:
Strabismic patients with BI had significantly lower QoL scores than those who did not, even after accounting for confounds influencing QoL and BiS. These data reveal that even in the absence of diplopia, strabismic patients with BI at low-contrast have reduced QoL.

References:

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Truth-telling and Nonorganic Vision Loss.

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Introduction:
Ophthalmologists face an ethical dilemma when communicating with patients diagnosed with non-organic vision loss (NOVL) – should they reveal the findings of the exam and diagnosis of NOVL risking an angry breakdown in trust; or should they offer something more acceptable to the patient, avoiding discussion of psychiatry or suspicions of pretending? This dilemma reflects the ethical obligation of physicians to weigh the principle of respect for autonomy against the principle of beneficence. We conducted an international survey of neuro-ophthalmologists to examine professional perspectives regarding diagnosis and management of NOVL for adults and children with the goal of promoting discussion of the ethical implications for clinical practice.

Methods:
All members of the North American Neuro-Ophthalmology Society listserv were surveyed with 240/500 responding (48%).

Results:
Using deceptive methods to prove visual acuity was viewed as ethically appropriate (99.2%). Confrontation involving the disclosure of a NOVL diagnosis was not favored in adults (11.4%) and children (4.9%) without a perceived secondary gain. In contrast, confrontation was favored in adults with a perceived secondary gain (49.2%). Treatment of children with a placebo (3.8%) was favored more highly than placebo treatment of adults (1.6%).

Conclusions:
Ophthalmologists adapt their disclosure of diagnoses and treatment to their patients, which imposes some limits on truth-telling. The best method for communicating the diagnosis of NOVL will need to balance ethical considerations with therapeutic benefit. When the therapeutic benefit of deception is unproven, physicians have a duty to disclose.

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Hemifield Slide Phenomenon As a Result of Heteronymous Hemianopia

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Introduction:
Patients with heteronymous hemianopia may experience diplopia due to loss of corresponding retinal points and dissociation of the uniocular visual fields, so-called hemifield slide phenomenon. Concomitant strabismus may complicate hemifield slide. Literature regarding strabismus surgery and restoration of single binocular vision in patients with hemifield slide is limited.

Methods:
In this case series, the medical records of patients with diplopia in the setting of heteronymous hemianopic visual field defects were identified and retrospectively reviewed.

Results:
Three patients were identified. One patient had binasal visual field defects and two patients had bitemporal visual field defects resulting in hemifield slide phenomenon. The two patients with bitemporal defects underwent strabismus surgery for their diplopia and underlying ocular deviation. One patient who underwent strabismus surgery demonstrated a missing strip of central vision or a duplication of central vision dependent on her adjustable suture placement. Two patients, one with binasal defects and one with bitemporal defects, experienced resolution of their diplopia after expansion of their visual fields.

Conclusions:
Hemifield slide phenomenon can occur with any heteronymous hemifield defect. Because of the absence of corresponding retinal points, diplopia may persist despite apparent ocular alignment with strabismus surgery. Expansion of visual field defects may restore corresponding retinal points, allow fusional mechanisms to function, and relieve diplopia. Strabismus surgery to restore binocular visual function can be performed in hemifield slide patients. Patients with improving visual fields may have a better sensory prognosis.

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Validity and Acceptance of Color Vision Testing on Smartphones

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**Introduction:**
Color vision testing (CVT) is an important part of the neuro-ophthalmic examination. The validity of CVT may be affected by the quality of the displayed image, background illuminance, image distance, and visual acuity. iPhone® and Android® smartphones provide diagnostic testing applications including CVT. There is minimal evidence to support the validity of these non-standardized smartphone applications. The purpose is to assess the validity of smartphone CVT by comparing results using the Eye Handbook (EHB) CVT application with Ishihara color plates (ICP).

**Methods:**
An IRB-approved prospective, randomized study was performed of 193 patients with near visual acuity of \(\geq 20/60\) at 14 inches. The study group included patients with ocular pathology. The control group included patients with no known pathology. CVT was performed with both ICP and EHB under a standardized background illuminance, randomized by order of testing and phone model. OD was the study eye. The testing was scored by number of correct plates out of eleven test plates for each modality. A paired-samples t-test was performed.

**Results:**
In the control group (n=80), mean score for ICP was 10.91 +/- 0.284 correct plates and for EHB was 10.94 +/- 0.291, with a difference of 0.0250 +/- 0.0274, p = 0.4176, SD= 0.274, 95% CI -0.036 to 0.086. In the study group (n=113), mean score on ICP was 10.08 +/- 2.109 correct plates and for EHB was 10.29 +/- 2.073, with a difference of 0.212 +/- 0.784, p = 0.0048, SD = 0.784, 95% CI 0.066 to 0.359. Using ICP as the “gold standard” for CVT, the sensitivity of EHB was 89% and specificity 99%. For all subjects, 60% preferred EHB, 12% preferred ICP, and 29% had no preference.

**Conclusions:**
In patients with ocular pathology, there was a statistically significant difference in CVT results comparing EHB with ICP. In control patients, this difference was not statistically significant. The majority of subjects preferred EHB to ICP testing.

**References:**
1. Eye Handbook Color Plate application (Copyright © 2009 Cloud Nine Development LLC).
   http://www.eyehandbook.com/

**Financial Disclosures:** The authors had no disclosures.

**Grant Support:** None.
Vision Testing is Additive to the Sideline Assessment of Sports-Related Concussion

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Introduction:
Visual signs and symptoms are common in sports-related concussion; adding a vision-based test may increase the diagnostic power for clinicians and others evaluating athletes on the sidelines. We examined the King-Devick (K-D) test, a vision-based test of rapid number naming that requires saccadic eye movements, as a complement to the Sport Concussion Assessment Tool, 3rd edition (SCAT3) for diagnosis of concussion.

Methods:
Baseline and post-concussion data for a Division I collegiate football, women’s soccer and women’s lacrosse program were collected, including K-D, Standardized Assessment of Concussion (SAC) and Balance Error Scoring System (BESS). Analyses examined changes in scores from baseline to post-injury. The relation of changes in scores for K-D vs. SAC, BESS and symptom scores from the Post-Concussion Scale (PCS) was determined. Immediate Post-concussion and Cognitive Testing (ImPACT) scores, obtained as part of routine clinical practice for concussion management, but not diagnoses, were also correlated with K-D and SAC scores at baseline.

Results:
Among 30 athletes with first concussion during their athletic season (n=217 total), differences from baseline to post-injury (witnessed event or time of reporting) showed worsening of K-D time scores in 79%, while SAC showed a 2-point worsening in 52%. Combining K-D and SAC captured abnormalities in 89%; adding the BESS identified 100% of concussions. Symptom severity scores on the PCS worsened from baseline with increases in K-D scores (p<0.001); among specific symptoms, light and noise sensitivities were particularly well correlated with K-D worsening. Baseline scores for the ImPACT testing visual motor speed sub-score were worse for athletes who required longer times to complete the K-D test at baseline (p<0.001, linear regression).

Conclusions:
Adding a vision-based test may allow us to detect more athletes with concussion. This is particularly important since not all athletes reliably report symptoms of concussion, including those related to visual function.

References:

Financial Disclosures: Dr. S. Galetta has received honoraria for speaking from Biogen-Idec, Questcor, Vaccinex and Teva. Dr. J. Clugston has received research support from Banyan Biomarkers. Dr. L. Balcer has received honoraria for consulting from Biogen-Idec, Novartis, Questcor, Vaccinex and Acorda she has served on scientific advisory boards for Biogen-Idec.

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Vision-Based Concussion Testing in a Youth Ice Hockey Cohort: Effects of Age and Visual Crowding

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Introduction:
Adding a vision-based test to concussion testing in youth sports may increase diagnostic power on the sidelines. Interpreting these tests in the context of developmental status and age is also important. We examined the King-Devick (K-D) test of rapid number naming as a complement to the Sport Concussion Assessment Tool (SCAT3/Child-SCAT3) in youth athletes.

Methods:
Members of a youth ice hockey league participated in a prospective study to examine three rink-side tests: K-D test, Standardized Assessment of Concussion (SAC, cognition) and timed tandem gait (balance). To perform the K-D test, athletes read numbers from three laminated test cards from left to right as quickly as possible. The cards become progressively more difficult due to changes in vertical spacing between lines; this is particularly notable for card 3.

Results:
Ninety-nine athletes (aged 10.8±3.0 years, range 6-17) underwent pre-season testing for this study. Athletes completed the K-D test in an average of 56.5 seconds (best of two baseline trials, range 27.5-159.8 seconds). Average total SAC scores were 26/maximum 30 points (range 17-30); average best of four trials for timed tandem gait was 15.9±6.0 seconds. All tests showed better scores among older athletes (p<0.001 for all, linear regression). K-D time scores were significantly slower (worse) for younger athletes (p<0.001). This association of worse K-D scores with younger age was most evident for K-D card 3, the card with the greatest degree of vertical visual crowding (average 3.9 seconds slower vs. card 1, p<0.001, linear regression).

Conclusions:
Scores for rapid sideline concussion tests may vary with age and developmental status of youth athletes; better scores in this cohort were noted among older players. Visual crowding, an age-dependent inability to perceive objects due to clutter, may in part explain the more dramatic association of slower time scores on test card 3 with younger age for the K-D test.

References:

Financial Disclosures: Dr. S. Galetta has received honoraria for speaking from Biogen-Idec, Questcor, Vaccinex and Teva. Dr. J. Clugston has received research support from Banyan Biomarkers. Dr. L. Balcer has received honoraria for consulting from Biogen-Idec, Novartis, Questcor, Vaccinex and Acorda she has served on scientific advisory boards for Biogen-Idec.

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Are Prosopagnosic Patients Truly Prosopagnosic? Selectivity for Visual Object Type and Sensory Modality in Acquired Deficits of Face Recognition.

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Introduction:
Whether the processing defect in acquired prosopagnosia is selective for faces has long been contentious. Generic object recognition has often been assessed, but pre-morbid visual expertise for these other objects has seldom been taken into account. Likewise, multi-modal people recognition deficits have usually been excluded by history only, without object assessment of recognition through other routes. Because of this, it has been recently questioned whether right anterior temporal lesions cause face-selective recognition deficits.

Methods:
We examined three domains of perception in an internet-recruited cohort of prosopagnosic patients with a variety of lesions, tested in person. We tested their perception of the handwriting or font of single word stimuli, another object class of high expertise in literate individuals. We next assessed them on a car recognition test that adjusted for pre-morbid expertise with a test of verbal semantic knowledge about cars. Finally we measured their ability to discriminate and recognize voices.

Results:
All subjects with right fusiform lesions were impaired on sorting text for handwriting style, with variable results in subjects with lesions of the anterior temporal lobe. Only one patient, with a right anterior temporal lesion, had definite evidence of normal expertise-adjusted car recognition; in particular, 4 other subjects who had significant car expertise showed impairments. Voice recognition was impaired in 2 subjects with bilateral anterior temporal lesions, but was spared in those with fusiform lesions alone and in one subject with a right anterior temporal lesion. One patient with extensive bilateral lesions also had impaired voice discrimination.

Conclusions:
The majority of patients with prosopagnosia have deficits in other expert-level visual processing. Altered face recognition with bilateral anterior temporal lesions may be part of a multi-modal semantic deficit in people recognition; however, a right anterior temporal lesion can cause an associative prosopagnosia that spares voice recognition.

References:

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Learning to Read Upside-down: A Study of Perceptual Expertise and Acquisition, of Relevance to Rehabilitation of Right Hemianopic Dyslexia

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Introduction:
Reading is an expert visual and ocular motor function, learned almost exclusively in a single orientation. Characterizing this expertise can be accomplished by contrasts between reading of normal and inverted text, in which perceptual but not linguistic factors are altered. Our goal was to examine this inversion effect in healthy subjects reading text, to derive behavioural and ocular motor markers of perceptual reading expertise, and to study these parameters before and after training with inverted reading.

Methods:
Seven subjects underwent a 10-week program of 30 half-hour sessions of reading novels with pages displayed inverted on computer monitors. Before and after training we assessed reading of upright and inverted single words for response time and word-length effects, and reading of paragraphs for time required, accuracy, and ocular motor parameters.

Results:
Subjects gained about 1.2 words/minute n reading speed with each session, or a substantial 35 words/minute over the entire training period. Before training, inverted reading was characterized by long reading times and large word-length effects, with eye movements showing more and longer fixations, more and smaller forward saccades, and more regressive saccades. Training partially reversed many of these effects in single word and text reading, with the best gains occurring in reading aloud time and proportion of regressive saccades, and the least change in forward saccade amplitude.

Conclusions:
We conclude that reading speed and ocular motor parameters can serve as markers of perceptual expertise during reading, and that training with inverted text over 10 weeks results in gains of about 30% in reading expertise. This approach may be useful in the rehabilitation of patients with hemianopic dyslexia, as inverted reading has the potential of restoring parafoveal preview and visual span in front of the currently fixated letter, in a manner that current approaches focused on training reading saccades cannot.

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Persistent Positive Visual Phenomena Revisited

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Introduction:
Patients occasionally report persistent positive visual phenomena (PPVP) with features that differ from those typically associated with visual migraine. Often, such PPVP are described, or can be interpreted, as being consistent with “visual snow.” We report a series of patients with PPVP and “visual snow” that provides additional clinical commentary of the visual and clinical features of this disorder.

Methods:
A retrospective analysis of all patients who presented to a single Neuro-Ophthalmologist from 2009-2013 with “visual snow” was performed. The charts coded with the diagnosis of “visual snow” were reviewed for information in regard to 17 features of the medical history and visual presentation. All patients were interviewed by telephone to clarify the details of our chart review.

Results:
A total of 20 patients with “visual snow” were identified. The majority of patients reported visual symptoms only of “visual snow.” In all cases, the qualitative descriptions were remarkably similar, nearly stereotypical. No patient with isolated “visual snow” experienced disruption of function. MRI scans of all patients were normal. No patient had evidence of neurological disease. Anxiety and depression were present in a minority of patients. Most patients’ symptoms persisted without significant variation for months to years. No treatment attempted by any patient seemed to be effective. A minority of patients reported visual symptoms in addition to the visual snow. Many patients had a history of migraine.

Conclusions:
PPVP with features of “visual snow” is a benign phenomenon that does not require diagnostic investigation or medical intervention. The etiology of visual snow is not known, and migraine remains a plausible factor. The fact that the spontaneous description of visual snow is so stereotypical strongly suggests that it is caused by some biological perturbation, and is not simply a reaction secondary to psychological factors, as is sometimes suggested.

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Alice in Wonderland Syndrome in Posterior Cortical Atrophy

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Introduction:
Posterior Cortical Atrophy (PCA) is a neurodegenerative disorder affecting visuospatial function, most commonly attributed to Alzheimer’s disease pathology. Individuals with PCA have a myriad of complex and perplexing visual disturbances that include prolonged color after images, difficulty reading large rather than small text, and perception of motion of static images (1). Alice in Wonderland Syndrome is a phenomenon characterized by distortions of shapes (metamorphoses), and is most commonly attributed to migraines or seizures.

Methods:
A 65 year old woman with a 9 year history of progressive visual dysfunction characterized by elements of Gerstman syndrome, Balint syndrome, prosopagnosia and eventually memory loss, complained of distortions of common objects. She described that people's fingers appeared either elongated or shorter than they should be and that cars appeared "taller". She also perceived she was farther from objects than she actually was. She had a normal ophthalmologic examination. An EEG and MRI of the brain were performed.

Results:
She met clinical criteria for PCA. An EEG was normal. An MRI of the brain showed characteristic bilateral occipital lobe atrophy.

Conclusions:
We report the first case of "Alice in Wonderland Syndrome" in a patient with clinical features of PCA.

Metamorphopsias and distortions of objects that may make one suspect Alice in Wonderland syndrome, should raise consideration of posterior cortical atrophy as an etiology, especially when this occurs in patients between 50 and 65 years of age.

References:


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Grant Support: None.
Reversal of Visual Field Defect in the Posterior Cortical Atrophy Syndrome Associated with Low Pressure Hydrocephalus.

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Introduction:
Posterior cortical atrophy is a neurodegenerative syndrome that presents with cortical visual dysfunction including visual neglect, constructional dyspraxia, spatial disorientation, and elements of both Balint’s and Gerstmann’s syndromes in the absence of demonstrable stroke or tumor. Visual field defects are common and usually identified by both confrontational techniques and more sensitive automated threshold sensitive perimetry. We treated a patient with PCA and low pressure hydrocephalus with progressive visual field loss documented by serial perimetry in whom the visual field improved following reduction of shunt valve opening pressure.

Methods:
Case report and literature review.

Results:
A 79 year old male with gait dysfunction and Parkinsonian features underwent shunt placement for low pressure hydrocephalus in 2006. Six years later, signs of early cognitive difficulties developed. MRI scans showed significant hydrocephalus and the shunt was revised. Several months later perimetry obtained to screen for glaucomatous defects demonstrated a left homonymous hemianopsia. The following year, over a course of several months gait again deteriorated as did cognitive function. Higher cortical functional defects now included spatial disorganization, constructional and dressing apraxia, achromatopsia, and elements of simultanagnosia (i.e. cookie theft test). The patient was unable to drive or dial a telephone, and became lost in his home. Repeat MRI scans showed right posterior atrophy and persistent unchanged ventriculomegaly. The patient correctly counted fingers and recognized motion in both hemifields. Automated perimetry showed a persistent left homonymous field defect but also repeatedly a right superior homonymous defect. Shunt adjustment to lowest opening pressure was accomplished. Subsequent serial perimetry showed resolution of the right field defect. However, left hemifield defect persisted.

Conclusions:
In PCA automated field perimetry may demonstrate visual defects not apparent confrontationally. In this case, abnormal intraventricular pressure dynamics degraded visual performance in visual association pathways which improved with shunt manipulation.

References:


Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Introduction:
When assessing patients with Graves’ Orbitopathy (GO) in an endocrinology outpatient setting, it is desirable to have a diagnostic laboratory tool to complement the clinical activity score (CAS) to distinguish between patients with moderate-severe active GO requiring high-priority ophthalmological care from those with mild or inactive GO who can be electively scheduled, and to assess response to treatment.

Methods:
A retrospective study evaluating the correlation between TRAb-Fast-ELISA results and CAS in patients with GO seen at a tertiary referral center between 2000-2009. Anti-TSH receptor antibody level quantification was performed using a commercial third-generation TRAb ELISA assay. Other variables analysed included smoking status, gender, age and TSH levels. In addition to this case-series, a comparative review of methods to test TSH-receptor antibodies will be presented, addressing both efficiency and cost.

Results:
Fifty-five patients with GO had a documented CAS within a mean of 22 days from the recorded TRAb-Fast-ELISA test level. An increase of TRAb-Fast-ELISA levels by 1 unit was associated with a 15% (95% CI: 7% to 24%) increase in the odds ratio of elevated CAS. A TRAb-Fast-ELISA result ≥ 10 was analyzed as a diagnostic tool to predict a CAS level of ≥3, with a specificity of 86.7% and a sensitivity of 87.2% for moderately-severe GO.

Conclusions:
Our results demonstrate the ability to predict a patient’s GO activity level by antibody titers. A TRAB-FAST-ELISA ≥10 can be used as a diagnostic tool to predict a CAS level of ≥3.

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Grant Support: None.
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A Non-Touch Slit-Lamp Exophthalmomtry, A Novel Technique

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Introduction:
Exophthalmometry is frequently used in neuro-ophthalmology practice. We describe a novel non touch exophthalmometry technique performed with the basic ophthalmology slit lamp device, and compare the measurements results with those of the Hertel exophthalmometer.

Methods:
A millimeteric graph paper covered by transparency is attached to the slit-lamp table. The slit-lamp is first focused on the center of the cornea and the position of the microscope is marked on the transparency, then the slit lamp is focused on the lateral orbital rim and a second mark is drown. The distance between the two lines as measured on the graph paper represents the exophthalmometry score. 60 patients with suspected orbital disease underwent both slit-lamp and Hertel exophthalmometry and the results were compared.

Results:
Exophthalmometry mean results for the right eye were 19.8±3.3 mm with the slit lamp and 19.5±3.4 with the Hertel. Mean measurements for the left eye were 19.3±4 mm with the slit lamp and 19.6±3.8 with the Hertel. t test for paired samples did not show statistically significant difference in the measurements between the two methods. In only 6 out of 120 measurements there was more than 2 mm of difference between the two techniques.

Conclusions:
Slit lamp exophthalmometry is a reliable non-touch technique which does not require the use of an exophthalmometer.

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Acute Tension Orbital Emphysema: Mechanism and Treatment with Needling Decompression

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Introduction:
Orbital emphysema is a common finding following orbital wall fractures. On general, it is a benign finding and no treatment is required. On rare cases acute tension orbital emphysema might occur causing orbital compartment syndrome leading to visual loss. We will present a patient with acute tension orbital emphysema in whom drainage of air was performed by a simple technique. The mechanism by which it was derived will be presented.

Methods:
A 61 year-old female was struck in her right eye by an airbag during a road accident. She had decreased vision in her left eye mainly due to a submacular hemorrhage. On orbit CT two medial wall and one inferior wall fractures with few orbital small air bubbles were seen. Thirty six hours following trauma, the patient complained of left orbital pain and on examination there was left eye proptosis, a frozen globe and an afferent pupillary defect that was not seen previously. Orbit CT showed acute tension orbital emphysema. An immediate lateral canthotomy and lower lid cantolysis improved her symptoms only mildly. Drainage of air was performed by insertion of a 22 gauge needle to the inferior retrobulbar air compartment. Video Recording of the maneuver will be presented.

Results:
Although immediate improvement in proptosis and eye movements and partial improvement of the afferent pupillary defect were seen, visual acuity did not improve due to optic neuropathy and macular scaring.

Conclusions:
It is essential to recognize early these rare cases of acute tension orbital emphysema that may cause vascular compromise due to orbital compartment syndrome and thus may lead to optic neuropathy or central retinal artery occlusion. Needle drainage of acute tension orbital emphysema is a simple and safe procedure that may prevent visual loss. It is a unique treatment only suitable for orbital compartment syndrome due to orbital emphysema.

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Poster 76

Lateral Rectus Muscle Enlargement in Multiple Myeloma

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Introduction:
Multiple myeloma (MM) is a systemic disease that is part of a spectrum of disorders ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukemia, characterized by a proliferation of malignant plasma cells and production of monoclonal proteins. Extra-skeletal involvement in MM is rare and orbital involvement are extremely rare. The most common clinical presentation includes mass effect with subacute, painful or painless swelling involving the eye and periorcular tissue, proptosis, diplopia, and decreased vision. We report a 73 year-old man with a recent diagnosis of MM who developed rapidly progressive painful right eye proptosis, diplopia and vision loss.

Methods:
This is a case report with retrospective chart review including radiographic imaging studies. Literature search using terms: orbital MM, extra-ocular muscle involvement in MM.

Results:
A 73 year-old man with a recent diagnosis of multiple myeloma involving the left clavicle developed rapidly progressive painful right eye proptosis, binocular horizontal diplopia and vision loss of the right eye of 2 weeks duration. Neuro-Ophthalmologic examination revealed a visual acuity of 20/50 on the right (OD) and 20/25 on the left (OS), pupils showed a right RAPD. Diffuse conjunctival injection and chemosis with complete ophthalmoplegia were noted on the right. Extraocular motility was full on the left. Exophthalmometry showed 5 mm of proptosis on the right with mild resistant to retropulsion. Magnetic Resonance Imaging of the orbit with and without contrast revealed marked enlargement of the right lateral rectus muscle throughout its length with homogeneous signal intensity and enhancement with effacement of the CSF surrounding the right optic nerve at the orbital apex.

Conclusions:
MM should be considered in the differential diagnosis of proptosis and diplopia, in a patient with history of MM or unusual findings of the optic nerve, rectus muscle and/or enhancement on orbital imaging.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: The authors have no conflicts of interest to disclose
A Rare Case of SOX2 Gene Deletion Associated with Bilateral Anophthalmia and Complete Absence of the Visual Pathways and Septum Pellucidum

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Introduction:
Introduction: We report the initial presentation, evaluation, treatment, and follow up of a rare case of congenital bilateral anophthalmia with complete absence of the anterior and posterior visual pathways and septum pellucidum, associated with deletion of the SOX2 gene.

Methods:
Methods: Chart review of the patient was performed, including full patient and family history, imaging and laboratory findings, and history of care, with a review of relevant literature for anophthalmia and SOX2 mutation syndromes.

Results:
Results: The patient was first examined shortly after birth, following an uncomplicated 40-week pregnancy to a healthy G1P0 29 year-old woman. The neonate was noted to have shortened palpebral fissures with no visible globes, reduced orbital volume, dolichocephaly, and no other facial or digital anomalies. Orbital ultrasonography and MRI Brain and Orbits revealed absence of bilateral globes, orbital musculature, optic nerves, chiasm and tracts, optic radiations, and septum pellucidum. Endocrine workup revealed low follicular hormone, luteinizing hormone, and cortisol levels; ACTH stimulation testing was within normal limits. Decreased hearing was found on the right. Full metabolic and infective disease workup, echocardiography and renal and thyroid ultrasonography were within normal limits. Chromosomal microarray analysis revealed an 895 Kb deletion at 3q26.33, including the SOX2 gene. The patient is undergoing socket expansion with serial conformer placement.

Conclusions:
Conclusion: Anophthalmia is a rare condition affecting 1.5-3 of every 100,000 births [1], and is usually bilateral [2]. De novo genetic mutations comprise 10-20% of bilateral cases [3], SOX2 being the most commonly found mutation. Other associated findings in patients with SOX2 mutations include mental retardation, pituitary maldevelopment, neurological abnormalities, facial abnormalities, growth failure, esophageal and genital anomalies [4]. To our knowledge, this is the first reported case of a SOX2 mutation in a child with bilateral anophthalmia with complete absence of the septum pellucidum, anterior and posterior visual pathways, and endocrine abnormalities.

References:


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Grant Support: None.
A Case Of Traumatic CSF Blepharocele Presenting As Fluctuating Eyelid Edema

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Introduction:
Cerebrospinal fluid (CSF) leaks complicate 2% of all head trauma and occur in 12-30% of all basilar skull fractures. Otorrhea or rhinorrhea are more common presentations, although rarely, CSF may leak into the orbit (orbitocele) or the eyelid (blepharocele). Only a handful of cases have been described in the past 55 years. Most of these have occurred in children, which may be due to the immaturity of a child’s frontal sinus.

Methods:
We present a case of an isolated CSF blepharocele in an 89 year old male after blunt head trauma. The patient’s unique clinical presentation resulted in delayed diagnosis of the CSF leak.

Results:
The patient presented after a fall from standing that resulted in a hip fracture and blunt head trauma with facial bruising and edema. CT scan of the head revealed trace pneumocephalus without evidence of fractures. One week later we were consulted to evaluate persistent right upper lid swelling. While the patient was sitting up, the eyes were white and quiet eye with a mildly edematous right upper lid. However, upon supine positioning, we observed a rapid increase in eyelid edema. Eyelid transillumination suggested a focal accumulation of non-hemorrhagic fluid. Facial CT with coronal reconstruction subsequently revealed a fracture of the right orbital roof and a large subdural hygroma. Contrast - enhanced MRI of the head demonstrated communication between the intracranial CSF space and the right upper eyelid.

Conclusions:
Our patient suffered an extremely rare complication of an occult skull base fracture. His age, the position-dependent nature and the possible delayed onset of the CSF leak lead to this diagnostic challenge. Eyelid edema is often discounted in a patient with blunt head trauma. However, CSF leaks may manifest months or years after the initial trauma. Therefore, clinical exam findings suspicious for a posttraumatic CSF leak warrant comprehensive neuro-imaging.

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The “V sign”: Severe Tenting of the Globe in a 3 Year Old Patient with Acute Hemorrhage into an Intraorbital Vascular Malformation

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Introduction:
We present a case of a low flow venous-lymphatic malformation acutely enlarging after a viral illness presenting with acute proptosis, acute angle closure glaucoma and optic neuropathy.

Methods:
Retrospective case report.

Results:
3-year-old girl presented with severe proptosis of the right eye over 2 days. Exam was notable for rAPD, complete ophthalmoplegia and ptosis, intraocular pressure of 57, shallow anterior chamber, swollen nerve, and attenuated and tortuous veins. She also had a recent history of coxsackie virus, a petechial rash, and elevated LDH and platelets. Initial CT showed a homogeneous mass completely filling the right orbit and tenting the globe into a sharp V shape. The orbital vessels seen in the scan were attenuated. MRI performed at presentation showed significant progression and a nonenhancing lesion with fluid levels on T2-weighted images. The patient underwent emergent decompression and biopsy to establish diagnosis and protect the vision. Surgical findings were consistent with a giant distended venous malformation with chocolate colored fluid and coffee grind like material within the vessels. Histopathology was consistent with a vascular malformation, specifically a mixed vascular malformation with frequent vessels including arteries, veins and lymphatics in a disorganized architecture.

Conclusions:
Acute proptosis in a child from an infiltrative tumor may cause an optic neuropathy that is irreversible if not treated promptly. In some haematopoietic conditions steroids can lead to tumor lysis syndrome with renal failure. Initial history and exam was concerning for an infiltrative malignancy, however the different radiographic characteristics of this tumor, along with the pathology, was more consistent with a vascular malformation. Explosive proptosis such as that demonstrated in this child is more consistent with haemorrhage from a low flow vascular malformation. Magnetic resonance imaging better delineates venous malformations from neoplastic lesions of childhood. Emergent surgical intervention can both establish the diagnosis and preserve visual function.

References:

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Grant Support: None.
Endoscopic Bimanual Approach to an Intraconal Cavernous Hemangioma of the Orbital Apex with Vascularized Flap Reconstruction

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Introduction:
The purpose of this presentation is to describe a unique transnasal endoscopic 4-handed surgical technique for removal of an intraconal orbital apex cavernous hemangioma with repair of the defect with a vascularized flap.

Methods:
A case presentation and surgical video are used to demonstrate this technique.

Results:
A 39-year old female, who presented with unilateral visual loss and proptosis, was found to have an intraconal orbital apex mass consistent radiographically with cavernous hemangioma. Because of its extreme posterior and medial location within the orbit, an endoscopic transseptal 4-handed technique was utilized for surgical removal of the tumor. The lesion was excised in toto and the patient had no complications.

Conclusions:
This approach is an excellent surgical option for these difficult to reach lesions. In addition to providing direct access to the tumor, it avoids the morbidity of transcranial surgery and the cutaneous facial scar associated with other approaches. The medial wall flap reconstruction may reduce the risk of post-operative diplopia and enophthalmos.

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A Retrospective Review of Bisphosphonate-Induced Orbital Inflammation

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Introduction:
Orbital inflammatory disease comprises a spectrum of entities that may affect the various structures within the orbit. The etiology of the inflammation is often idiopathic, although some progress has been made in recent years to elucidate specific causes. This study documents the largest series to date of patients presenting with orbital inflammation in whom it was determined that recent systemic bisphosphonate treatment was the likely causitive factor.

Methods:
This retrospective case series reviews 6 patients with orbital inflammatory disease secondary to intravenous or oral bisphosphonate treatment for osteoporosis or cancer. Collected data includes clinical history and examination, type of bisphosphonate drug, radiographic imaging, treatment regimen and clinical outcome.

Results:
Six patients (2 males, 4 females) with an average age of 62.2 years had onset of orbital inflammatory symptoms 1 to 11 days after intravenous bisphosphonate infusion or, in 1 case, 4 weeks after initiation of oral bisphosphonate treatment. Four patients were being treated for osteoporosis and 2 for metastatic lung cancer. Radiographic imaging revealed diffuse orbital involvement in 3 cases, isolated lateral rectus muscle involvement in 2 cases, and superior rectus-levator complex involvement in 1 case. Two patients symptoms resolved spontaneously within 2 weeks, 3 responded rapidly and completely to steroid therapy, and the 1 patient on oral bisphosphonate had a slower but complete response to steroid treatment.

Conclusions:
Clinicians should be aware of the association between acute orbital inflammation and recent treatment with systemic bisphosphonate medications in patients being treated for cancer or osteoporosis.

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Infiltrative Optic Neuropathy Caused by Hematologic and Lymphomatous Malignancies (HLM)

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Introduction:
Malignancies can cause optic neuropathy by invading the perineural sheath or the optic nerve and HLM seems to account for the majority of such cases. Overall, 5-9% of non-Hodgkin’s lymphoma and 20% of leukemia patients have CNS involvement. There have been a few case reports of optic neuropathy with HLM in the past and the diagnosis is often delayed because of the lack of familiarity with this entity. However, high mortality of CNS and optic nerve involvement makes early diagnosis very valuable.

Methods:
A PubMed literature review from 1978 to 2012 revealed 24 cases of vision loss secondary to HLM. We performed a retrospective review of patients presented to our center with a new-onset optic neuropathy with HLM and a clinical presumption that the malignancy caused the optic neuropathy.

Results:
Six patients were identified. The clinical presentations were: temporal 16%, altitudinal 16%, arcuate 8%, restrictive 8% and diffuse 8%, and severe central vision loss (16%), optic nerve head swelling (66%), retinal hemorrhage (50%), and optic nerve atrophy (33%) and no pain. One patient (16%) developed severe central vision loss. Only one patient (16%) did not have a diagnosis of a malignancy prior to the vision loss. Four patients had positive, one had negative and one had no CSF cytology.

Conclusions:
To our knowledge this is the largest number of patients with optic neuropathy secondary to HLM that have been reported in a single study. The clinical presentations of optic nerve involvement in HLM are non-specific and variable. One must have a high index of suspicion in patients with known HLM. A presumption of this diagnosis should prompt consideration of obtaining repeat neuroimaging and lumbar punctures, steps that would not normally be taken in patients with a presumption that they have a more common form of optic neuropathy, especially if visual loss is not progressive.

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Poster 83

Ipilimumab-Related Orbital Inflammation and Hypophysitis in Patients with Metastatic Melanoma: A Brief Case Series.

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Introduction:
Ipilimumab is a monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 used for the treatment of metastatic melanoma. The most frequent adverse reactions associated with Ipilimumab have been autoimmune disorders, including enteritis, uveitis and arthritis. Myasthenia Gravis and hypophysitis have also been previously identified as potential adverse events, but orbital inflammation has not been well established as a potential adverse affect of this medication yet, with only one case previously described.

Methods:
On this short case series we describe two patients with orbital inflammation and hypophysitis following this treatment, as well as a third patient with hypophysitis only.

Results:
Two of our patients developed diplopia and bilateral orbital edema shortly after initiating this chemotherapy (a few days after the second and third cycles respectively) with evidence of orbital inflammation on exam, and were later found to have enlargement of the pituitary gland with evidence of hypophysitis. The first patient had fluctuating symptoms, with consideration of possible ocular myasthenia, but extensive evaluation was unremarkable, including acetylcholine receptor antibody and anti-MuSK antibody, as well as repetitive stimulation EMG and single fiber EMG. The second patient developed acute onset of diplopia and periorbital edema, with consideration of thyroid disease as possible culprit, but hormonal studies were unremarkable at that time, with later development of hypophysitis as well. Our third patient developed hypophysitis only and had no ocular findings.

Conclusions:
We described two patients with orbital inflammation attributed to Ipilimumab, known to cause autoimmune adverse effects. The same patients and a third subject also developed hypophysitis, and notably neither had visual field defects, with all ocular symptoms likely associated with myositis as an adverse effect.

References:


Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Bilateral Sequential Optic Neuropathy Secondary to IgG4 Infiltrative Disease

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Introduction:
A 49 year old Peruvian woman noted acute, painless decrease in right eye vision. She visited an optometrist, followed by a retinal specialist who raised suspicion for non-organic visual loss. Given progressive visual loss, she presented to our institution 2 months after initial onset.

Methods:
Interventional case report

Results:
She was previously healthy, no medications, and ROS was negative for systemic concerns. We noted VA 20/400 OD, 20/80 OS, absent color vision OU, subtle right RAPD, normal IOP, and depressed visual fields OU, greater depth of scotoma centrally OU. Orbital, adnexal, and SLE revealed no relative proptosis, nor signs of inflammation or infection. DFE demonstrated an absence of optic atrophy or swelling, however arcuate bundle RNFL thickening was evident. Enhanced MRI brain/orbits, LP, and syphilis, lyme, SPEP, and LHON serologies were ordered. Imaging demonstrated optic nerve sheath complex enhancement OU, diffuse pachymeningeal thickening, and an intraconal right orbital infiltrate posterolateral to the globe, which was biopsied urgently. Immediately following a negative fungal stain, high dose IV solumedrol was given. Vision improved to 20/30 OU within 24 hours. Biopsy revealed IgG4+ predominant lymphoplasmacytic inflammatory cells (>50 IgG+ cells/HPF, >60% of plasma cell fraction). CSF profile and bloodwork was normal, except elevated IgG -- IgG subclass analysis showed IgG4 predominance. CT chest/abdomen: paraortic inflammation, no pancreatitis or retroperitoneal fibrosis. At 3 month follow up, 20/30 vision OU is maintained but decreases when prednisone falls below 40 mg daily – she will begin rituximab shortly

Conclusions:
We are becoming increasingly aware of potential optic nerve, orbital and intracranial involvement in IgG4-disease. Recognition of this entity carries major systemic implications since multi-organ involvement is common. Early diagnosis can lead to dramatic recovery, as many cases are exquisitely sensitive to steroid therapy. Neuro-ophthalmic presentations are diverse, ranging from orbital inflammatory disease to infiltrative optic neuropathy as in our case.

Financial Disclosures: The authors had no disclosures.

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Giant Cell Arteritis Presenting as Bilateral Orbital Inflammation Disease

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Introduction:
Giant Cell Arteritis (GCA) is a systemic granulomatous vasculitis. Orbital inflammatory disease is an extremely rare presentation of GCA, and when it occurs, is typically unilateral. We present two cases of GCA presenting with bilateral orbital inflammation.

Methods:
Case series and review of the literature.

Results:
Case 1: A 68 year old man presented with one week of bilateral “red eyes,” headaches and horizontal, binocular diplopia. Visual acuity was 20/20 OU. Examination revealed bilateral prominent, indurated superficial temporal arteries, chemosis and abduction deficits. Funduscopy was normal. Brain and orbital MRI showed temporal artery wall enhancement bilaterally and intraconal fat-stranding. ESR was 103 µg/L and CRP was 14 mg/L. Intravenous methylprednisolone led to marked improvement. Temporal artery biopsy confirmed GCA. Funduscopy later showed a cotton wool spot and fluorescein angiogram revealed patchy choroidal filling. Case 2: An 87 year old woman admitted for failure to thrive developed sudden painless vision loss in her left eye. Visual acuity was 20/25 OD and count fingers OS. There was a left afferent pupillary defect and pallid disc edema OS. ESR was 73 µg/L, CRP was 19.43 mg/L and platelet count was 545. Workup was negative for infectious etiologies or malignancy. Brain and orbital MRI showed bilateral intraconal orbital inflammatory changes, dramatic contrast enhancement of the superficial temporal and carotid arteries and anterior and posterior circulation infarcts bilaterally. She was started on IV methylprednisolone.

Conclusions:
Orbital inflammation has been reported in under 20 cases of GCA, with only 5 bilateral cases reported in the literature. We report two unique cases of bilateral orbital inflammation, one of which was accompanied by carotid artery wall enhancement and anterior and posterior circulation infarcts. As early recognition and treatment of GCA may prevent severe, irreversible visual loss, GCA should be considered in elderly patients presenting with idiopathic orbital inflammation.

References:

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Acute Compressive Optic Neuropathy Due To Spontaneous Orbital Varix Thrombosis

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Introduction:
A 76 year old woman with a prior history of right abducens palsy and Horner syndrome related to multiple sclerosis presented with acute left-sided proptosis and ptosis associated with mild pain, nausea and one episode of vomiting. She denied any recent trauma, headache or foreign body sensation. She was unaware of any change in vision at that time. An initial evaluation within hours of her presentation revealed hand motion vision and a relative afferent pupillary defect in her left eye. Acuity OS was 20/30 six months prior. There was marked ophthalmoplegia in all planes and slightly elevated intraocular pressure OS at 24 mm Hg.

Methods:
A contrast-enhanced CT Orbits revealed a large, well-circumscribed intracanal left orbital mass causing severe left-sided proptosis and mass effect on the left globe and optic nerve. There was a focal high-density material within the mass, suspicious for thrombus, and the lesion was interpreted as an orbital varix with thrombosis. CTA was consistent with the diagnosis. Conventional angiography ruled out arteriovenous fistula or aneurysm. She underwent a left lateral orbitomy and excisional biopsy of the hemorrhagic mass, which was described as benign fibroadipose tissue and blood.

Results:
Sequential exams revealed progressive improvement in extraocular motility and visual acuity. At six-month follow-up, her visual acuity was 20/60 but her visual field was markedly restricted with preservation of an inferotemporal island. The afferent pupillary defect as well as the partial third and fourth nerve palsies persisted. Her dilated exam showed pallor OS.

Conclusions:
Orbital varix thrombosis is an extremely rare complication but should be considered in the differential diagnosis of a patient presenting with acute vision loss, proptosis, and/or pain. The compressive effects of a varix thrombosis can lead to severe long-term ophthalmological morbidity. To the best of our knowledge, this is the first reported case of an acute compressive optic neuropathy due to spontaneous orbital varix thrombosis.

References:

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Poster 87

An Unusual Presentation After Blunt Orbitocranial Trauma

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Introduction:
Traumatic cerebrospinal fluid (CSF) leak usually manifests as otorrhea or rhinorrhea. Rarely CSF may also leak into the orbit manifesting tearing (“oculorrhea”) [1-5]. We report an additional case, the first to be documented by beta-transferrin testing of subconjunctival fluid.

Methods:
A 34 year old policeman struck by a car developed orbito-cranial fractures. The marked conjunctival chemosis was puzzling until copious tearing appeared upon leaning the patient’s head forward.

Results:
Needle aspiration of subconjunctival fluid was positive for beta 2-transferrin, a specific marker for CSF. Without intervention, oculorrhea ceased within 6 days.

Conclusions:
Oculorrhea is a rare manifestation of orbitocranial fracture. It may be overlooked in the chemotic orbital tissues. Prompt recognition is critical because meningitis, reported in 2 cases (2,5) is a threat. Diagnosis may be confirmed by testing needle aspirate of subconjunctival fluid for beta-transferrin positivity.

References:

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Grant Support: None
Eye on the Ball: A Case Report

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Introduction:
We report an unusual presentation of a patient with orbital apex syndrome caused by invasive fungal sinusitis

Methods:
Single case referred to a tertiary-level academic center

Results:
A 73 year old woman was seen by the ophthalmology consultation service for progressive vision loss, ptosis, and decreased eye movements in the left eye. Past medical history was significant for rheumatoid arthritis on extensive iatrogenic immunosuppression. Examination was concerning for left optic neuropathy with no light perception vision associated with 3rd, 6th, and V1 cranial nerve deficits. The patient’s initial neuroimaging was reviewed and was concerning for subtle enhancement of the left posterior sphenoid sinus, Initial sinus endoscopic examination was unremarkable. Given the patient’s lack of improvement on broad spectrum antibiotics and antiinflammatories, neuroimaging was repeated and revealed worsening left posterior sphenoid sinus sinus involving the left orbital apex. The patient was taken to the operating room and a large necrotic collection was removed from the sphenoid sinus. Pathology revealed numerous invasive septate hyphae consistent with Aspergillus infection. The patient was started on antifungals systemically and immunosuppression was titrated lower. Unfortunately the patient’s respiratory status decompensated and she expired one week after diagnosis.

Conclusions:
Fungal disease should always be included in the differential diagnosis of orbital apex disease, especially in the immunocompromised patient. Invasive fungal sinusitis carries an extremely high mortality. Successful treatment depends on early diagnosis, institution of antifungals, and careful titrating of immunosuppression as tolerated.

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**Poster 89**

**Orbital Ultrasonographic Findings in Tumors to the Extraocular Muscles**

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**Introduction:**
The ultrasound characteristics of extraocular muscle (EOM) enlargement can help to differentiate thyroid orbitopathy from other causes such as neoplasm and inflammation¹. There are few reports in the literature describing ultrasonographic features in patients who present with neoplastic EOM enlargement¹-³. Our objective was to characterize the nature of ocular misalignment and describe the orbital ultrasonographic findings in patients presenting with tumors to the EOMs.

**Methods:**
A retrospective chart review of all patients who underwent orbital ultrasonography for EOM enlargement from 2001-2013 was conducted. The details of clinical presentation and ultrasonographic features of EOM enlargement in patients with neoplastic causes were recorded. The reflectivity of the enlarged muscle was compared to ultrasonographic findings in patients with thyroid eye disease and myositis.

**Results:**
Amongst eight patients identified as having tumors to the EOMs, six of the eight patients had low reflectivity of the enlarged muscle when compared with its contralateral counterpart. The enlargement was 2-3 times the normal width of the muscle. Six of these patients had a past history of cancer while in two patients the EOM enlargement was the presenting feature of an underlying neoplasm. The most common symptoms were diplopia, eye redness, proptosis, swelling, restricted gaze and tearing. Seven of the eight patients exhibited some form of strabismus. Of this seven, four had paretic deviation, two had restrictive and one had a combined restrictive and paretic cause. Seven of the eight patients had one EOM involved whereas one patient had two EOMs involved.

**Conclusions:**
Patients with tumors to the EOM often have an underlying history of cancer. Our results demonstrate that these patients have a low reflective enlargement of the involved muscle and paretic patterns of deviations are more prevalent as compared to patients with thyroid eye disease. This enlargement is on the order of two to three times the thickness of its contralateral counterpart.

**References:**


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Evaluation of Retinal Nerve Fiber Layer in patients with idiopathic Optic Perineuritis using Optical Coherence Tomography

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Introduction:
The aim of this study is to assess the effect of optic perineuritis (OPN) on retinal nerve fiber layer (RNFL), and the ability of optical coherence tomography (OCT) to evaluate the retinal nerve fiber loss after idiopathic optic perineuritis.

Methods:
The diagnosis of idiopathic OPN was made in patients who had an acute optic neuropathy and typical optic nerve sheath enhancement in fat suppression and contrast enhancement orbital magnetic resonance imaging (MRI), normal laboratory findings. Subjects were underwent by Cirrus Spectral Domain-OCT (Carl Zeiss Meditec, Inc., Dublin, CA) and the OCT parameters, optic nerve head and RNFL thickness, was calculated automatically by the equipment’s software at initial visit and 12 months follow-up.

Results:
4 patients were studied in this study. All patient showed that RNFL, especially temporal sector RNFL (Papillomacular bundle), was significant thinner in affected eye when compared to normal value and the other sound eye at 12 months after acute OPN.

Conclusions:
Our study suggests that retinal nerve fiber loss was observed in idiopathic optic nerve sheath inflammation and OCT was good technique for axonal loss and disease severity indicator in OPN

Financial Disclosures: The authors had no disclosures.

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A Case of Silent Sinus Syndrome Caused by a Dacryocystorhinostomy Presenting as Myasthenia Gravis

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Introduction:
Silent Sinus Syndrome (SSS) is a rare entity defined as spontaneous, progressive enophthalmos and hypoglossus from maxillary sinus hypoplasia due to chronic maxillary sinus obstruction. We present a unique case of silent sinus syndrome caused by a dacryocystorhinostomy presenting as myasthenia gravis.

Methods:
A 58-year-old woman presented to ophthalmology clinic for evaluation of 6 months of vertical binocular diplopia worsening over the course of the day. She also reported that her right eye would get smaller throughout the day. She had a past medical history of epiphora for which she underwent a dacryocystorhinostomy (DCR) of her right eye one-year prior. She had no history of trauma, allergic rhinitis, or any other symptoms. Physical exam revealed a left hypertropia with no specific pattern. She had fatigueable ptosis of her right eye. Her right eye was enophthalmic (right eye 15.5mm; left eye 18mm) on exophthalmometry. Levator function was 15mm on the right and 18mm on the left. Her lid crease was 8mm on the right and 3mm on the left. Given her fluctuating symptoms and fatiguable ptosis, workup included acetylcholine receptor binding, blocking, and modulating antibodies to evaluate for myasthenia gravis.

Results:
Acetylcholine receptor antibodies were negative. At follow-up, she brought an outside maxillofacial CT that had previously been read as normal. The CT showed inferior bowing of the right orbital floor and inward-bowing of the lateral wall of the right maxillary sinus. The sinus was opacified with an obstructed osteomeatal complex. These findings are consistent with SSS.

Conclusions:
Silent sinus syndrome often presents as hypoglossus and diplopia. This patient uniquely had fluctuating symptoms, presumably from upright posture during the day causing worsening hypoglossus mimicking the variable ptosis and diplopia sometimes seen with myasthenia gravis. SSS should be considered in the differential of patients presenting with variable diplopia or ptosis and a history of orbital surgery or trauma.

References:

Financial Disclosures: The authors had no disclosures.

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Functional Characterization of FOXP1 and Its Possible Pathogenic Role in Thyroid-associated Ophthalmopathy

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Introduction:
The pathogenesis of thyroid-associated ophthalmopathy (TAO) is still unclear, although several evidences suggest that it is autoimmune. Two candidate auto-antigens are TSH-R and the novel protein, forkhead box P1 (FOXP1). This study is aimed to characterize the expression of FOXP1 in the extrocular muscle (EOM) and explore its function in muscle cells.

Methods:
Immunohistochemistry and western blot were used to examine the FOXP1 expression. IP-western was performed to investigate its interacting protein. In C2C12 cell (myoblast cell line) culture, the role of FOXP1 in muscle differentiation was examined by RNAi and over-expression.

Results:
Foxp1 protein is expressed in the cytoplasm of human EOM in a striated pattern, which interacts with actin. It is also expressed on the cell membrane of human EOM. FOXP1 will translocate from nucleus to cytoplasm in C2C12 cells during muscle differentiation, which could be inhibited by PKC and PI3K inhibitors. Knocking down FOXP1 expression may decrease muscle differentiation, while over-expressing FOXP1 may induce muscle differentiation in C2C12 cells.

Conclusions:
Foxp1 protein is expressed within the cytoplasm and on the cell membrane of human EOM. Thus, it may act as an auto-antigen for the TAO. FOXP1 may translocate from nucleus into cytoplasm during muscle differentiation, and interact with actin to form the cytoskeletal structure. It plays an important role in muscle differentiation.

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Poster 93

Metastatic B cell lymphoma mimicking Tolosa-Hunt syndrome

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Introduction:
Tolosa-Hunt syndrome is a painful ophthalmoplegia secondary to idiopathic granulomatous inflammation of the orbital apex that responds dramatically to parenteral steroids. However, steroids may improve lymphoma as well.

Methods:
Case report: We present a case of a 77-year-old male with past medical history of large cell lymphoma reporting right retrobulbar pain for 4 months without visual changes.

Results:
He received empiric valacyclovir and oral prednisone for suspected viral infection of the right eye. A week later, experienced onset of horizontal binocular diplopia and right ptosis. Brain and orbit Magnetic resonance imaging (MRI) and cerebrospinal fluid analysis were negative for lymphoma or infection, thus a presumptive diagnosis of Tolosa-Hunt syndrome was made. He was placed on intravenous methylprednisolone followed by oral taper, resulting in improvement of his pain and ptosis, but was complicated with hyperglycemia, myopathy, perforated diverticulitis and pneumocystis pneumonia. During the taper, he developed bilateral 6th nerve palsy and right pupil sparing 3rd nerve palsy. Repeat CSF analysis was negative for malignancy. A month later he presented with recurrence of right eye pain, worsening right ptosis, right pupillary dysfunction, and right-sided facial numbness. With the progression of his cranial neuropathies, a repeat MRI of the brain and orbit was ordered and revealed multiple osteolytic lesions, the largest of which, involving the sphenoid abuts the right carotid canal. He was also found to have multiple areas of hypermetabolism on PET/CT involving the orbit. He underwent radiation treatment to the orbit with partial improvement of his 3rd nerve palsy.

Conclusions:
High index of suspicion is mandatory in high risk patients with evolving multiple cranial neuropathies to rule out malignancy. Tolosa Hunt is diagnosis of exclusion.

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Metastatic Carcinoid Tumor Invading The Lateral Rectus Muscle And Compressing The Optic Nerve

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Introduction:
Carcinoid is a slow-growing neuroendocrine tumor that typically arises in the gastrointestinal tract. Metastasis to the orbit can involve the extraocular muscles, yet rarely presents with compressive optic neuropathy.

Methods:
We review the literature and describe a 48-year-old patient with a history of gastrointestinal carcinoid metastatic to the liver with recurrence following surgical resection and systemic chemotherapy. Headaches prompted magnetic resonance imaging (MRI) of the brain which detected a right orbital mass. A focal heterogeneous enhancing lesion was described along the inner aspect of the right lateral rectus muscle near the apex displacing the optic nerve. Whole body planar octreotide imaging also demonstrated uptake in the right orbit. Clinical examination showed no visual acuity changes, diplopia or proptosis. However, the right eye manifested a mild afferent pupillary defect and demonstrated central depression on visual field testing. Detailed review of a year-old positron emission tomography fused with computed tomography (PET/CT) showed a right orbital mass which was labeled meningioma at the time.

Results:
A right lateral orbitotomy was preformed and exploration showed the mass invading into the posterior most aspect of the right lateral rectus. Total resection of the orbital tumor and a partial lamellar wedge myectomy were performed. Histopathology confirmed carcinoid with negative surgical margins. Following resection the afferent pupillary defect resolved completely. The patient suffered a right sixth nerve palsy which partially resolved. A two-year follow up documented no orbital recurrence and no signs of visual compromise.

Conclusions:
Neuroendocrine tumors metastatic to the orbit grow slowly and have a propensity to invade the extraocular muscles. In the context of systemic metastasis a high index of suspicion for orbital involvement should be maintained prompting regular ophthalmic evaluations. In selective cases resistant to chemotherapy with a growing orbital mass and compressive optic neuropathy surgical resection remains an option.

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Blepharospasm in the Pediatric Population

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Introduction:
Determine if blepharospasm is seen in the pediatric as well as the adult population.

Methods:
We conducted a retrospective chart review at the University of Utah and Johns Hopkins University to determine the presence of blepharospasm in children. We queried our databases for diagnoses of blepharospasm and tic disorder over the past 10 years in adults and children. Charts were reviewed to confirm the diagnosis and a questionnaire was sent to these subjects to document their symptoms and treatments. We randomly identified 50 adult blepharospasm subjects to act as a comparison group.

Results:
We found a total of 20 cases of blepharospasm in patients under the age of 18. We confirmed blepharospasm in 4 of these cases. All 4 subjects returned the questionnaire. Ten of the 50 adult subjects completed and returned the questionnaire. Of the four children diagnosed with blepharospasm, all were still symptomatic, but all had noted improvement in the severity and frequency of their symptoms. One spontaneously improved and the other three improved after treatment. One was treated with FL-41 tint glasses, another with lamotrigine and botulinum toxin A, and the fourth was treated with botulinum toxin A and myectomy. All of the ten adults who returned questionnaires were still symptomatic and on treatment with a combination of botulinum toxin A, medication, and FL-41 tinted spectacles. None of these adults reported symptoms suggestive of blepharospasm as a child.

Conclusions:
Although rare, blepharospasm can occur in the pediatric population and is not a disease restricted to adults.

References:

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Paradoxical Enophthalmos and Orbital Breast Metastasis

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Introduction:
Enophthalmos denotes posterior displacement of the eye in the orbit. While tumors of the orbit typically cause proptosis, rare reports exist in the literature of breast cancer metastasis associated with enophthalmos. Imaging can be vague and tissue diagnosis can also be elusive initially. We perused the database of a large neuro-ophtalmology practice to identify cases of orbital masses with associated enophthalmos.

Methods:
A retrospective case series including three subjects. Imaging studies were reviewed.

Results:
Subject one was a 74 year old woman who had diplopia and clinical findings suggested thyroid eye disease initially; she then developed progressive enophthalmos of the right globe. Orbital biopsy revealed lobular primary breast carcinoma. Subject two was a 58 year old woman with ptosis, diplopia, and left enophthalmos. Biopsy showed a metastatic carcinoma consistent with lobular breast carcinoma. Subject three was a 65 year old woman with a five year history of a left orbital mass and diplopia. There was enophthalmos OS. Despite several negative biopsies, enucleation revealed adenocarcinoma consistent with breast metastasis. Imaging confirmed enophthalmos and the presence of a soft tissue mass behind the globe in question in each subject.

Conclusions:
We identified three patients with the paradoxical finding of enophthalmos associated with breast metastases. Scirrhous breast carcinoma produces fibrosis and retraction, seen both at the breast and at the site of metastasis, resulting in enophthalmos in the orbit. A review of the literature did not reveal enophthalmos associated with any other type of orbital mass. Although the lack of reports in the literature does not exclude the possibility of other tumors causing enophthalmos, the finding of enophthalmos in a patient with an orbital mass should allow the practitioner to consider a breast metastasis as the pathologic mechanism in the setting of a normal prior orbital biopsy.

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Primary Localized Orbital Amyloidosis Involving Extraocular Muscle

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Introduction:
Amyloidosis is a variety of disorders caused by the abnormal deposition of insoluble protein in extracellular space of tissues or organs. It is an uncommon condition and primary orbital involvement is extremely rare. The presentation of primary orbital amyloidosis highly varies, which commonly delays the correct diagnosis. We present a case of primary localized orbital amyloidosis presenting with diplopia.

Methods:
An 82-year-old man with history of coronary artery disease presented with binocular vertical diplopia for 2-3 months. The initial evaluation only revealed a small angle of right hypertropia with slight limited depression in adduction in the right eye. MRI of brain was unremarkable. The workup for ocular myasthenia gravis was negative. He was given Fresnel prism and was followed in clinic. The examination was stable until 12 months later when elevation deficit was noticed in the same eye. MRI of orbit demonstrated an ill-defined, mildly enhanced lesion involving right inferior rectus.

Results:
The laboratory examination for chronic inflammatory and infectious process was unrevealing. The patient underwent orbital tissue biopsy and the diagnosis of amyloidosis was confirmed by the presence of amyloid deposits with Congo red staining. An extensive workup to rule out systemic amyloidosis was performed, which included bone-marrow biopsy and abdominal fat pad biopsy. There was no systemic disease identified.

Conclusions:
Primary localized orbital amyloidosis is rare, but should be considered as a differential in patients with unexplained persistent diplopia.

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Optic Canal Hemangioblastoma Treated with Canal Decompression in a Patient with von-Hippel Lindau Disease

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Introduction:
To report a patient with an optic canal hemangioblastoma associated with von Hippel-Lindau (VHL) disease, which was treated with canal decompression.

Methods:
A 25-year-old man presented with progressive temporal visual loss in the left eye over 3 months. Visual acuity was 20/20 right eye and 20/30 left eye with a left afferent pupillary defect. Humphrey visual field was normal right eye (MD -0.30 dB) and constricted left eye (MD -19.83 dB). Left optic nerve swelling and a small far peripheral lesion consistent with a retinal hemangioblastoma in the right eye were found. Ganglion cell layer analysis revealed an average thickness of 79 microns right eye and 52 microns left eye. The patient’s father has VHL disease. MRI demonstrated a left retrobulbar enhancing lesion confluent with the apical and canalicular portion of the optic nerve as well as a cerebellar enhancing lesion consistent with hemangioblastomas. Further systemic imaging revealed the presence of pancreatic and renal cysts. The patient underwent neurosurgical intervention for resection of the lesion.

Results:
The hemangioblastoma was found to be intertwined with the left optic nerve and sharing the blood supply, therefore resection was not attempted. The optic canal was unroofed to decompress the optic nerve. Post-operatively, the vision was better subjective with expansion of the visual field from -19.83 to -17.78 dB with preservation of central visual acuity.

Conclusions:
VHL is an inherited neoplastic syndrome consisting of retinal and central nervous system hemangioblastomas, as well as pancreatic, adrenal and kidney lesions. Orbital and intracanalicular hemangioblastomas are exceedingly rare. Resection is often not possible without further optic nerve damage. Decompression is a potential palliative treatment option.

References:
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Why Isolated Lateral Rectus Muscle Enlargement is Unique?

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Introduction:
Extra-ocular muscles (EOM) enlargement can result from a broad range of different diseases. While Graves' disease is the most common cause of enlarged EOM, other disorders may mimic thyroid orbitopathy. Orbital myositis may cause enlargement of a single EOM but is an acute, painful process. EOM enlargement in malignant diseases has been described only sporadically with a prevalence less than 0.5%. Metastatic malignancies are commonly breast, prostate and lungs. B-cell lymphomas are the most frequent malignant tumor in the orbit, of which MALT lymphoma is the most common.

Methods:
This is a case report with retrospective chart review. Literature search using terms: lateral rectus muscle enlargement, EOM involvement in lymphoma.

Results:
A 53-year-old female with past medical history of hypothyroidism presented with a one year history of progressive painless right eye (OD) proptosis. Magnetic resonance imaging (MRI) of the brain and orbit revealed marked enlargement and enhancement of the right LR muscle with mass effect upon the right optic nerve. Neuro-Ophthalmologic examination revealed a visual acuity of OD 20/30 and OS 20/20. The pupils were isocoric with a right RAPD. Color vision was OD 10/12 and OS 11/12. Exophthalmometry at base of 104 mm were OD 21.5 mm and OS 19 mm. There was conjunctival injection OD. IOP were OD 49 and OS 19 mm Hg. Automated threshold perimetry showed non-patterned depression OD. Funduscopy showed temporal pallor OD. Biopsy of the LR muscle demonstrated small B-cell lymphoma; plasmacytic differentiation CD20 and CD21 positive, CD5 and CD10 negative. Plasma cells were kappa light chain restricted consistent with marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT).

Conclusions:
Although isolated EOM enlargement is likely to be due thyroid orbitopathy, isolated LR muscle enlargement is unique and should raise the suspicion of primary or metastatic tumors. Why this clinical correlation is true is speculative.

References:

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Poster 100

Valsalva-Induced Optic Neuropathy

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Introduction:
Orbital varices could cause an optic neuropathy. History, examination findings, and imaging are key to making a diagnosis.

Methods:
A case report of an orbital varix causing an optic neuropathy will be presented. A short video of the patient exhibiting Valsalva-induced ptosis will be shown.

Results:
A 62-year-old male started experiencing Valsalva-induced episodic blurring of vision OS without any other associated signs and symptoms in 2001. 2013 examination was remarkable for mildly impaired distance visual acuity, severe dyschromatopsia, and generalized depression on VF testing OS. There was a 0.9 unit relative afferent pupillary defect OS. LEFT optic disc was pale and had a cup-to-disc ratio of 0.8. OCT fast RNFL scans showed atrophy OS. Contrast MRI of the brain and orbits, MR angiogram and venogram were normal. On follow up, the patient reported involuntary closure of his LEFT eye everytime he bends over. CTA of the head done with the patient doing the Valsalva showed an orbital varix.

Conclusions:
Orbital varices may present with episodic proptosis, dilated lid veins, retrobulbar hemorrhage, periorbital bruising, pain, and thrombophlebitis. An estimated 15% of cases may result in blindness because of optic nerve compromise. An orbital varix could be verified by ultrasound, CT or MR angiography, and conventional catheter angiography. Its presence could remain elusive unless a provoking maneuver (Valsalva) is done during the study. Optic neuropathy from an orbital varix may result from a variety of mechanisms: ischemia secondary to direct compression, ischemia secondary to “vascular steal”, secondary glaucoma. The exact mechanism in this case is unclear, but is possibly from direct compression of the optic nerve. Management of orbital varices includes careful observation for asymptomatic cases. For patients with severe episodic proptosis and pain and/or visual compromise, embolization of the varix with surgical resection could be considered. Gamma knife radiosurgery has also been presented as an option.

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Poster 101

Not so Indolent: Marginal Zone lymphoma with Optic Nerve Infiltration and Early Chemorefractive Meningeal Disease

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Introduction:
Lymphomatous meningitis in Marginal Zone Lymphoma (MZL) is very rare. Only four cases of early, secondary central nervous system (CNS) involvement with MZL have been reported. We describe an unusual case with early optic nerve and meningeal infiltration responsive only to systemic chemotherapy.

Methods:
Case Report

Results:
A 67-year-old hypertensive patient presented with a one week history of left eye floaters and photopsia. A left superotemporal retinal tear was treated with retinopexy and cryotherapy. Routine blood tests over the next 4 weeks identified MZL. Subsequently, he developed left-sided visual distortions. Examination revealed a swollen left optic disc with haemorrhages and mild right disc edema, with normal visual acuity (20/20), visual fields and intraocular pressures. Neurology review was taken for possible raised intracranial pressure. Patient reported bilateral foot numbness following a spinal anaesthetic and long-standing tremor, with no identifiable neurological deficit. Initial MRI revealed subtle high signal in the left optic nerve. Lumbar puncture showed a normal opening pressure with lymphocytic pleocytosis. Extensive CSF workup for infective, autoimmune, inflammatory and paraneoplastic pathologies was negative. CSF flow-cytometry confirmed CNS MZL disease. Intra-thecal methotrexate was started, however, serial lumbar punctures showed chemorefractive disease with persistent normal opening pressures. Repeat MRI showed bilateral swollen optic nerves, increased signal change in cerebral deep white matter and extensively throughout the cord, and cauda equina thickening. Deteriorating visual symptoms (transient visual obscurations, left relative afferent pupillary defect and scotoma) led to systemic chemotherapy with steroids, cyclophosphamide and rituximab. This resulted in sustained improvement of visual symptoms and clearance of mono-clonal B cells from blood, CSF and bone marrow.

Conclusions:
This case demonstrates unusual early meningeal involvement in MZL that is usually observed with late chemorefractive disease or high grade transformation. It also shows that an excellent response can be achieved with systemic chemotherapy.

References:


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Current Trends in Pediatric Idiopathic Intracranial Hypertension (IIH): A Multicenter Study of Treatment and Outcomes

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Introduction:

Methods:
A retrospective multi-center chart review identified children (4-17 years) diagnosed with IIH from 2002-2012. Gender, age, body mass index (BMI), opening pressure, optic nerve head (ONH) edema, treatment and outcomes were identified.

Results:
Fifty-four patients were divided into group 1 (4-8 years), group 2 (9-12 years) and group 3 (13-17 years). The average age was 11.5 years, differing significantly between males and females (9.7 versus 13.3 years, p=0.001). Females represented 67% of all patients (26/54) and 86% of patients in group 3 (18/21). Group 2 represented the most patients overall (23/54), split evenly between males and females (52% versus 48%, respectively). ONH edema was most severe in group 3 and higher in females (median grade 4). The average opening pressure was 45mm water, highest in females (55) and in group 2 (42.8), and lowest in group 1 (30.9). Medical treatment was the predominant management method (41/54), of which 63.4% were female (26/41). In the medical group, the average ONH edema was grade 2 (p=0.04) with median visual acuity of 20/25 pre-intervention and 20/20 post-intervention. ONH edema post-intervention revealed a median of grade 0. Thirteen children underwent surgical intervention, of which 70% were female (9/13). In the surgical group, the average grade of ONH edema was grade 3 (p=0.04) with median visual acuity of 20/70 pre-intervention and 20/25 post-intervention. The median ONH edema post-intervention in the surgical group was grade 1. The recurrence rate was 13%.

Conclusions:
The epidemiology of IIH differs in children and is age-dependent. Although both treatment groups demonstrated improvement in vision and ONH edema, outcomes were worse in the surgical group. Pubescent female patients require more invasive treatment methods and have worse visual prognosis.

References:

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Neuroimaging Features of Idiopathic Intracranial Hypertension Persist After Resolution of Papilledema

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Introduction:
Idiopathic intracranial hypertension (IIH) is characterized by elevated intracranial pressure of unknown etiology. Papilledema is a key clinical finding associated with IIH and is used to both diagnose and monitor the course of the disease. Newer criteria allow the diagnosis of IIH without papilledema, provided certain neuroimaging findings are present. These findings have previously been shown to occur in patients with active papilledema. Using a retrospective cross-sectional study, we analyzed the persistence of these features following resolution of papilledema.

Methods:
Three groups of patients were selected for analysis: a control group with no history of papilledema, a group with active papilledema who met modified Dandy criteria for IIH, and a group with no active papilledema by modified Frisen scale grading who had previous fundoscopic and clinical evidence of IIH. All patients must have received an orbital MRI within four weeks of fundoscopic evaluation for papilledema. Images were reviewed by a neuroradiologist blinded to clinical status for features such as pituitary flattening, optic nerve protrusion, and distension of the perioptic subarachnoid space. Nonparametric rank tests were used to compare neuroimaging findings among the three groups.

Results:
Six patients were enrolled in each group. The active and resolved papilledema groups had greater pituitary flattening and optic nerve protrusion compared to the control group. Measurements of perioptic subarachnoid space distension were not different between any of the three groups.

Conclusions:
Pituitary flattening and optic nerve protrusion on MRI may persist after clinical papilledema resolves in IIH patients. These findings indicate that neuroimaging may be useful in the diagnosis of IIH even after clinical papilledema has resolved, and that the presence of these imaging findings may not necessarily indicate ongoing elevated intracranial pressure.

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Poster 104

SPHENOID SINUS EXPANSION: A RADIOGRAPHIC SIGN OF INTRACRANIAL HYPOTENSION AND THE SAGGING BRAIN, SUNKEN EYES SYNDROME

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Introduction:
"Sunken eyes, sagging brain syndrome" refers to a newly recognized syndrome characterized by intracranial hypotension and consequent enophthalmos from orbital volume expansion. (1) To test the hypothesis that bone remodeling is not limited to the orbits, in this study volumetric analysis of the sphenoid sinus is performed.

Methods:
In this university based retrospective case controlled study the dimensions of the sphenoid sinus were measured in four patients (2 males, 2 females, mean age 26.3 years, range 16 to 38 years) out of five individuals identified with sagging brain, sunken eyes syndrome. Three measurements were taken: the distance between the orbital apices, the posterior extension of the sphenoid sinus posterior to the orbital apices and the maximal horizontal width. The mean of each was determined and compared to that of the control group (5 males, 5 females, mean age 35.6 years old, range 23 to 45 years).

Results:
Posterior extension and width of the sphenoid sinus were markedly larger in the enophthalmic than the control group: posterior extension (26.3±4.1mm vs. 13.4±6.3mm, p=0.0015, student’s t-test), width (39.2±8.7mm vs. 25.1±6.9mm, p=0.0035, student’s t-test). Mean distance between the orbital apices was slightly greater (36.3±1.7mm vs. 34.1±2.1mm, p=0.047, student’s t-test).

Conclusions:
Skull remodeling occurring in association with intracranial hypotension after VPS is not limited to the orbits. In this study we have demonstrated expansion of the sphenoid sinus. This finding adds to our knowledge and understanding of the scope bony changes that occur with intracranial hypotension and elucidates a clinically useful radiographic sign.

References:


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Ultrasound Guided Lumbar Puncture in Idiopathic Intracranial Hypertension

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Introduction:
Lumbar puncture (LP) remains the predominant method of intracranial pressure measurement. This procedure is often challenging in the idiopathic intracranial hypertension (IIH) population owing to body habitus and loss of anatomical landmarks. Opening pressure (OP) is often the most important piece of information and can be measured inaccurately by repeated punctures. Often, patients require fluoroscopy guidance, and the radiation dose may be significant, especially when considering the need for repeated LP over the frequently long course of this disease. Finally, the conventional method of LP is often associated with morbidity in the form of post-dural puncture low tension headache and cerebrospinal fluid (CSF) leaks, requiring further intervention. The purpose of the current investigation is to describe a method of lumbar puncture using ultrasound guidance and to report our experience using this method in IIH patients.

Methods:
10 IIH patients underwent 11 ultrasound guided lumbar punctures with a low frequency curvilinear probe. Either a 4” 24 gauge Pencan pencil-point needle or a 4.75” or 6”, 24 or 22 gauge Sprotte pencil-point needle was used, depending on the length needed.

Results:
In 10/11 procedures, only one attempt at puncture was required, and OP was obtained as was sufficient CSF for multiple studies. No subject had a post-puncture headache, and only 2 post-procedure complications occurred including serous drainage at the puncture site in one subject, which resolved without intervention; and paresthesia in one subject that resolved after a single dose of dexamethasone.

Conclusions:
Ultrasound guided lumbar puncture can be used in IIH patients to obtain accurate OP and sufficient CSF for laboratory investigations. Used with non-cutting needles, this method has a high success rate with low morbidity. More importantly, this procedure reduces the cumulative radiation dose in IIH patients, which can be quite high over the lifetime of an average patient.

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Pediatric Primary Pseudotumor Cerebri Syndrome (PTCS): New Insights from Detailed Endocrine Assessments

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Introduction:
Obesity, sex, and pubertal status influence the risk for pediatric PTCS. Previous studies were limited by their use of age-dependent assumptions regarding puberty. Using pediatric-specific endocrine assessments, this study examines the relationship between anthropometrics and secondary sexual characteristics in primary pediatric PTCS.

Methods:
At a tertiary pediatric hospital, an electronic database search using ICD9 code 348.2 and a pediatric neuro-ophthalmologist’s database identified 398 cases of possible PTCS. Retrospective data were collected using bioinformatics-based and manual abstraction, and stored using a secure web-based application (www.project-redcap.org). Tanner staging and standardized growth charts were used to determine development of secondary sexual characteristics and age-/sex-specific height, weight, and BMI Z-scores. Exploratory principal component and k-means clustering analyses were performed to identify clinical sub-groups.

Results:
Using updated PTCS diagnostic criteria (Friedman et al., 2013), interim analysis of 230 records identified 47 cases of definite primary PTCS (67% female, mean age 12.5±4.0yrs). Mean BMI Z-score(±SD) was 1.15±1.27(n=30). There was a positive association between BMI Z-score and age(r=0.69, p<0.001; n=30). Tanner staging for pubic hair was available in 12 cases. Two cases were Tanner I. Cases in Tanner II+III were taller for age and sex compared with cases in Tanner IV+V(p=0.03). Clustering analysis identified 3 groups: [1] Childhood(7yrs), 43% female, normal weight, [2] Adolescent(12yrs), 69% female, overweight, tall, and [3] Older adolescent(17yrs), 90% female, obese. Cases with confirmed Tanner II+III and IV+V segregated into Groups 2 and 3, respectively.

Conclusions:
Previously two cohorts of pediatric PTCS have been described: a young, normal weight cohort, equally male and female [our Group 1], and an older, obese, and female cohort [our Group 3]. We illustrate that overweight, early adolescent females with evidence of endogenous androgen production (Tanner II+III pubic hair) and growth acceleration (tall stature for age) may represent a previously unrecognized subset of pediatric PTCS patients, providing insight into the endocrine pathogenesis of this complex condition.

References:

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MRI Findings of Elevated Intracranial Pressure in Pseudotumor Cerebri Syndrome with and without Papilledema

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Introduction:
Revised criteria for pseudotumor cerebri syndrome (PTCS) (Friedman et al. 2013) incorporate the presence of 3 of 4 MRI signs into the diagnosis of PTCS without papilledema (PTCS WOP), but prior studies examined these signs primarily in patients with papilledema. MRI findings include optic nerve sheath distention (ONSD), reduced pituitary gland height (PGH), flattening of the posterior globe (FPG), and transverse sinus stenosis (TSS). We compare MRI findings in PTCS with papilledema (PTCS WP), PTCS WOP, and controls.

Methods:
Radiology and neuro-ophthalmology databases were searched for adult patients who underwent MRI for PTCS or migraines. PTCS WP was defined by published criteria (Friedman et al. 2013). Patients meeting those criteria, but without papilledema, were considered to have PTCS WOP. Control patients had episodic migraine (fewer than 4 per month). The brain MRIs were reviewed in a masked fashion.

Results:
36 patients had PTCS WP, 11 had PTCS WOP, and 37 had migraines. Average ONS diameter differed between groups (p<0.001) and was greatest in PTCS WP. PGH was reduced in PTCS WP and PTCS WOP. FPG was seen in 1 migraine patient (specificity 97.3%; OR 1.0), 67% of PTCS WP patients (OR 67.1; p<0.001), and 36% of PTCS WOP patients (OR 18.7; p=0.008). Stenosis of at least 1 transverse sinus was present in 78% of PTCS WP patients, and bilateral TSS was present in 65%. Three of 4 imaging signs (ONSD >5.5 mm, PGH<4.8 mm, FPG, and TSS) were present in 64% of PTCS WP patients, 36% of PTCS WOP patients, and no migraine patients.

Conclusions:
The presence of 3 of 4 MRI signs is highly specific and moderately sensitive for PTCS with or without papilledema. These findings suggest the proposed use of MRI abnormalities for the diagnosis of PTCS WOP is valid.

References:

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Long-term intracranial pressure monitoring and obesity-induced intracranial hypertension in the rat

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Introduction:
From patients with idiopathic intracranial hypertension it is known that obesity is connected to the regulation of CSF. To study this relation in a preclinical setting, we aimed to set up a valid long term intracranial pressure (ICP) monitoring method in a rat model.

Methods:
The method should be minimally invasive; hence we chose the epidural site for our ICP recordings. To validate the method we measured ICP simultaneously in the lateral ventricle and in the epidural space of rats. The two pressures were recorded twice a week for 59 days and the correlation was established. The influence of obesity on ICP was investigated in obese Zucker rats and in lean controls. Furthermore, the presence of papilledema is currently being examined in histological sections of the eyes and optic nerves from these animals.

Results:
The correlation between epidural and ventricular pressure was analyzed by linear regression and on all measuring days the $R^2$ value was between 0.99-1.0. Several complications occurred with the long-term ventricular, but not the epidural ICP-recordings. With this new method we also showed that obese rats have significantly elevated ICPs compared to lean controls ($p = 0.009$).

Conclusions:
We set up and validated a novel method for long term ICP monitoring in the epidural space of rats. This method is cheap, safe, and relatively easy to perform and remains reliable for at least 59 days. We used this new method to compare ICP values of lean and obese rats and found that obesity induces intracranial hypertension.

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Poster 109

Outcomes from CSF diversion surgery for idiopathic intracranial hypertension

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Introduction:
The outcomes of patients who underwent cerebrospinal (CSF) diversion surgery for idiopathic intracranial hypertension (IIH) in a regional neurosciences centre are presented.

Methods:
A retrospective chart review was conducted for 50 consecutive patients who underwent CSF diversion surgery for IIH. The mean radial degrees (MRD) of the I4e isopter of the Goldmann visual field were measured pre- and post-operatively (1).

Results:
All of the patients were female, with a mean age of 32 years, a mean body mass index of 37.2 and a mean post-operative follow-up of three years (range 13 days to 9 years 8 months). A ventriculo-peritoneal shunt was the first procedure in 38 patients and a lumbo-peritoneal shunt in 12. The mean decimal visual acuity of the worse affected eye improved from 0.74 (standard deviation [SD] 0.37, n=50) to 0.84 (SD 0.38, n=49), p=0.011. The MRD score of the worse affected eye improved on average from 25.6° (SD 18.0°, n=44) to 35.2° (SD 18.2°, n=47), p<0.0001. In those with significant pre-operative visual impairment in their worse affected eye (defined as a MRD score ≤ 30°), the MRD score improved on average from 10.3° (SD 8.5°, n=23) to 26.5° (SD 19.5°, n=21), p=0.0008. The mean number of surgical procedures for each patient was 2.7 (range 1–12). Taking all surgical procedures into account, post-operative complications were experienced by 30 patients. At last follow-up, 25 patients still complained of headache, 8 of whom had the intervention performed primarily for headache.

Conclusions:
CSF diversion can improve visual function in patients with IIH. There is significant post-operative morbidity and often the need for repeated procedures. Headache also commonly remains in these patients. There is a need for a randomized controlled trial of operative interventions in IIH. Sample size calculations for such a trial will be presented.

References:


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Introduction:
IIH has been recognized for almost 100 years including more recent emphasis on the potential damage to visual function. In patients nonresponsive to weight reduction or medical therapy, CSF diversion procedures (subtemporal decompression, lumboperitoneal and ventriculoperitoneal shunts) can be are successful in lowering pressure. More recently, there has been an increased interest in venous pressure in the development of an IIH picture (sleep apnea, etc.) The last 18 years have seen a number of cases and small case series of balloon venoplasty and subsequently venous stenting for reported venous stenosis as a possible etiologic goal in IIH. Although there have been “good” technical and clinical responses, the mechanism of the stenting remains unclear.

Methods:
This is a pilot study for an ongoing prospective study of venous stenting in IIH patients. Two patients were evaluated during venous stenting with an intracranial bolt monitor in place. The patients had evidence of increased intracranial pressure, papilledema, and optic neuropathy with arcuate visual field defects.

Results:
Both patients demonstrated significant gradient across narrowed portions of the transverse and sigmoid sinuses. This was immediately reduced by deployment of venous stenting. Correspondingly intracranial pressure measured by continuous ICP monitoring showed immediate reduction in pressure. Patients showed subsequent improvement in their clinical signs and findings.

Conclusions:
Although venous stenosis may represent an epi-phenomena secondary to increased intracranial pressure, in at least some patients, resolution of the transvenous pressure gradient with stenting may result in decrease in intracranial pressure. The exact role of stenting remains to be determined with a larger series.

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A Comparison of Clinical Features of Pseudotumor Cerebri Secondary to Tetracyclines and Idiopathic Intracranial Hypertension

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Introduction:
Pseudotumor cerebri (PTC) is a syndrome characterized by increased intracranial pressure with normal brain parenchyma, including absence of hydrocephalus, mass lesion, and underlying infection or malignancy. The primary form of PTC, idiopathic intracranial hypertension (IIH), accounts for the majority of cases. A variety of secondary causes have been identified, including PTC due to tetracycline antibiotics (PTC-T). We hypothesize that there are important clinical differences between these two groups.

Methods:
We retrospectively reviewed charts of patients evaluated for PTC at a single neuro-ophthalmic referral center. We identified patients who developed PTC after therapy with minocycline, doxycycline, and tetracycline and those with IIH. All patients met the recently revised diagnostic criteria for PTC. Patients with PTC-T and IIH were compared by demographics, body mass index (BMI), visual exam at presentation, treatment, course of illness, and visual outcomes.

Results:
We identified 32 cases of PTC-T and 124 cases of IIH. Minocycline was the most common cause of PTC-T, accounting for 24 of 32 cases (75%). All patients were being treated for acne vulgaris. Significant differences seen between the two groups (PTC-T vs. IIH) include mean age at presentation (19.8 vs. 27.5 years), BMI <30 kg/m² (50.0% vs. 22.7%), mean symptom duration prior to presentation (7.0 vs. 30.8 weeks), CSF opening pressure at presentation (422 vs. 357 mm H2O), mean duration of illness (19.5 vs. 73.5 weeks), and recurrence of PTC (6.3% vs. 17.5%). Treatments and visual outcomes, including persistent decrease in visual acuity and/or residual visual field defects, were similar between the two groups.

Conclusions:
Patients who develop PTC-T are younger, frequently non-obese, and have higher CSF opening pressures at presentation. Despite a significantly shorter duration of illness, these patients experience persistent visual loss just as frequently as those with IIH. Recurrences are less frequent.

References:

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Clinico-Radiological Correlation of Magnetic Resonance Imaging and Ocular Symptoms and Signs in Patients with Idiopathic Intracranial Hypertension.

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Introduction:
The purpose of this study was to correlate magnetic resonance imaging (MRI) findings in patients with idiopathic intracranial hypertension (IIH) to their presenting complaint, severity of vision loss, and laterality of ocular symptoms and signs.

Methods:
The last fifteen years of medical records of a neuro-ophthalmologist were reviewed to identify patients diagnosed with IIH. This patient list was cross-referenced with the MRI database locally, to identify patients who had imaging at the time of diagnosis. Clinical information was retrospectively collected. Neuro-radiology review (blinded to the presenting symptoms and signs) was performed, and radiographic features of IIH identified. Statistical analysis was carried out to investigate whether a correlation exists between the presence of neuro-imaging findings and clinical symptoms and signs. The main outcome measure was the correlation between neuro-imaging findings and each clinical symptom and sign.

Results:
Eighty eight patients with the initial diagnosis of IIH were identified. Thirty one patients met the inclusion criteria, and data was analyzed. We found statistically significant correlations between the following: colour vision and the amount of perineural fluid around the optic nerve on MRI (p = 0.0036), the severity of optic nerve edema of fundoscopy and intraocular optic nerve protrusion seen on MRI (p = 0.004), and the severity of optic nerve edema and amount of perineural fluid around the optic nerve on MRI (p = 0.03).

Conclusions:
We found that some magnetic resonance imaging features are correlated to the severity of idiopathic intracranial hypertension. These features, including the amount of perineural fluid and intraocular nerve protrusion on MRI, can be used in conjunction with clinical data to prioritize those patients who require more urgent intervention and treatment to avoid disease sequelae.

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Etiology and Prognosis of Central Vision Loss at Presentation in Idiopathic Intracranial Hypertension

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Introduction:
Early central vision loss in idiopathic intracranial hypertension (IIH), while not common, can result from different mechanisms, including subretinal fluid, papilledema/optic neuropathy, choroidal folds, hyperopic shift, macular hemorrhages macular edema, or rarely subretinal neovascularization.¹,³ The mechanism of the visual loss is important to determine to help guide management decisions, such as the need for early surgical intervention. This study examines the etiology and prognosis of central vision loss in IIH at presentation, and provides objective measures to predict visual outcomes.

Methods:
A retrospective review of 605 patients with IIH (2009 - 2013) identified 28 patients (4.6%) with best-corrected visual acuity of 20/25 or worse on presentation. Fundus photography, spectral-domain optical coherence tomography (OCT) of the disc and macula, and perimetry were used to determine the causes of central vision loss and evaluate visual prognosis. Segmentation of the macula OCT was performed with the Iowa Reference Algorithm⁴ to determine the retinal ganglion cell-inner plexiform layer complex (GCL-IPL) thickness and subretinal fluid volume. The correlation between the subretinal fluid volume and visual acuity was examined. GCL-IPL thinning on OCT was considered indicative of optic neuropathy as a contributor to central vision loss.

Results:
Outer retinal changes alone caused decreased central vision in 10 patients: subretinal fluid in 6, chorioretinal folds in 3, and peripapillary choroidal neovascularization in 1. The vision loss was reversible except in the patients with chorioretinal folds. Papilledema/optic neuropathy alone caused decreased central vision in 7 patients. Co-existing outer retinal changes and optic neuropathy caused central vision loss in 11 patients, whose outcome was largely dependent on the degree of optic neuropathy.

Conclusions:
Central vision loss in IIH can be caused by both outer retinal changes and optic neuropathy. The correlations between visual acuity, GCL-IPL, and subretinal fluid volume may be useful to predict reversibility.

References:

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**Poster 114**

**Long-term clinical outcomes as a function of BMI of pseudotumor cerebri patients who have been stented for severe cerebral venous sinus stenosis.**

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**Introduction:**

Pseudotumor cerebri (PTC) can devastate vision, preferentially afflicting obese females. A subgroup of patients with severe cerebral sinus stenosis appears to benefit from sinus stenting. We hypothesized a retrospective analysis of patients at our institution who received such stenting would reveal those with a BMI >35 did not experience long-term clinical benefit while those with a BMI <30 did.

**Methods:**

The charts of 21 patients who otherwise met modified Dandy criteria for the diagnosis of PTC and who subsequently received cerebral sinus stents were included for clinical and statistical analysis. BMI at time of stenting and their clinical course to time of chart review were evaluated.

**Results:**

Mean time from stenting to chart review was 33.4 months (range 4.8-68.7). Only one patient was male. He had a BMI >35 and experienced sustained resolution of all active signs and symptoms clearly attributable to PTC. Of the seven others with a BMI >35, three continued to clinically deteriorate, two mildly to moderately improved and two had sustained resolution. Five patients had a BMI between 30-35. Three worsened; the other two mildly improved. Eight patients had a BMI <30. One of these worsened. The remaining seven experienced sustained resolution of all active signs and symptoms attributable to PTC. Outcome was significantly linked to BMI as a continuous variable (p=0.0286), to specific BMI categories (<30, 30-35 and >35, p=0.012), and to race (white vs. non-white, p=0.05).

**Conclusions:**

Long term outcomes of patients who have been stented for severe cerebral venous sinus stenosis associated with PTC are significantly correlated to BMI. Patients with a BMI <30 at time of stenting are more likely to benefit than those with a BMI >30. Non-white patients suffer worse outcomes. Two disease processes may be at play. A prospective, randomized study is needed.

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Protective effect of the optic nerve sheaths fenestration on optic nerve injury caused by intracranial hypertension in patients with cerebral venous sinus thrombosis

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Introduction:
Study on the protective effects of the optic nerve sheaths fenestration on optic nerve injury caused by intracranial hypertension in patients with cerebral venous sinus thrombosis (CVST).

Methods:
Thirty six cases of patients with papilledema, impaired vision, and visual field defect induced by CVST related intracranial hypertension from June 2007 to December 2010 underwent the optic nerve sheaths fenestration operation with the method of conjunctiva approach. The efficacy of the operation was evaluated by comparing the degree of the improvement of the operated eyes with themselves before operation on the items of the vision, the visual fields and the thickness of retinal nerve fibre layer at day-3, 7, 30, 90,180 and 360 after operation; and the safety was estimated by observing the status of local bleeding at the operative site and the changes of the intracranial pressure.

Results:
A total of 67 eyes underwent the optic nerve sheaths fenestration operation at the days of (37.25±20.40) after the onset of clinical symptoms. The average interacranial pressure before operation was 334.72±44.75mmH2O, visual acuity was 0.40±0.24, visual field defect was -16.21±7.34, and the thickness of retinal nerve fibre layer was 269.16±62.66μm. All the items above were improved remarkably at day 7 after operation ( see Table-1, p=0.018, P<0.01, P<0.01 ) . The visual acuity, visual field and thickness of retinal nerve fibre layer increasingly recovered after operation during 360 days of dynamic observation, the peak of the recovery appeared at about day 90 to 180 after operation. The recovery contitue thereafter (Figure 1-A to D, p=0.711). No local bleeding and intracranial hypertension aggravation appeared in the cohort of patients during the preoperative period.

Conclusions:
Optic nerve sheaths fenestration may be an effective and safe method on saving optic nerve injury caused by intracranial hypertension in patients with CVST.

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Evidence of multidomain mild cognitive impairment in Idiopathic Intracranial Hypertension

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Introduction:
Idiopathic Intracranial Hypertension (IIH) is a disorder of unknown etiology that may occur in all age groups, but is most common in young women, especially those with obesity. It is well known that IIH can cause damage in visual functions, possibly leading to blindness; the major goal of treatment is to preserve vision and prevent intractable headache. Cognitive function is currently not addressed routinely during clinical evaluation of IIH patients. NeuroTrax is a practical and technologically advanced computerized tool which provides professional-grade cognitive assessment. The aim of this study was to evaluate cognitive functions in IIH patients using the NeuroTrax testing, which offers a broad profile of cognitive function and has been shown precise and easy to use with good re-test reliability and discriminate validity for mild cognitive impairment.

Methods:
Prospective study. All participants completed a NeuroTrax battery for cognitive impairment (testing time: 30 minutes) sampled non-verbal memory, executive function, visual spatial processing, attention, motor skills, problem solving and information processing speed.

Results:
Thirty consecutive IIH patients participated, including 3 males and 27 females. Mean age at time of testing was 34.4 years. Mean scores for all domain index scores were below average for age and education. The global cognitive score, attention and visual spatial indices had the lowest scores.

Conclusions:
Our results reflect mild cognitive impairment in IIH using a computerized neuropsychological test battery. All domain measures apart from memory showed a statistically significant difference from normal individuals, indicating that there is a form of multi-domain cognitive impairment in IIH.

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Asymmetric papilledema in idiopathic intracranial hypertension (IIH)

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Introduction:
Truly asymmetric papilledema in IIH is rare and poorly characterized. Our goal was to determine the prevalence and the clinical and radiologic features of IIH with highly asymmetric papilledema.

Methods:
Retrospective review of all definite IIH patients seen by us between 1989 and 2013. Papilledema was graded (modified Frisén scale¹) by reviewing fundus photographs. Asymmetric papilledema was defined as ≥2 grades difference between the 2 eyes. Clinical and radiologic characteristics were reviewed.

Results:
Of 725 IIH patients, 18 (2.5%) had ≥2 grades difference papilledema between the 2 eyes at initial evaluation [age: 38±11 year-old; 15 women (83%); 11 white (65%); 6 black (35%); all overweight (BMI=43.7±20.3kg/m²); 3 with sleep apnea, 2 taking vitamin A-derived medications, 1 with anemia]. CSF opening pressure was 32.2±9.0cm H₂O. 11/18 patients (61%) had the highest-grade edema in the left eye; papilledema was unilateral in 8 patients (44.5%). 6/18 patients (33%) presented with isolated transient visual obscurations (TVOs) and 6/18 patients (33%) were asymptomatic. Brain imaging (6 MRI, 1 CT), was available for review in 7 patients. Optic canal measurement showed larger area cross-section on the side of the highest-grade edema by 3.4±3.6mm² for all 3 patients in whom this technique was available. 4/7 patients (57%) showed prominent peri-optic nerve CSF; it was always greatest on the side of the highest-grade edema. There was no relationship between the side of the highest transverse venous stenosis and the side of the highest-grade edema.

Conclusions:
Asymmetric papilledema is rare in IIH. Clinical presentation differs from classic IIH by the frequency of isolated TVOs at presentation, and of asymptomatic IIH. Asymmetric edema may originate from difference in size of both optic canals, with the larger canal allowing CSF pressure to be transmitted more easily to the optic disc, which may explain the prominent peri-optic CSF on the side of the high-grade edema.

References:


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A Novel Superonasal Transconjunctival Approach To Optic Nerve Sheath Decompression Without The Disinsertion Of Extraocular Muscles

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Introduction:
We wish to introduce a novel superonasal transconjunctival approach to optic nerve sheath decompression (STONeD) that does not require the disinsertion and reinsertion of any extraocular muscles.

Methods:
We will present data from approximately 15 consecutive patients undergoing optic nerve sheath decompression without disinsertion of extraocular muscles at our institution since January 1, 2013.

Results:
We will describe the rate of stability or improvement of visual acuity and visual fields, as well as any postoperative complications, at the 1-week and 6-week post-operative visits. We will compare operative times and intra-operative and post-operative complications with a previously reported retrospective cohort that used surgical techniques requiring disinsertion and reinsertion of extraocular muscles. Video of this technique will be presented.

Conclusions:
To our knowledge, this is the first report of a superonasal transconjunctival approach to optic nerve sheath decompression that does not require the disinsertion of extraocular muscles. STONeD has the potential advantages of reduced intra-operative time, fewer post-operative complications, and a flatter learning curve for fellowship training compared to previously reported techniques. In addition, there are no differences in visual outcome using this procedure compared to other techniques.

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Persistent Intracranial Hypertension After Successful Drainage Of Colloid Cyst Of The Third Ventricle In A Pregnant Obese Woman

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Introduction:
To present a unique case of persistent papilledema in a 27 week pregnant woman subsequent to third ventriculostomy for drainage of a symptomatic colloid cyst.

Methods:
A 25 year-old obese woman, 27 weeks pregnant, presented with left eye visual loss and diminished peripheral vision. Six weeks prior, she saw an outside ophthalmologist for diplopia and was found to have bilateral optic disc edema. MRI Brain and Orbits revealed a colloid cyst of the third ventricle with obstructive hydrocephalus. She underwent urgent neurosurgical endoscopic third ventriculostomy with colloid cyst drainage. One week after surgery, there was persistent CSF egress from her incision site and staples were replaced with water-tight sutures. In the ensuing 2 weeks, she developed progressive visual loss. On presentation, visual acuity was 20/20 OD and 20/50 OS, with severely constricted visual fields OU. Funduscopic examination showed grade IV papilledema OU. MRI/MRA showed improved hydrocephalus, and MRV excluded venous sinus thrombosis. Lumbar puncture opening pressure was 30 cm H₂O with normal CSF contents. On oral acetazolamide, she developed nausea, vomiting, dehydration, and extremity paresthesias.

Results:
Given persistent papilledema with severely constricted visual fields and poor tolerance for conservative measures, left optic nerve sheath fenestration (ONSF) was performed with improved visual function. In her second trimester of pregnancy, she was not an ideal candidate for a CSF shunting procedure.

Conclusions:
This is the first case of persistent papilledema after successful drainage of a colloid cyst of the third ventricle in a young pregnant obese woman. It is proposed that she had both pseudotumor cerebri syndrome and obstructive hydrocephalus from a colloid cyst of the third ventricle. This case reinforced the dilemma of management of papilledema with visual loss in pregnant women.

References:

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Hypophosphatemic Rickets as the Etiology of Papilledema and Early Visual Field Loss from Craniosynostosis

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Introduction:
We report a case of papilledema and early visual field loss from craniosynostosis related to hypophosphatemic rickets in a six-year-old girl. Hypophosphatemic rickets is caused by decreased reabsorption of inorganic phosphates in the renal tubules, leading to hyperphosphaturia and impaired bone mineralization¹.

Methods:
The patient was referred to neuro-ophthalmology for work-up of papilledema found incidentally by her general ophthalmologist. On neuro-ophthalmologic examination, acuity was 20/20 and color vision was full OU. There were bilateral abducens palsies. Fundoscopy revealed Frisen grade III papilledema OU. Goldmann visual fields demonstrated severely enlarged blind spots and inferonasal depressions OU.

Results:
The patient underwent MRI brain which revealed dilation of the optic nerve sheaths, a partial empty sella, and flattening of the posterior globe contours. She was also noted to have low-lying cerebellar tonsils. A CT scan of the head demonstrated near complete fusion of the coronal, sagittal, and lambdoid sutures, with associated scaphocephaly. A lumbar puncture was deferred given a crowded foramen magnum. She was referred to neurosurgery for cranial vault remodeling. Post-operatively, she had continued papilledema and was started on acetazolamide. Six-months post-surgery, she no longer had papilledema or abduces palsies and only had mildly enlarged blind spots. At last follow-up, she was being weaned off acetazolamide.

Conclusions:
While there are many cases in the literature that associate papilledema and craniosynostosis, there are only a few cases where hypophosphatemic rickets is the proposed etiology¹ ² ³ ⁴ ⁵ ⁶. To our knowledge this is the fourth reported case, and the oldest patient, in which papilledema was the key diagnostic feature of craniosynostosis associated with hypophosphatemic rickets¹ ² ³ ⁴. It is the first case in which significant visual field loss was documented. This case highlights the importance of regular dilated fundoscopic screening in patients with hypophosphatemic rickets.

References:


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INCREASED OCULAR PULSE AMPLITUDE ASSOCIATED WITH UNILATERAL ABSENCE OF THE GREATER SPHENOID WING

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Introduction:
Intraocular pressure (IOP) is pulsatile due to the interdependence of ocular blood flow and the aqueous circulation,1 and can reflect systemic hemodynamic events.2 In addition, the amplitude of the pulsations may be affected by high intracranial pressures (ICP).3,4 Ocular pulse amplitude (OPA) is defined as the difference between systolic and diastolic IOP with average values in healthy subjects ranging from 1-4mmHg. We present a 55 year-old male with neurofibromatosis type 1 (NF-1) with an upper eyelid neurofibroma, absence of the sphenoid wing, and pulsating enophthalmos on the right.

Methods:
CT scan of the orbits was performed to further delineate the tumor, and this revealed absence of the right greater sphenoid wing including the lateral orbital roof and most of the lateral wall on the right. Pascal Dynamic Contour Tonometry (DCT) was performed prior to resection of the neurofibroma.

Results:
Pascal Dynamic Contour Tonometry average IOPs were 18.5mmHg OD and 16.8 mmHg OS with OPA's of 2.87mmHg OD and 1.47mm Hg OS, which was 16% and 9% of IOP, respectively. The right OPA waveform morphology more closely approximated the intracranial pulse waveform of the cerebrospinal fluid (CSF).

Conclusions:
When a significant portion of the orbital roof and lateral wall are absent, the CSF pulse is directly transmitted to the orbital tissues. We hypothesize that the greater OPA in this patient was due to stronger transmission of the intracranial pressure (ICP) waveform amplitude and morphology in the absence of the sphenoid wing. It is possible to repair the bony defect via a pterional craniotomy with a split thickness calvarial graft or titanium mesh. Presumably, repair of the bony defect would normalize the OPA compared to the contralateral side by significantly reducing the mechanical effect of the ICP pulse.

References:
2. Kassem JB; Katz SE; Roberts CJ; Mahmoud AM; Small RH; Raman SV. Ocular Pulse Amplitude Waveform Reflects Ventricular Bigeminy and Aortic Insufficiency. IOVS 2013; 54:ARVO E-abstract 4673.
4. Katz SE; Mahmoud AM; Okon M; Bolisetty K; Small RH; Roberts CJ. Changes in Intracranial Pressure (ICP) and Ocular Pulse Amplitude (OPA) in Patients with Idiopathic Intracranial Hypertension (IIH). IOVS 2013; 54:ARVO E-abstract 4367.

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Grant Support: None.
Unusual Cause of Sixth Nerve Palsy and Headache

Introduction:
A case of severe headache associated with unilateral sixth nerve palsy is presented with particular reference to the interpretation of the appropriate imaging.

Methods:
Case report

Results:
A 36 year old male with no previous surgery or trauma was admitted for severe orthostatic headache for which non-enhanced CT brain and MRI brain with MRA was unremarkable. He subsequently developed a sixth nerve palsy a few days later. MRI brain with contrast revealed diffuse smooth pachymeningeal enhancement and dural venous engorgement in the retro-clival region, consistent with intracranial hypotension. His signs and symptoms resolved with an epidural blood patch.

Conclusions:
Recognition of the characteristics of the headache and MRI findings is the key to diagnosis of spontaneous intracranial hypotension, a condition that is not infrequently misdiagnosed. Downward displacement of the brain may cause stretching of the abducens nerve resulting in acute diplopia due to sixth nerve palsy.

References:

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Macular Outer Retinal Abnormalities in Severe Papilledema

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Introduction:
Pseudotumor cerebri syndrome (PTCS) is a common cause of papilledema in young, obese women. Macular edema (ME) in the setting of PTCS has been previously described. However, the effects on specific macular retinal layers in patients with PTCS and ME have not been depicted.

Methods:
We report a 24 year-old Hispanic woman with fulminant PTCS with severe papilledema and ME. Macular imaging was performed with Heidelberg Spectralis spectral domain optical coherence tomography (SD-OCT) (Carlsbad, CA).

Results:
The patient initially presented with bilateral decreased vision, photosensitivity, phonophobia, nausea, and a severe, throbbing headache. Lumbar puncture opening pressure was 50 cm H₂O. Dilated funduscopic examination (DFE) showed severe grade 5 papilledema with cotton wool spots and disc hemorrhages. Visual acuity on presentation was 20/40 OU with rapid decline to 20/400 OD and 20/150 OS and significant constriction of visual fields. A ventriculoperitoneal (VP) shunt was placed urgently with subsequent improvement in symptoms and visual function. At 2 week follow up, there was persistent grade 4 papilledema with macular exudates and pigmented disruption OU. Seven months after initial presentation, SD-OCT revealed minimal subretinal fluid and disruption of the photoreceptor inner segment-outer segment junction (IS/OS line) in the areas of macular pigmentary disruption with an intact retinal pigment epithelium (RPE). Visual acuity at last follow up was 20/25 OD and 20/30 OS with much improved visual fields.

Conclusions:
This is the first report of late photoreceptor disruption on SD-OCT in a patient with severe papilledema and ME associated with PTCS. We suggest that disruption of the photoreceptors, not the RPE, is responsible for pigmentary changes observed in the macula in the setting of severe papilledema with ME. This finding warrants further investigation to characterize the natural history and correlation with central visual function.

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Grant Support: None
JAK2 V617F mutation associated with cerebral venous thrombosis: a rare cause of intracranial hypertension

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Introduction:
We present a case of cerebral venous thrombosis secondary to an unusual mutation, the Janus kinase 2 (JAK2 V617F) mutation. The patient complained of symptoms consistent with idiopathic intracranial hypertension (IIH). The initial imaging as well as hypercoagulable and infectious workup were unremarkable. We present this case as a rare clinical example of secondary intracranial hypertension.

Methods:
Retrospective chart review of a patient seen at USC Eye Institute from June 2013 to October 2013.

Results:
A 34-year-old African American woman with no past medical history presented with transient obscuration of vision, pulsatile tinnitus, occasional nausea and dizziness. Subsequent tests demonstrated normal magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) studies, mildly elevated opening pressure, papilledema, and enlarged blind-spot and arcuate defect on visual fields. She was placed on oral acetazolamide for presumed IIH. However, she rapidly developed multiple systemic venous thromboses, leading to two strokes. Further imaging including magnetic resonance venography (MRV) revealed cerebral vein thrombosis with dural venous sinus thrombosis of the distal superior sagittal sinus, straight sinus, and right transverse sinus. Extensive hypercoagulable workup was unremarkable and genetic testing revealed JAK2 V617F mutation, which is the primary molecular marker of the Philadelphia chromosome-negative myeloproliferative neoplasms. The mutation causes constitutive activation of JAK2, which results in myeloproliferation independent of cytokines, mobilization of blood cell progenitors, and spontaneous formation of endogenous erythroid colonies.

Conclusions:
Our patient was initially misdiagnosed as IIH. However, her symptoms did not improve with acetazolamide. Only on the subsequent MRV was dural sinus thrombosis detected. Even though the value of JAK2 V617F in cerebral venous thrombosis is controversial given its low prevalence, it confirmed the underlying etiology in this case. IIH is therefore a diagnosis of exclusion. In atypical cases, it is important to obtain MRV in addition to MRI to rule out secondary causes of intracranial hypertension.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Central Neurocytoma: A Cause of Vision Loss from Delayed Diagnosis of Papilledema

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Introduction:
Central neurocytoma is a slow-growing supratentorial tumor of neuroepithelial origin that frequently arises from the septum pellucidum or lateral ventricular wall. The main presenting symptom is headache and the main sign is papilledema. Although histopathology is benign and surgical resection is often curative, many surgeries may be necessary and diagnosis is made too late to prevent vision loss from chronic papilledema.

Methods:
A 21 year old healthy man developed headache, flashes of light and visual field disturbances, with marked optic disc edema. Brain imaging revealed a huge intraventricular mass obstructing the foramen of Monro.

Results:
Surgery showed diffuse immunoreactivity for synaptophysin and negativity for glial fibrillary acid protein (GFAP). MIB-1 proliferation index was relatively high at 4.7% (Mackenzie method), yielding a diagnosis of atypical central neurocytoma. Tumor adherence to the ventricular wall and excessive bleeding prevented gross total removal even after 3 surgeries. Although the patient was neurologically intact, and tumor growth was arrested, unrelenting headaches and non-resolving papilledema led to external beam radiation. Persistent papilledema led to bilateral optic atrophy, manifesting as persistent visual acuity and visual field loss.

Conclusions:
Despite its benign histopathology, central neurocytoma can cause problems. Delayed diagnosis is associated with post-papilledema optic neuropathy. Incomplete surgical removal is associated with tumor recurrence in 21%, requiring multiple surgeries and sometimes radiotherapy.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: none
Neurosarcoidosis masquerading as meningioma

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Introduction:
Sarcoidosis is a multisystem inflammatory disease that can affect the central and/or peripheral nervous system approximately 5-15% of the time. When the nervous system is involved, there are a variety of ophthalmic manifestations that can be seen including cranial nerve palsies, direct optic nerve involvement or papilledema. Here we present a case of a diagnostically challenging case of neurosarcoidosis.

Methods:
Case review of a 55 year old woman presenting with white floaters as "static" over her vision for many months, progressively worsening.

Results:
A 55 year old Caucasian woman presented with floaters and blurred vision in both eyes for several months, described as white spots or static fuzz that she could still see through. The symptoms have progressively worsened over months, with acute worsening over the last 2 weeks. She denied eye pain, diplopia, pain with eye movements, but did endorse intermittent headache. Approximately one year prior, she was diagnosed with multiple meningiomas after vague symptoms of lightheadedness, nausea decreased hearing. On presentation, she was wheelchair bound because of unsteadiness in gait and lower extremity weakness, vision was 20/20-1 OU, full color vision, full ductions and normal pupils without RAPD. HVF showed enlargement of the blind spots. Fundus showed florid disc edema bilaterally with OCT RNFL average thickness of 411 and 397 respectively. Repeat MRI and lumbar puncture revealed interval enlargement of prior lesions, a lymphocytic pleocytosis with WBC>300 and negative cytology, and an elevated opening pressure of 45 cm H2O. Biopsy of frontal lobe lesion demonstrated granuloma with giant cells consistent with sarcoidosis. She was started on steroid therapy with rapid symptomatic improvement.

Conclusions:
This case is unique because of the patient’s smoldering course and delayed diagnosis as her MRI was very suggestive of multiple meningiomas. After repeated lumbar punctures were non-diagnostic, meningeal biopsy was ultimately necessary to arrive at a diagnosis.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Utilizing Optical Coherence Tomography in Diagnosing a Unique Presentation of Chiasmal Hypoplasia-variant of Septo-Optic Dysplasia

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Introduction:
Septo-optic dysplasia (SOD) is a rare and heterogeneous disorder characterized by optic nerve hypoplasia, pituitary hormone abnormalities, and midline brain defects such as agenesis of the septum pellucidum and/or corpus callosum. We describe an unusual case of septo-optic dysplasia that presents with horizontal optic disc cupping, bitemporal hemianopia, and generalized thinning of the circumpapillary retinal nerve fiber layer.

Methods:
A 13 year old adopted white male was referred for abnormal optic nerve appearance. On examination, the visual acuity was 20/20 OU, intraocular pressure (IOP) was 13 mmHg OD and 14 mmHg OS, and funduscopic examination revealed bilateral excavated and pale optic nerves. Retina nerve fiber layer (RNFL) analysis by spectral-domain optical coherence tomography (OCT) was remarkable for decreased RNFL thickness in the nasal and temporal segments consistent with a bow-tie configuration atrophy in both eyes. Automated visual field testing revealed bitemporal hemianopia. The visual field pattern lead to urgent magnetic resonance imaging (MRI) of the brain, which was remarkable for absence of septum pellucidum and chiasmal atrophy. Based on these findings, the diagnosis of chiasmal hypoplasia-variant SOD was made.

Results:
Our patient presented with optic nerve cupping raising suspicion for juvenile open angle glaucoma. However, the OCT RNFL analysis revealed thinning of nasal and temporal quadrants, unlike glaucomatous damage which typically involves thinning of superior and inferior quadrants. In the context of normal IOP, juvenile glaucoma was ruled out as a cause of the optic disc cupping. The relatively preserved superior and inferior RNFL bundles correlated well with the findings of bitemporal hemianopia and the MRI findings of chiasmal hypoplasia.

Conclusions:
To the authors’ knowledge, this is the first description of OCT RNFL analysis in the chiasmal hypoplasia variant of SOD. OCT RNFL analysis was instrumental in differentiating non-glaucomatous from glaucomatous optic nerve cupping, and aided in correlating structure and function.

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Differentiating Mild Papilledema and Buried Optic Nerve Head Drusen Using Spectral Domain Optical Coherence Tomography

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Introduction:
To evaluate the clinical utility of spectral domain optical coherence tomography (SD-OCT) in differentiating mild papilledema from buried optic nerve head drusen (ONHD).

Methods:
16 eyes of 9 patients with ultrasound-proven buried ONHD, 12 eyes of 6 patients with less than or equal to Frisén grade 2 papilledema due to idiopathic intracranial hypertension, and 2 normal fellow eyes of patients with buried ONHD were included. A raster scan on the optic nerve and retinal nerve fiber layer (RNFL) thickness analysis was performed on each eye using SD-OCT. Eight eyes underwent enhanced depth imaging SD-OCT. Images were assessed qualitatively and quantitatively to identify differentiating features between buried ONHD and papilledema. Five clinicians trained with a tutorial and masked to the underlying diagnosis reviewed the SD-OCT images of each eye independently to determine the diagnosis.

Results:
We found no statistically significant difference in RNFL thickness between buried ONHD and papilledema in any of the four quadrants. Diagnostic accuracy among the readers was low and ranged from 50-64%. The kappa coefficient of agreement among the readers was 0.35 (95% Confidence interval: 0.19, 0.54).

Conclusions:
SD-OCT is not clinically reliable in differentiating buried ONHD and mild papilledema.

References:

Financial Disclosures: The authors had no disclosures.

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Comparison Of Optic Nerve Head Topography and Retinal Nerve Fiber Layer Thickness in Non-glaucomatous Optic Neuropathy (NGON) and Normal Tension Glaucoma (NTG)

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Introduction:
The objective of this study is to compare the peripapillary retinal nerve fiber layer thickness (RNFLT) and optic nerve head topography findings in eyes affected by non-glaucomatous optic neuropathy (NGON) & normal-tension-glaucoma (NTG), using spectral-domain optical coherence tomography (OCT).

Methods:
In this retrospective case-control study, 23 eyes with various causes of NGON (excluding arteritic/non-arteritic anterior ischemic optic neuropathy) of at least 6 months’ duration from onset were identified. Twenty-three eyes from 23 age-matched subjects with progressive NTG and at least 3 years follow-up were included. All eyes underwent Cirrus HD-OCT (Carl Zeiss Meditec) optic disc scan protocol. Baseline demographics, visual field parameters, optic disc topographic findings and RNFLT in Cirrus OCT were compared between the 2 groups.

Results:
There was no significant difference in best corrected visual acuity, visual field parameters, average RNFLT and disc area between the 2 groups. Average RNFLT per rim area, cup volume & vertical cup-disc-ratio (VCDR) were all significantly higher in NTG eyes (p<0.001) while sectoral RNFL analysis of nasal (p=0.002) & temporal (p=0.015) quadrants were significantly thinner in NGON. Among all parameters, VCDR and nasal rim RNFLT were most significant in binary logistic regression analysis in distinguishing NGON from NTG. Using ROC analysis, the optimal cutoff value of VCDR for differentiating between NGON and NTG eyes was determined to be 0.725 with the sensitivity and specificity of 91.3% and 73.9% respectively (AUC =0.889). To achieve 95% specificity, the cut off value of VCDR was noted to be 0.795.

Conclusions:
For a similar extent of RNFLT loss in age-matched subjects, NTG eyes have thinner neuro-retinal rim, more cup excavation and higher VCDR while NGON eyes have more generalized RNFL loss. In addition to clinical history and examination, our study demonstrated that OCT may serve as an objective tool in helping to differentiate between NGON and NTG eyes.

References:


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Reproducibility of Circumpapillary Retinal Nerve Fiber Layer Measurements Using Hand-held Optical Coherence Tomography in Sedated Children with Optic Pathway Gliomas

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Introduction:
Hand-held optical coherence tomography (HH-OCT) measures of circumpapillary retinal nerve fiber layer (cpRNFL) thickness have a close relationship to vision loss (visual acuity and or visual field) in children with optic pathway gliomas (OPGs). The intravisit reproducibility of cpRNFL measurements using HH-OCT in sedated children was investigated.

Methods:
HH-OCT (Bioptigen) measures of cpRNFL were acquired in children with and without OPGs undergoing sedation for a clinically indicated MRI. A 6 x 6 mm volume (isotropic 300x300 or non-isotropic 1000x100 samplings) was acquired over the optic nerve. Children with two or more acceptable scans (same sampling volume and eye) acquired during a single imaging session were included. Subjects could contribute scans from one or both eyes and sampling types. Automated software segmented the volume and determined the cpRNFL thickness (3.4 mm circle centered on the geometric center of the optic nerve head, which was manually delineated). The coefficient of variation (CV) for the global average and anatomic quadrant cpRNFL thickness was calculated.

Results:
375 eligible HH-OCT scans (N=270 isotropic volumes; N=105 non-isotropic volumes) from 101 subject eyes (33 unique subjects) were analyzed (age range 1.75-8.9 years). Seventy-seven subject eyes had OPGs, of which 17 had experienced vision loss. The isotropic volumes (median 4 scans per eye) demonstrated the best CV for the global average (4.3%), followed by the superior (5.5%), inferior (6.6%), temporal (8.3%) and nasal (8.3%) quadrants. For non-isotropic images (median 2 scans per eye), the global average (2.9%) demonstrated the best CV, followed by inferior (4.7%), superior (5.0%), nasal (5.6%), and temporal (6.2%) quadrants. Subject eyes with vision loss had an increased CV (p <0.01) compared to those with normal vision.

Conclusions:
cpRNFL measures acquired with HH-OCT during sedation demonstrate good reproducibility. HH-OCT has the potential to monitor progressive optic neuropathies in young children who have difficulty cooperating with traditional OCT devices.

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The relationship between optical coherence tomographic (OCT) and perimetric findings in patients with papilledema

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Introduction:
Optical coherence tomography (OCT) provides quantitative ocular imaging in conditions causing optic neuropathy. Correlation of OCT-identified structural change to visual function has been well established in multiple sclerosis patients. I compared measures of retinal and optic nerve head (ONH) anatomy to standard perimetry in patients with papilledema associated with intracranial hypertension.

Methods:
I studied 26 patients with papilledema (22 with idiopathic intracranial hypertension) and no alternative ocular pathology. Fourteen patients were tested twice, at least 3 months apart. Using spectral-domain OCT, I quantified retinal nerve fiber layer (RNFL) thickness, total macular volume and ONH volume in each eye and compared values with standard automated static perimetry. Optic disc elevation was confirmed with 3-dimensional image reconstruction.

Results:
For most eyes, there was no relationship between the degree of RNFL or ONH swelling and perimetric mean deviation. In this group, even eyes with severe swelling showed normal or only mildly reduced mean deviation and RNFL thickness correlated positively with ONH volume. In a smaller group of eyes with ONH volumes at the lower end of the supranormal range, RNFL thickness and macular volume were paradoxically subnormal and perimetry showed moderate to severe impairment. In 4 eyes of this latter group, serial testing showed stable or improved visual fields despite declining RNFL thickness within the subnormal range.

Conclusions:
Quantitative measures of tissue swelling do not correlate with visual field loss in most patients with papilledema. In a minority of eyes, RNFL and macular thickness may be subnormal despite optic disk swelling, implying a combination of swollen and thin or missing axons. These eyes may show significant visual field loss, but further RNFL thinning does not always portend perimetric deterioration.

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Correlation of ganglion cell layer thickness with post-geniculate homonymous visual field loss: evidence for trans-synaptic degeneration

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Introduction:
Controversy remains regarding the occurrence of optic nerve degeneration following post-geniculate hemianopsia. We performed a retrospective analysis of ganglion cell layer (GCL) and retinal nerve fiber layer (RNFL) thickness using spectral domain optical coherence tomography (SD-OCT) in patients with homonymous visual field loss from post-geniculate disease.

Methods:
Clinic charts from January 2010 to October 2013 of patients with a CPT code for homonymous hemianopsia were reviewed. Out of 222 patients, 22 had undergone SD-OCT. After excluding five patients with a diagnosis of glaucoma, 17 patients remained. For GCL, the combined thickness of the two left sextants (nasal sextants of right eye and temporal sextants of left eye) was subtracted from the combined thickness of the two right sextants (temporal sextants of right eye and nasal sextants of left eye) to generate a right-left asymmetry score for each eye. For RNFL, right and left quadrants were used rather than sextants. Patients were screened for asymmetry scores ≥ 5 microns in both eyes, where the direction of asymmetry correlated with the side of cortical injury. Data regarding etiology of the visual field defect and its time course were gathered.

Results:
In 9 of the 17 patients, both eyes showed GCL thinning contralateral to the homonymous visual field defect and ipsilateral to the side of cortical injury. Of the remaining 8 patients, none demonstrated thinning in both eyes that was ipsilateral to the homonymous field defects. RNFL thinning that was contralateral to the homonymous field defect in both eyes was demonstrated in only 1/17 patients. Excluding patients with tumors of indeterminate onset, the shortest duration between injury and evidence of corresponding GCL thinning was 4 years.

Conclusions:
Using SD-OCT, thinning of the GCL, but not RNFL, correlates with post-geniculate visual pathway pathology, thus providing new insights regarding trans-synaptic degeneration of the visual system.

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The use of Spectral Domain Optical Coherence Tomography for differentiating long-standing Central Retinal Artery Occlusion and Nonarteritic Anterior Ischemic Optic Neuropathy

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Introduction:
Optic atrophy is the end result of both central retinal artery occlusion (CRAO) and nonarteritic anterior ischemic optic neuropathy (NAION). The aim of the present study was to report on the efficacy of macular and optic nerve Spectral Domain Optical Coherence Tomography (SD-OCT) in differentiating between these conditions.

Methods:
24 patients (mean age 65 years) with optic atrophy secondary to CRAO (12 patients) and NAION (12 patients) were recruited into this study. The 24 uninvolved eyes served as controls. All patients underwent SD- OCT of the macula and optic nerve at least three months following acute vision loss. SD-OCT results were compared both qualitatively and quantitatively between both groups and controls.

Results:
Macular SD-OCT scans in eyes with CRAO demonstrated complete atrophy of the neurosensory retinal layers, loss of stratification of the inner retinal layers and loss of the foveal pit whereas in eyes following NAION there were only loss of RNFL and ganglion cell layers. In patients with longstanding CRAO there was a significantly greater thinning (P<0.001) of the macula relative to the fellow uninvolved eye (-59.7 ± 31.8µm) than in patients with longstanding NAION (-19.9 ± 8.4µm) even though both conditions caused a similar (P=0.726) degree of peripapillary RNFL loss (-42.4±18.5µm and -44.1±12.4µm, respectively).

Conclusions:
SD-OCT macular scans can be used as an adjunctive tool for differentiating between long-standing CRAO and NAION.

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Grant Support: None.
When OCT May Obscure Pathology

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Introduction:
The introduction of OCT as an anatomic study of the nerve fiber layer in vivo has been one of the greatest advances since the invention of the ophthalmoscope. This technology allows a reproducible quantitative assessment of the anatomy of the optic nerve in patients with evidence of optic nerve pathology. The potential for under calling optic atrophy due to the delay in nerve fiber layer thinning has been recognized. Less clear is the potential for disc swelling to mask progressive optic nerve pathology.

Methods:
A retrospective study of three patients with progressive compressive optic neuropathy and evidence of optic nerve pathology (acuity, fields, and afferent pupillary defect) were seen where the OCT showed normal nerve fiber layer thickness, or even subtle thickening (unaccompanied by clear disc edema). To further investigate changes in OCT a retrospective search discovered 22 patients coded as orbital apex syndrome. Fifteen of these had OCT studies done. Separately, 11 patients in the last 5 years were coded for optic nerve sheath meningiomas.

Results:
All 15 of the patients with orbital apex pathology showed subtle or significant NFL thinning. Two of the 11 optic nerve sheath meningiomas had NFL thickening. The presumptive mechanism in the “obscured” patients was that pressure on the optic nerve could result in mild disc edema which masked ongoing damage to the nerve fiber layer. Anything that results in disc swelling (including low intraocular pressure) may mask ongoing or previous damage to the optic nerve.

Conclusions:
One additional artifact in OCT is the potential for disc edema to mask ongoing or previous damage to the optic nerve. The disparity between psychophysical function (fields, acuity) and physiologic studies (afferent pupillary defect, VEP) with the anatomic findings of OCT should engender a search for possible potential confounding mechanism.

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Predicting Visual Recovery after Optic Neuritis

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Introduction:
Spectral-domain optical coherence tomography (OCT) provides a sensitive means of capturing axonal damage [retinal nerve fiber layer (RNFL) loss] and neuronal degeneration [macular volume (MV) and ganglion cell layer (GCL) loss] after optic neuritis (ON). The purpose of this study was to determine whether early markers of clinical and structural integrity in the afferent visual pathway could be used to predict recovery after ON.

Methods:
In this prospective cohort study, 50 ON patients underwent ophthalmic and SD-OCT testing at baseline (within 30 days of symptom onset), 3-months, 6-months, and 12-months. Descriptive statistics were calculated for patient demographics. For analysis of correlated data random effects mixed model was fitted to account for effects of follow up when determining the relationship between SD-OCT measures and visual recovery, and structural changes (RNFL, MV, GCL) over time. To test predictors of change in RNFL anf GCL values, multiple linear regression analysis was used.

Results:
The mean age of patients was 36 years (42 females). The RNFL, MV, and GCL values in ON eyes significantly decreased up to 6-months, and inter-eye differences in SD-OCT measures were significant across all time points. The logMAR visual acuity and visual field mean deviation scores significantly improved in the post-acute phase. One-month RNFL measures in ON eyes predicted change in RNFL thickness at 6-months (P <0.0001) and 12-months (p <0.0001), and the extent of logMAR acuity change at 6-months (p = 0.02). One-month GCL values predicted the change in visual field mean deviation noted at 6-months (p = 0.03) and 12-months (p= 0.002), change in log MAR visual acuity at 12 months (p = 0.001), and change in RNFL thickness at 6-months (p = 0.009). Gender and age were independent variables identified, which predicted change in RNFL after ON.

Conclusions:
SD-OCT measures captured 1-month after symptom onset correlate with structural and functional measures of recovery after ON.

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Quality of Life After Optic Neuritis in MS: New Data for the 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25

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Introduction:
The 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 is designed to capture quality of life (QOL) and symptoms in multiple sclerosis (MS), optic neuritis (ON) and other neurologic disorders affecting the afferent and efferent visual pathways. We examined how the 10-Item Supplement could distinguish patients with MS and ON vs. disease-free controls in an ongoing collaborative study of visual function and optical coherence tomography (OCT).

Methods:
Participants completed the 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) and 10-Item Neuro-Ophthalmic Supplement. Low-contrast letter acuity (LCLA), visual acuity (VA) and spectral-domain (SD) OCT were performed to determine peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell + inner plexiform layer (GCL+IPL) thicknesses.

Results:
Analyses of data from 203 patients with MS (406 eyes, age 46.7±11.7 years) and 16 disease-free controls (32 eyes) showed reduced RNFL thickness for patients with history of ON (176 eyes, 81.1±20.1 microns) and for patients with no history of ON (221 eyes, 87.8±10.8 microns). The 10-Item Neuro-Ophthalmic Supplement had a greater capacity to distinguish MS patients with a history of ON vs. those without ON (area under the ROC curve = 0.67, p=0.001, logistic regression accounting for age) compared to the NEI-VFQ-25 composite score (ROC=0.61, p=0.021). Both the 10-Item Supplement and NEI-VFQ-25 composite were excellent discriminators of MS patients vs. controls; combining the NEI-VFQ-25 + Supplement resulted in an ROC area of 0.93 (p<0.001, accounting for age). The Supplement score was a better predictor of peripapillary RNFL thickness in MS eyes (p=0.009, GEE models accounting for age and within-patient, inter-eye correlations) than GCL+IPL thickness (p=0.04).

Conclusions:
The 10-item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 is a more powerful predictor of MS, ON and other neurologic disorders of the visual pathway. Targeted MS vision-based QOL measures may better represent visual pathway axonal injury as well as patient-reported visual dysfunction in MS and ON.

References:

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Using enhanced-depth imaging optical coherence tomography (EDI-OCT) features to distinguish pseudopapilledema and true papilledema

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Introduction:
In patients with tilted, anomalous optic discs, pseudopapilledema (PP) may be difficult to differentiate from true papilledema (TP). Patients with suspected TP may be subjected to expensive and invasive testing such as MRI and lumbar puncture. In this study, we aim to identify features on spectral domain optical coherence tomography (SD-OCT) that may help distinguish pseudopapilledema (PP) from true papilledema (TP).

Methods:
This was an IRB-approved prospective study. Ten patients with presumed PP, 10 patients with TP, and 10 control patients with normal-appearing optic nerves were recruited. Patients with optic nerve head drusen were excluded. TP patients presented with symptoms and signs of intracranial hypertension (ICH), with documented neuroimaging and lumbar puncture. Only TP patients with mild papilledema modified Frisén grade I and II were included, as their optic nerve appearance is clinically similar to those with PP. All patients underwent ophthalmologic examination with automated perimetry, stereo disc photographs, and SD-OCT. Both Zeiss Cirrus™ and Heidelberg Spectralis® images were acquired and analyzed. Enhanced-depth imaging (EDI) OCT was also performed.

Results:
In PP and controls, average RNFL thickness as measured by SD-OCT was within normal limits, whereas it was significantly increased in TP. In addition in TP, the prelaminar neuroglial tissue bulges into the peripapillary region in all directions, whereas in PP and controls, it is more likely to bulge into the nasal area only. Peripapillary intraretinal fluid pockets are more likely to be seen in TP, but not in PP or controls. Finally, the optic discs tend to be tilted in PP with elevation of the nasal aspect only.

Conclusions:
SD-OCT may be a useful, non-invasive tool for clinicians to help distinguish PP from TP, sparing patients the need for neuroimaging and lumbar puncture.

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Measurement of Retinal Nerve Fiber Layer and Macular Ganglion Cell- Inner Plexiform Layer with Spectral-Domain Optical Coherence Tomography Device in patients with Optic Nerve Head Drusen

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Introduction:
Purpose: To evaluate prospectively the retinal nerve fiber layer (RNFL) and macular ganglion cell-inner plexiform layer (GCIPL) in eyes with optic nerve head drusen (ONHD) using Cirrus OCT.

Methods:
Fifty-seven eyes of thirty patients with ONHD and thirty-eight eyes of twenty control subjects underwent circumpapillary and macular scanning using Cirrus OCT. Differences in means between subgroups were tested with Student's T or with Mann Whitney U test. Chi square was used for color-code comparison. Color code disagreement among average RNFL thickness and average and minimum GCIPL was measured using Cohen's kappa test. The relationship between these analyses was evaluated using intraclass correlation coefficient (ICC) and Band-Altman plots.

Results:
Abnormal color-code results in both average and minimum GCIPL and in RNFL thickness (defined as borderline / yellow or severe / red thinning) were associated with the severity of ONHD. GCIPL thickness yielded abnormal results in 35% and 45% of cases (average and minimum GCIPL respectively ) vs 2% of control eyes ($P = 0.000$). Average RNFL thickness revealed abnormal thinning in 33% of eyes with ONHD vs 0% control eyes ($P = 0.002$). Eyes with buried ONHD (0 grade) had an abnormal thinning rate significantly higher for both minimum and average GCIPL (30.4% and 8.7% respectively) than for average RNFL analysis (4.3%; $P = 0.002$). 26% of these eyes had abnormal GCIPL exams but normal RNFL thicknesses. Eyes with ONHD III grade had an abnormality rate similar for RNFL and GCIPL analysis (80%). In eyes with ONHD the highest abnormality rate was found in the superior sector for both GCIPL and RNFL analysis ($P = 0.017$ and $P = 0.001$ respectively).

Conclusions:
Both RNFL and GCIPL analysis reveal significant thinning in eyes with ONHD, directly correlated with drusen severity, however in eyes with buried ONHD the abnormality rate was significantly higher with GCIPL compared to RNFL evaluation suggesting that GCIPL analysis could define damage earlier.

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DIAGNOSTIC ACCURACY OF GANGLION CELL-INNER PLEXIFORM AND RETINAL NERVE FIBER LAYER MEASURES FROM TWO SPECTRAL DOMAIN OCTs IN MULTIPLE SCLEROSIS

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Introduction:
PURPOSE: To determine the diagnostic ability of ganglion cell-inner plexiform layers (GCIPL) thickness analysis by Cirrus (Carl Zeiss Meditec AG, Jena, Germany) optical coherence tomography (OCT) system compared to peripapillary retinal nerve fiber layer (pRNFL) thickness analysis using Cirrus and Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany) OCTs in eyes of patients with relapsing-remitting multiple sclerosis (RRMS).

Methods:
A prospective cross-sectional study was performed. Seventy patients with RRMS and seventy age and gender-matched healthy subjects underwent pRNFL and GCIPL thickness analysis using Cirrus OCT, and pRNFL using the Spectralis OCT system at the Ramon y Cajal University Hospital in Madrid. Patients with RRMS underwent a complete neuro-ophthalmological examination including best corrected visual acuity, Humphrey 24-2 visual field and Expanded Disability Status Scale scoring. Receiver operating characteristic (ROC) curves were obtained for average and minimum GCIPL thickness (Cirrus) and average and temporal pRNFL thickness (Cirrus and Spectralis). Areas under the ROC curve (AUC) were the main outcomes. Factors related to GCIPL thickness were analyzed using generalised estimating equations.

Results:
Minimum GCIPL thickness had the maximum AUC among all analyzed measurements (AUC=0.862; p<0.001). Sensitivities were higher for GCIPL measures than for RNFL measures globally and in subgroup analysis according to the optic neuritis antecedent. Generalised estimating equation analysis accounting for intereye correlation revealed that age (p=0.030), optic neuritis antecedent (p=0.001) and disease duration (p=0.002), were associated with abnormal results in average GCIPL thickness in patients with RRMS.

Conclusions:
GCIPL thickness has a better diagnostic ability than pRNFL thickness in patients with RRMS.

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Comparing the Classic 2 Repetitions Per Second (2RPS) Visually Evoked Potential (VEP) with a New Metric using the Standard 60-Second Arc Check Size Driven by a Binary M-Sequence in a Group of Multiple Sclerosis Patients and Controls

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Introduction:
Newer display technologies like liquid-crystal-on-silicon (LCOS) are rapidly supplanting the antiquated CRT methods, mandating a critical analysis of the altered VEP responses. Newer stimulators optimized for multi-focal stimulation currently only generate qualitative results. Additionally these newer stimulators can be tightly calibrated allowing for multi-center studies. Utilizing the binary m-sequence which when applied to a conventional standard checkerboard VEP allows for a new test with shorter testing times, higher signal-to-noise ratios and a single quantitative result. We aim to compare the classic 2 repetitions-per-second (2RPS) visually evoked potential (VEP) with a newer conventional VEP test using the standard 60-second arc check-size generated by a binary m-sequence to test its viability and specificity in a group of multiple sclerosis (MS) patients and controls.

Methods:
Patients with a history of MS and retinal nerve fiber damage, as measured by ocular coherence tomography (OCT), and a control group were tested using two separate methods. All tests were performed using a VERIS system with a FMS3 LCOS stimulator and analyzed using VERIS Science 6.4 software. A standard 10-20-electrode pattern was used. Each subject was tested using a VEP and then m-sequence VEP (m-seqVEP) protocols.

Results:
Ten MS patients with prior optic neuritis were compared with a ten healthy control subjects. The classic VEP results in both groups were comparable with previously published studies. The m-seqVEP test, however, had a quantifiable result on more subjects and ROC analysis showed a higher degree of specificity.

Conclusions:
Using the m-sequence paradigm, in conjunction with a standard checkerboard framework, may represent a more pragmatic and innovative solution, capable of achieving the necessary utility for reorganizing VEP testing. For clinical and research purposes, the combination of the standard checkerboard with m-sequence stimulator may provide greater sensitivity and specificity in more patients and with greater specificity.

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Correlation of Thickness in Optic Disc Optical Coherence Tomography and Clinical Grading System of Papilledema

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Introduction:
To demonstrate the correlation between the nerve fiber layer thickness in optic disc optical coherence tomography (OCT) and clinical grading system of papilledema (modified Frisén scale, MFS)

Methods:
Optic disc OCT for retinal nerve fiber layer (RNFL) thickness and optic disc photographs were obtained in pseudotumor cerebri (PTC) cases with papilledema documented as clinical grading system. We analyzed the average thickness in each quadrant and in total and demonstrated them with MFS and also calculated Spearman rank correlation of RNFL and MFS.

Results:
The data were obtained from 53 cases of PTC. In grade 0, the average thickness is 85.3 (61-114) μm (temporal/superior/nasal/inferior = 59.7/100.45/63.95/116.05 μm). In grade I, the average thickness is 97.31 (79-127) μm (temporal/superior/nasal/inferior = 68.88/98.38/70.06/148.94 μm). In grade II, the average thickness is 185.25 (136-264) μm (temporal/superior/nasal/inferior = 125.75/195.75/134.75/269 μm). In grade III, the average thickness is 287.33 (259-390) μm (temporal/superior/nasal/inferior = 234.22/304.89/236.67/374.33 μm). In grade IV, the average thickness is greater than 500 μm and in grade V, the average thickness is greater than 600 μm. RNFL thickness and MFS correlates well (R=0.95 in overall, 0.8 between grade 0 and I, 0.67 between grade I and II, 0.99 between grade II and III, 0.97 between grade III and IV, 1 between grade IV and V). Among the four quadrants, RNFL thickness in inferior quadrant correlates better (R=0.93) than other quadrants (R=0.78 in temporal, 0.73 in superior, 0.80 in nasal).

Conclusions:
For higher grades (III, IV, V) of papilledema, MFS itself may be sufficient to evaluate the disc swelling. For lower grades (0, I, II) optic disc OCT may be useful as an adjunct method to confirm and differentiate the severity of disc swelling. Especially the change or difference of RNFL thickness in inferior quadrant may imply progress of disc swelling better than other quadrants.

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Hiding In Plain Sight: Uncommon Presentations Of Digoxin Ocular Toxicity

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Introduction:
Visual symptoms of digoxin toxicity include photopsias, frosted vision, chromatopsias, and vision loss, which can occur even at therapeutic levels. Full field electroretinogram (ERG) easily supports the diagnosis and should be used even in atypical presentations.

Methods:
Case reports of two patients with digoxin-related visual loss, in which the diagnosis was not considered by their physicians because of variations in clinical presentation.

Results:
Case 1: An 81 YO male with macular degeneration OU, on digoxin for congestive heart failure, complained of difficulty reading for 2 months. His retinologist, noting no change in his exam, referred him for outside neuro-ophthalmology consultation that attributed the symptoms to ARMD. He was seen in second opinion and his vision was 20/100 OU with Humphrey visual fields 24-2 showing generalized depression OU. ERG showed profound delays in cone and rod implicit times and decreased amplitudes. Serum digoxin level was 2.2 (therapeutic range 0.5-2.0). 2 weeks after stopping digoxin, the patient reported he could read again. ERG showed improved responses. Case 2: A 74 YO female on digoxin for atrial fibrillation presented with recurrent periods of decreased vision for several months. After outside neuro-ophthalmologic consultation was inconclusive, she presented for second opinion, confused about her medications. Her vision was CF at 5 feet OD and 20/400 OS. Humphrey visual fields 24-2 showed generalized depression OU. ERG showed profound delays in both cone and rod implicit times and decreased amplitudes. Serum digoxin level was 2.3. 3 weeks after stopping digoxin the patient’s visual acuity improved to 20/30 OU. Repeat ERG showed improving rod and cone function.

Conclusions:
ERG can indicate a retinal origin of visual loss in digoxin toxicity even with prior macular problems, as the whole retina is affected and the majority of photoreceptors lie outside the macula. Spontaneous improvement is possible because of variations in compliance and metabolism.

References:

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Relationship between Pattern electroretinogram, Frequency Domain-OCT and Automated perimetry in Chronic papilledema from Pseudotumor Cerebri Syndrome

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Introduction:
Purpose: To evaluate the ability of transient pattern electroretinogram (PERG) parameters to differentiate between eyes of patients with resolved papilledema from pseudotumor cerebri syndrome (PTC) and controls, to compare PERG and OCT with regard to discrimination ability, and to assess the correlation between PERG, FD-OCT and visual field measurements (VFs).

Methods:
VFs and full-field stimulation PERGs based on both 48 and 14-min checks were obtained from 24 patients with PTC (40 eyes) and 22 controls (26 eyes). In addition, FD-OCT peripapillary retinal nerve fiber layer (RNFL) and segmented macular layer measurements were obtained and their correlation coefficients were determined.

Results:
Compared to controls, PERG N95 and the P50+N95 amplitude measurements with 48-min checks were significantly reduced in eyes with resolved chronic papilledema from PTC. Both PERG N95 amplitude and OCT parameters were able to discriminate papilledema eyes from controls although the macular thickness parameters were more efficient at detecting abnormalities. Significant correlations were found between PERG amplitude values and OCT-measured macular ganglion cell layer and RNFL thickness and with total retinal thickness. PERG amplitude was also significantly associated with VF sensitivity loss.

Conclusions:
PERG measurements were able to detect axonal loss in PTC eyes with a performance comparable to OCT. PERG amplitude measurements were reasonably well correlated with OCT-measured parameters.

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Macular microcysts in mitochondrial optic neuropathies: a non-specific feature due to vitreous traction

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Introduction:
To assess the prevalence of macular microcysts (MM) in patients with Leber’s hereditary optic neuropathy (LHON) and dominant optic atrophy (DOA) and investigate the thickness of the different retinal layers in patients with and without MM.

Methods:
We prospectively enrolled all patients with genetically confirmed LHON or DOA referred to the Neurologic Unit of the University of Bologna between 2010 and 2012. We evaluated the presence of MM by optical coherence tomography (OCT). The patients with MM were then compared to two control groups: 1) a sample of LHON and DOA patients without MM matched by age, age at onset, RNFL thickness, optic nerve head (ONH) area, visual acuity and type of LHON mutations (19 patients), and 2) 22 healthy individuals.

Results:
Macular microcysts were identified in 5 patients out of 90 with LHON (5.6%) and 3 patients out of 58 with DOA (5.2%). Total macular thickness, INL and ONL were thicker in patients with MM compared to patients without MM and healthy controls, whereas the average RNFL and GCL-IPL thickness failed to show significant differences. As regards LHON and DOA patients, total macular thickness, INL and ONL were significantly increased in patients with MM compared to patients without MM.

Conclusions:
The present study reveals that MM occurs in about 5% of patients with mitochondrial optic neuropathies, i.e.LHON and DOA. Detailed OCT analysis by retinal segmentation of LHON and DOA patients with MM compared with those without MM and healthy controls shows that the INL and ONL are significantly thicker in patients with MM. We postulate that in conjunction with a loss of RNFL and GCL-IPL thickness, MM formation is due to posterior vitreo-retinal traction in the macular region due to persistent vitreo-macular adhesion and vitreo-papillary adhesion. In this view MM are not a specific biomarker for inflammatory optic neuritis.

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Early macular retinal ganglion cell loss in dominant optic atrophy: genotype-phenotype correlation

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Introduction:
To assess the peripapillary retinal nerve fiber and macular retinal ganglion cells (RGCs) loss in patients with dominant optic atrophy (DOA) stratified by OPA1 mutation typeThirty-seven patients from 20 pedigrees with DOA harboring heterozygous mutations in the OPA1 gene and 45 healthy subjects were enrolled.

Methods:
The retinal nerve fiber layer (RNFL) and ganglion cell layer-inner plexiform layer (GC-IPL) of DOA patients were studied by optical coherence tomography (OCT) and compared to 45 age-matched healthy subjects. Patient’s eyes were divided in four groups based on increasing severity of visual loss (DOA1 to DOA4) and were further stratified by OPA1 mutation type.

Results:
RNFL analysis showed a significant reduction of the average, superior and inferior quadrants thickness in the DOA4 group compared to DOA1. GC-IPL analysis showed a significant thinning in the ST and S sectors in DOA2 compared to DOA1. Stratifying by mutation type, average, superior and nasal RNFL thinning was significantly more severe in missense compared to haploinsufficiency mutations. Among the latter there were further differences among individual mutation types.

Conclusions:
The present study demonstrates that in DOA loss of macular RGCs is the earliest pathological event, better reflected by GC-IPL measurements, whereas RNFL thickness is a measure of spared axons in late stages of the disease. A clear genotype/phenotype correlation emerged stratifying OCT measures by OPA1 mutation type, being missense mutations the most severe.

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Distinctive Patterns of Retinal Ganglion Cell Loss on OCT May Differentiate Various Optic Neuropathies

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Introduction:
Improvement in OCT technology and resolution allows for better retinal segmentation and measurement of the macular ganglion cell layer. The peripapillary retinal nerve fiber layer (RNFL) thickness, as measured by OCT is typically used as an indicator of optic nerve pathology. Some studies have demonstrated that ganglion cell layer (GCL) thickness in patients with MS correlates better than retinal nerve fiber layer measurements with regard to visual acuity and quality of life. We have found that GCL analysis shows distinctive patterns which correlate better with visual function than RNFL measurements do.

Methods:
We selected several patients seen in our neuro-ophthalmology clinic with different types of optic neuropathy and measured both peripapillary RNFL thickness and macular GCL thickness using Cirrus SD-OCT measurement protocols. These findings were correlated with visual fields.

Results:
Six patients with low tension glaucoma, demyelinating optic neuritis, chronic papilledema, non-arteritic anterior ischemic optic neuropathy, hereditary optic neuropathy, and chiasmal compression from pituitary adenoma had evidence of GCL thinning. Some of the cases had corresponding defects in retinal nerve fiber layer as measured by OCT while others did not. Ganglion cell layer changes corresponded well with visual field findings.

Conclusions:
Ganglion cell layer analysis shows distinctive patterns of loss in various optic neuropathies. There appears to be a dissociation in the thinning of GCL and RNFL in some cases. However, in others there may be a strong correlation. Ganglion cell loss can precede RNFL thinning especially where there is RNFL swelling. In some cases the patterns of GCL thinning may be pathognomonic.

References:

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Macular Microcystic Changes on OCT in Optic Neuropathy

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Introduction:
Spectral domain optical coherence tomography (SD-OCT) in patients with various forms of optic neuropathy has shown small hyporeflective spaces within the inner nuclear layer in the parafoveal region of the retina. Initially described in cases of demyelinating optic neuritis, these findings may also occur in compressive, nutritional/toxic, and hereditary optic neuropathies.

Methods:
We describe five patients with non-demyelinating optic neuropathies who had microcystic changes in the retina on SD-OCT.

Results:
Nine eyes in 5 patients with optic neuropathy demonstrated parafoveal areas of discrete hyporeflective spaces in the inner nuclear layer on SD-OCT. The patients ranged in age from 8 to 78 years old. The diagnoses were as follows: optic atrophy secondary to hydrocephalus, dominant optic atrophy, pseudotumor cerebri with optic atrophy, probable hereditary optic atrophy, and probable nutritional optic atrophy. In 9 of the 10 eyes these changes were located nasal to the fovea. In all cases the microcystic changes were associated with decreased retinal nerve fiber layer and ganglion cell layer thickness.

Conclusions:
Microcystic changes in the inner nuclear layer of the retina were initially identified by OCT in patients with demyelinating optic neuropathy on OCT. These changes were previously described histopathologically in animals with optic nerve trauma. Macular microcysts are seen on OCT in a variety of optic neuropathies and may be due to retrograde trans-synaptic degeneration.

References:

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Introduction:
A 25 year old man presents with painless central loss of vision in his right eye to 6/60 over a week. Left vision at 6/6. He was. Otherwise well though admits to stress. He smoked 7.5 gm of tobacco and four standard drinks a day. Clinical, slit lamp and fundus exam normal apart from noted to have slightly swollen hyperaemic discs with a possible Drance haemorrhage on the left. No afferent pupil defect. Frequency doubled perimetry showed central scotoma right eye and some scattered defects peripherally on the left. CT brain and venogram was normal as was subsequent ant MRI scan. Standard serology was ordered and was negative. A presumptive diagnosis of optic neuritis was made and he received a course of IV methylprednisolone over 3 days without improvement. A Goldman perimetry was ordered to exclude functional vision loss and found to be normal. Humphrey Perimetry showed bilateral central scotoma. OCT scan of discs and macula were within normal limits but ganglion cell layer was markedly pathological. Mitochondrial DNA (mDNA) screening indicated homoplasmic 1178 G>A defect indicating Leber’s Hereditary Optic Neuropathy.

Methods:
Numerous Case reports of various pathologies including OCT ganglion cell layer maps are presented with clinical and perimetry correlates. Pathologies include glaucoma, occipital stroke, and optic neuropathies including Leber’s, Charcot Marie Tooth, chiasmal pathologies with bitemporal hemianopia

Results:
The Ganglion Cell layer investigation has a high correlation with perimetry, is predictive of future perimetry progression and is a highly sensitive, specific and discriminatory test of pathologies ranging from occiput to the optic nerve. Cases of false positive GCL test artefact are also described.

Conclusions:
The Ganglion Cell layer is the most useful element of the OCT exam from a neuro-ophthalmic perspective.

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Imaging and neuroophthalmology: some clues to avoid mistakes

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Introduction:
Imaging plays a mandatory part in multiple neuro ophthalmological pathologies. Both clinician and radiologists may be aware of errors leading to misdiagnosed or missed lesions and should figure out ways to avoid them.

Methods:
Selection of chosen cases among a four year study of neuro ophtalmological cases with a wrongly analyzed MRI, either because of poor clinical data or radiological mistakes. This presentation will propose several typical examples of both usual clinical and radiological mistakes leading to moderate or severe misdiagnosis.

Results:
Most common mistakes are due to both clinical and radiological sideClinician: lack of clinical information provided to the radiologist, miserable handwriting, use of complicated abbreviations often not or misunderstood by the radiologist.Radiologist: Poor knowledge of ophthalmological pathology and/or visual and oculomotor pathways, leading to inadequate imaging (wrong sequence or lack of useful sequence) or to poor reading of the images. Misreading of specific aspects of the pathology Wrong interpretation of nonspecific lesion Previous imaging not taken into account

Conclusions:
Clinician should always provide a detailed prescription and be critical when the patient comes back with his imaging (it fits the clinical data?? ).Radiologist should always consider clinical data while establishing the MRI protocol or reading the images. They should keep in mind that some lesions may be small, even if clinical examination shows major impairment. They should not hesitate to perform further examination or repeat the MRI in case of atypical or nonspecific images. They should remain critical, even if the diagnosis seems established. They should improve their knowledge of the pathology they have to study_Communication between clinician and radiologist before the MRI is the best weapon against misdiagnosis.

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Poster 152

Frontal Intracranial Intraparenchymal Schwannoma; A Rare Entity

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Introduction:
Intracranial intraparenchymal schwannomas are very rare. Twenty-nine cases of frontal intraparenchymal Schwannomas have been reported to date. We present such a case.

Methods:
Case report.

Results:
A 60-year-old woman noted headaches, transient visual obscurations and pulsatile tinnitus for 2 weeks. Past medical history included osteoporosis and hypothyroidism and medications included alendronate, calcium and levothyroxine. She did not smoke nor consume alcohol. Examination showed an alert and oriented woman with normal vital signs. Visual acuity correction was 20/25 in the right eye and 20/25 in the left eye, Color vision 8 of 8 Ishiara plates in each eye. Automated perimetry showed enlarged blind spot and nasal defects in each eye in keeping with papilledema. Pupils measured 5 mm in each eye with 2+ reactivity; there was no RAPD. Ocular motility was normal. Intraocular pressures and anterior segment was normal. There was florid papilledema in each eye with splinter heme off each nerve and peripheral dot-and-blot heme on the right and a partial star on the right.

An MRI scan of the brain and orbits with and without fat suppression and gadolinium showed a subfrontal cystic mass with ring enhancement. Frontal craniotomy showed characteristic mixture of cell types present within a neurofibroma; there was also a lack of axons scattered throughout the tumor, which is typically present in neurofibromas. The final diagnosis was schwannoma (WHO Grade I). There were Antoni A, Antoni B and Verocay bodies.

Conclusions:
Frontal intraparenchymal schwannoma may mimic meningioma, astrocytic neoplasm, metastatic carcinoma, metastatic melanoma, a primary meningeal sarcoma and neurofibroma. This case highlights the rarity of this tumor in this location.

References:


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Risk of Glioma Development in Subjects with Neurofibromatosis Type 1 without Glioma on Initial MRI

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Introduction:
Vision loss occurs in nearly one-half of neurofibromatosis type 1 (NF-1) children with an optic pathway glioma (OPG), and is the main indication for systemic chemotherapy in this population. The purpose of this study was to determine whether, in children with NF-1 without an OPG on initial magnetic resonance imaging (MRI), other potentially concerning radiographic features predict later OPG development and associated decreased vision.

Methods:
Children with NF-1 who underwent orbital MRI at a national referral center between 1992 and 2005, and had >1 year of subsequent visual acuity (VA) data, were identified retrospectively. Three pediatric neuroradiologists independently reviewed the earliest available MRI to provide a consensus assessment. Eyes with optic nerve tortuosity (ONT) were identified using validated operational criteria.¹ Subjects with OPG on initial MRI were excluded. In parallel, the presence of nerve tortuosity, enhancement, or thickening was established based on clinical MRI reports. The value of these radiographic characteristics in predicting long-term OPG development and associated diminished VA (defined as ≥0.2 logMAR below age-matched normative value at last testing) was evaluated per eye using uni- and multivariate analyses.

Results:
133 evaluable subjects (264 eyes) with adequate imaging and neuro-ophthalmic follow up were identified. Median age at earliest MRI was 3.5 years; vision was followed 7.1 (mean) ± 0.3 years after the original MRI. Consensus review established 11 eyes (8.3%) of seven subjects with ONT. Sixteen subjects (12%) later developed a definite OPG, only one of whom experienced related vision loss. Eyes with potentially concerning imaging findings did not develop OPG or associated vision loss more frequently than controls.

Conclusions:
In patients with NF-1 without an OPG on initial imaging, potentially concerning radiographic features do not appear to substantially elevate the risk of vision loss. The excellent prognosis in this population supports less aggressive surveillance in asymptomatic patients without an OPG.

References:

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Incidence of Ophthalmic Artery occlusion following Endovascular Flow Diversion.

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Introduction:
Flow diversion stents are a relatively new technique of treating broad necked complex parapontic aneurysms. This results in the deployment of the stent across the ostium of the Ophthalmic artery (Oph A). The long term patency of the ophthalmic artery has not been documented. We present our observation of long term follow up in a cohort of 29 patients.

Methods:
We retrospectively analysed all angiograms of flow diverter in our institution to identify patients with one or more flow diverters deployed across the Oph A ostium. Patients were followed up with digital subtraction angiogram (DSA) at 6-8 months and 24 months after flow diversion. Angiographic appearances of the Oph A was assessed on immediate post procedure and follow up DSAs to assess the long-term patency of the Oph A.

Results:
30 Oph A were identified with flow diverter deployed across the Oph A ostium in 29 patients (mean age 53 years, range 25-71 years, 23 females). 31 aneurysms were treated. 29 patients had a 6-8-month follow up DSA with the Oph A remaining patent in 96.5% (n=28) of the patients. 17 patients had a 24-month follow up DSA with the Oph A remaining patent in 82.3% (n=14) of the patients. All patients with Oph A occlusion remained asymptomatic. Aneurysmal occlusion rate on 24 month DSA was 93.7%.

Conclusions:
Flow diversion use across the Oph A ostium is associated with asymptomatic angiographic occlusion in less than a fifth of the patients on long term follow up and is asymptomatic.

References:


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Utility of brain MRI in the diagnosis of Vogt–Koyanagi–Harada syndrome

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Introduction:
Vogt Koyanagi Harada syndrome (VKH syndrome) is a rare disease predominantly affecting women with an incidence of 1 to 6 per million in the US. The diagnosis is made clinically, however fluorescein angiography (FA) and optical coherence tomography (OCT) are used to support the diagnosis. Brain MRI is not a common imaging modality, however in the absence of FA and OCT, it can be helpful in the diagnosis.

Methods:
This is a case report where extensive review of history, laboratory evaluation and imaging of VKH syndrome is performed.

Results:
A 32 year old Indian man with a long history vitiligo presents with headache and progressive right (OD) vision loss to counting finger (CF) only. Past medical history is unremarkable and he denies ocular trauma. Fluorescein angiography shows focal areas of leakage in the retinal pigment epithelium while the brain MRI shows fluid collection in the choroid of the right eye with some meningeal enhancement. Prednisone was initially started, however because of persistent hyperglycemia, azathioprine was initiated while prednisone was tapered. Vision improved from CF to 20/20 OD while the left eye remained unaffected.

Conclusions:
Since VKH syndrome presents diversely, ancillary procedures like FA, ultrasound and OCT are commonly employed to arrive at a diagnosis, however the unavailability of OCT and FA in the rural setting makes this difficult. Brain MRI is useful especially in the absence of FA and OCT. The most distinguishing MRI feature of VKH syndrome include choroidal and retrobulbar contrast enhancement in the orbits, white matter abnormalities on FLAIR and meningeal enhancement.

References:

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Poster 157

The predictive value of brain MRI in acute optic neuritis for developing multiple sclerosis.

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Introduction:
Optic neuritis (ON) is often the first manifestation of multiple sclerosis (MS), but not all ON patients develop MS. The aim of this study was to review the results of 19 in order to determine the prognostic-factor of initial MRI of ON patients. When taking early MRI in ON patients into consideration, it may be possible to define a more detailed risk assessment for the prognosis and future development as well as a possibly beneficial medical treatment.

Methods:
This complete literature review comprises 19 studies published between 1988-2010. These articles have been reviewed, analysed and concluded upon.

Results:
Fifty-eight percent (26-80%) of all ON patients have abnormal baseline MRI. 48% (23-86%) of the ON patients with abnormal baseline MRI developed MS within an average of two years. The more lesions on baseline MRI, the greater risk was observed. Only 9% (0-25%) with normal baseline MRI developed MS. ≥1 Tesla and ≤4 mm. slices seemed to indicate greater sensitivity to detect lesions.

Conclusions:
This review shows that MRI of the brain provides an important predictive role in determining whether or not an ON patient will develop MS, and whether an expensive treatment with side effects should be administered. However, conventional MRI is not the ideal test to offer an accurate prognosis, so it is recommended to strive to find a better test.

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CT Diagnosis of Terson syndrome

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Introduction:
Terson syndrome is a known complication of subarachnoid hemorrhage (SAH) that causes potentially reversible vision loss, due to vitreous and subhyaloid hemorrhage. In some cases, a blood-vitreous level can be identified on CT scans, but this finding is often overlooked.

Methods:
We describe two patients with Terson syndrome. CT scans at presentation demonstrated extensive subarachnoid and intraparenchymal blood with obstructive hydrocephalus. Although the scans also demonstrated an intra-ocular blood-vitreous level, this finding was not reported by neuroradiologists interpreting the studies.

Results:
The first patient carried a diagnosis of Ehlers-Danlos syndrome and was found unresponsive. She was found to have diffuse subarachnoid and left frontotemporal hemorrhage due to a large left MCA bifurcation aneurysm. After surgical clipping, she remained minimally responsive for several days before gradually becoming alert. Weeks into her recovery she demonstrated severe aphasia. It was observed that she was unable to see. A dilated fundus examination revealed extensive vitreal clot in both eyes with no view of the posterior pole. The second patient was also found unresponsive due to extensive subarachnoid hemorrhage from a right MCA bifurcation aneurysm. After clipping of the aneurysm, she recovered consciousness but described severe visual loss in both eyes. Examination revealed hand motions vision in both eyes. Dilated examination demonstrated no view to the retina in either eye. Following the diagnosis of Terson syndrome, both patients underwent successful vitrectomy with restoration of normal vision.

Conclusions:
Careful evaluation of the initial CT scans in these patients demonstrated that both had bilateral intra-ocular blood-vitreous levels.

References:

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Brainstem Progressive Multifocal Leukoencephalopathy (PML) presenting with skew deviation

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Introduction:
PML is a common central nervous system opportunistic infection in HIV/AIDS that mostly involves the cerebral hemispheres. Brainstem involvement by PML is rare but is being seen with increased frequency in the HIV/AIDS population. We describe a unique presentation of PML with skew deviation and hemiparesis as the first opportunistic infection in a patient with HIV/AIDS.

Methods:
Single case report and review of literature

Results:
A 34 year old homosexual white male with a 12 year history of AIDS and no prior opportunistic infection presented with a 2 week history of right face and arm paresthesia, numbness and weakness. One week prior, he had developed blurred vision and binocular vertical diplopia. He had discontinued highly active retroviral therapy (HAART) a year ago due to intolerance to medications. At presentation he had right hemiparesis, right central facial palsy and left hypertropia. He had normal visual acuity and fields, pupillary reflexes and retinal examination. MRI head showed a T2 hyperintense lesion in the left pons extending to the left cerebral peduncle and involvement of bilateral centrum semiovale. Lumbar puncture demonstrated 5 white blood cells, 1093 red blood cells (traumatic tap), protein of 86, glucose of 58 and 120 copies of JC virus DNA by PCR. He had 120,000 copies of HIV-1 RNA in the blood.

Conclusions:
This report highlights an unusual and rare presentation of PML as the first opportunistic infection in a patient with HIV/AIDS

References:

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Acute Ophthalmoplegia Due to Brain-Stem Stroke With False-Negative Diffusion-Weighted Imaging.

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Introduction:
Diffusion-weighted imaging (DWI) is highly sensitive for the detection of acute ischemic stroke. However false-negative studies may occur.

Methods:
We reviewed the examination results and magnetic resonance images of 2 patients who presented with ocular motor findings due to an ischemic stroke with initial negative DWI studies.

Results:
The first patient presented with an acute nuclear left third nerve palsy following catheter angiography. Initial DWI of the brain performed 2 hours following onset of symptoms showed a small acute left cerebellar infarct. The deficit persisted and a repeat DWI study performed 35 hours after symptom onset showed multifocal areas of infarction including the brainstem, consistent with an embolic etiology. The second patient developed an acute right internuclear ophthalmoplegia and initial DWI performed 12 hours after symptom onset showed a small left frontal lobe infarct. A repeat DWI obtained 40 hours after symptom onset revealed an acute infarct involving the posterior paramedian midbrain/pontine junction.

Conclusions:
Although sensitive for the detection of acute cerebral ischemia, DWI may appear normal early in the course of an event. Our findings are supported by reports in the literature documenting false-negative DWI studies in up to 30% of brainstem ischemic events. Clinicians should be aware that follow-up imaging is essential when neurologic deficits persist despite an initial negative DWI study.

References:


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Sixth Nerve Palsy and The Clival Marrow Sign

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Introduction:
Sixth nerve palsy is a common manifestation of neoplastic infiltration of the clivus (¹,²). Even if the lesion does not expand the clivus, sixth nerve palsy occurs because the nerve is trapped in Dorello’s canal lying on the clival edge. Clival marrow is adipose-rich in adults and therefore hyperintense on pre-contrast T1 MRI (³,⁴). Infiltrating neoplastic disease causes loss of this high signal (“clival marrow sign”). We believe that this telltale sign is often overlooked, not only by clinicians, but also by radiologists. We describe three examples in which the clival marrow sign occurred as an isolated imaging finding or in combination with loss of high T1 signal in calvarial or vertebral marrow.

Methods:
Case reports and review of literature

Results:
Case 1: 72-year-old woman (RS) with history of uterine cancer presented with right sixth nerve palsy and concern for multiple myeloma. Imaging revealed signal change in the clivus, calvaria, and cervical vertebrae. Case 2: 75-year-old woman (MT) with adenocarcinoma of the lung with metastases to the liver and spine presented with right sixth nerve palsy. Imaging revealed signal change in clivus and cervical vertebrae but not calvaria. Case 3: 55-year-old woman (CD) with multiple myeloma presented with left sixth nerve palsy. Imaging revealed signal change limited to the clivus.

Conclusions:
Hematopoietic (red) marrow undergoes conversion to fatty (yellow) marrow in the clivus and calvaria by around age 15 and later in vertebrae (³,⁴). In adulthood, the clivus should have high signal on pre-contrast T1, seen best on the sagittal plane. This “clival marrow sign,” which need not be accompanied by an expansile bone lesion, should be sought in patients with sixth nerve palsy.

References:

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Using Resting State Functional Magnetic Resonance Imaging to Track Recovery After Optic Neuritis

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Introduction:
Optic neuritis (ON) is a common cause of vision loss in MS. Resting-state functional magnetic resonance imaging (fMRI) functional connectivity detects temporal correlations in spontaneous blood oxygen level-dependent (BOLD) signal oscillations. This study investigates how ON affects the functional connectivity of brain regions with primary visual cortex (V1).

Methods:
20 patients (mean age = 34; 2 males) with ON as a clinically isolated syndrome (CIS) or associated with MS and 12 healthy controls underwent 3 imaging sessions at baseline, 6-months and 12-months. Image acquisition was conducted using a 3T MR scanner and consisted of anatomical images for co-registration of fMRI data; task-related fMRI scan to localize primary visual cortex (V1); and two resting-state fMRI scans.

Results:
At baseline, controls have stronger functional connections between V1 and areas involved in processing vision, touch (somatosensory association cortex), movement (premotor cortex), sound (primary auditory cortex) and awareness (dorsal posterior cingulate cortex) than ON patients. Patients show increased functional connectivity between V1 and frontal and anterior temporal cortices 12 months post-ON with eyes open. With eyes open and eyes closed, MS patients show a unique pattern of functional connectivity as compared with CIS patients. Both controls and MS patients show an increase in functional connectivity between premotor, dorsolateral prefrontal, posterior cingulate cortices and V1 compared to CIS patients. In contrast, controls and CIS patients show an increase in functional connectivity between anterior prefrontal, anterior cingulate, secondary visual areas and V1 as compared to MS patients.

Conclusions:
Functional connections between V1 and other brain areas are altered in the presence of ON, specifically in areas involved with complex visual processing. An increase in functional connectivity 12 months after ON suggests compensatory mechanisms or cortical plasticity may be involved. ON patients with MS can be distinguished from CIS patients by comparing the resting-state functional connectivity between V1 and secondary visual areas.

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Further Characterization of the Melanopsin-Mediated Pupillary Light Reflex in Multiple Sclerosis

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Introduction:
Optic neuritis, the hallmark of multiple sclerosis (MS), causes well-documented dysfunction of the retinogeniculocalcine, and retinomesencephalic pathways. Recent work in our laboratory indicates that there is dysfunction of the intrinsically photosensitive melanopsin containing retinal ganglion cells (ipRGCs), which are responsible for the vast majority of the input into the retinohypothalamic tract, and to a degree the retinomesencephalic tract. It has been postulated that this dysfunction could contribute to the symptomatology of multiple sclerosis, specifically affecting sleep-wake cycles, sexual drive, glucose homeostasis, and other neuroendocrine reflex arcs. Previous studies have shown dysfunction of this ipRGC-mediated retinomesencephalic tract in multiple sclerosis; however, exactly where along this tract the dysfunction lies is undefined.

Methods:
Normal controls, and patients with MS were recruited through our clinical center. Using a pupillometer with highly selective light frequencies and pupil tracking software, we preferentially stimulate the ipRGCs and measured the consensual light reflex. We also correlate selective pupillary light reflexes with spectral domain optical coherence tomography, looking specifically at both longitudinal and depth axes, duration of disease, subtype of disease, and other metrics.

Results:
Further localization of the drivers of the melanopsin-mediated pupillary light reflex yields results that are consistent with human histological studies. This defect correlates with metrics of disease activity using rigorous statistical analysis.

Conclusions:
Retinohypothalamic dysfunction is a potential contributor to fatigue, depression, and disease burden in multiple sclerosis. Our work indicates retinohypothalamic dysfunction is a potential contributor to MS symptoms that may be amenable to future therapeutic intervention.

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Amaurosis fugax induced by carotid body tumor

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Introduction:
A 60 year-old Romanian female with a one-year history of 10-20 minute episodes of painless visual loss OS, accompanied by a droopy eyelid OS. Review of systems revealed a five year history of hoarseness, intermittent face and neck tightness and dyspnea. PMH: HTN, CHF, hypothyroidism, emphysema, and adrenelectomy for pheochromocytoma. Family history of pheochromocytoma in four members. Visual acuity ( hyperopic correction) was 20/50 OD, 20/100 OS. She had bilateral neck masses, larger on the left, 2 mm ptosis OS, 2.5 mm nonreactive pupil OD, and 3 mm trace reactive pupil OS. She was on pilocarpine 2% and timolol/brimonidine OU. Anterior chambers were shallow with a patent iridotomy OS, and nuclear cataracts OU. Intraocular pressures were 15 OD, 16 OS. The cup/disc ratio was 0.4 OD, 0.8 OS. Threshold perimetry was constricted. Work up for transient visual loss was initiated.

Methods:
MRI of head nonspecific ischemic white matter lesions. CT/CTA/MRI Neck w&w/o contrast: hypervascular mass at carotid bifurcation: 4X6X6 cm on left, 3X3X3.5 on right, splaying the ICA and ECA. Embolization of tumor in the left side with percutaneous injection of Onyx, followed by resection of vascular mass was done.

Results:
PATHOLOGY: Well-circumscribed mass with nests of cells separated by fibrous bands and hyalinized stroma. Cells with abundant cytoplasm, salt and pepper chromatin, and slight pleomorphism. embolization material within vessels. Calcified, large vessel with plaque. Amaurosis Fugax improved after resection of the carotid body tumor.

Conclusions:
Amaurosis fugax and Horner syndrome due to carotid body tumor. The etiology of vision loss in this case reflects multiple potential mechanisms: The arterial supply to the ophthalmic artery was compromised by the tumor compression, while the elevated intraocular pressure may decrease perfusion pressure. dx of Horner’s syndrome obscured by miotic Pilocarpine use. Hereditary Paraganglioma/Pheochromocytoma (PGL/PCC) syndrome: Mutations in mitochondrial enzyme succinate dehydrogenase (SDH) complex, inherited in an autosomal dominant manner.

References:

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Clinical Features, Diagnostic Findings and Treatment of Susac Syndrome: A Case Series

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Introduction:
Susac syndrome (retinocochleocerebral microvasculopathy) is a rare, presumed autoimmune condition characterized by the clinical triad of branch retinal artery occlusions, sensorineural hearing loss, and encephalopathy. The aim of this presentation is to discuss clinical features, diagnostic findings, differential diagnoses, treatment, and outcomes of Susac syndrome (SS).

Methods:
Five patients with SS (age 21-52 years, 4 men) diagnosed and treated at two tertiary care centers since 2009 were compiled for analysis. The observation period was 7-57 months.

Results:
The clinical presentations included concomitant development of the complete clinical triad in 3 cases, and encephalopathy with delayed retinal and cochlear involvement in 2 cases. Brain MRI in all cases revealed areas of restricted diffusion during the active phase of the disease and white matter FLAIR hyperintensities with typical callosal involvement. CSF analysis showed elevated total protein and mild lymphocytic pleocytosis in all cases. Brain histopathology in the 2 biopsied cases demonstrated pauci-inflammatory microangiopathy. Histopathology of a transient skin rash in 2 patients revealed nonspecific inflammatory changes. The interval between symptom onset and final diagnosis was 3-7 months; ADEM, MS, vasculitis and intravascular lymphoma were initially considered. Pursued treatment strategies included pulse doses of methylprednisolone, intravenous immunoglobulins (IVIg), cyclophosphamide, methotrexate, mycophenolate mofetil, and/or rituximab. Immunosuppressive treatments were sustained for up to 4 years. Of the 4 patients treated with corticosteroids and IVIg alone, all experienced further clinical progression until additional immunosuppressive therapy was instituted. Residual cognitive impairment was noted in all cases; 3 patients developed permanent hearing loss.

Conclusions:
The rarity of the condition, its frequently incomplete presentation, and the nonspecific imaging findings invariably led to delayed diagnosis. Empiric management with corticosteroids and/or IVIg alone may be insufficient in cases presenting with encephalopathy. Further investigations into the etiology and potential therapeutics for SS are warranted.

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Introduction:
Nonorganic vision loss (NOVL) is characterized by the onset of a visual deficit or disturbance that cannot be explained by organic pathology. Typically, patients present with subjective visual complaints, but extensive diagnostic imaging, labs, and exams reveal no abnormalities. We present an unusual presentation of NOVL in which a child presents with an abrupt onset of a persistent monocular visual field deficit.

Methods:
A 12 year old girl was referred for evaluation of an abrupt onset of monocular visual field loss. Prior to presentation, multiple Humphrey Visual Field (HVF) tests confirmed the presence of a left monocular temporal hemianopsia. Three magnetic resonance imaging studies of the brain all yielded normal results. Upon clinical examination, visual acuity, pupils, Ishihara color plate testing and sensorimotor testing were unremarkable. Slit lamp and dilated fundus examinations revealed no pathology.

Results:
The patient underwent both automated HVF and manual perimetry. Automated HVF testing was consistent with her prior evaluations. Monocular and binocular manual perimetry were subsequently performed. The left temporal defect persisted with binocular testing, defying organic explanation and confirming the diagnosis of nonorganic vision loss. Further questioning revealed academic stressors that coincided with the onset of symptoms.

Conclusions:
NOVL is common, occurring in up to 5% of pediatric ophthalmology patients. Diagnosis of NOVL requires an absence of findings attributable to the vision loss, as well as positive test results that are physiologically inconsistent with the presenting complaints. Patients are frequently subjected to protracted workups that are expensive, frustrating, and time-consuming. It is valuable to include NOVL in the differential when evaluating patients with visual complaints that are inconsistent with normal exam findings. If there is reasonably high suspicion that a psychosocial stress or traumatic event is present, then referral for psychiatric evaluation may be helpful; however, reassurance and follow-up are likely sufficient.

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Incidence of Giant Cell Arteritis: Diabetes Mellitus is Not Protective

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Introduction:
Previous reports suggest a protective effect of diabetes mellitus (DM) against giant cell arteritis (GCA). One recent retrospective study found a lower prevalence of diabetes among patients with a positive temporal artery biopsy (TAB) than with a negative TAB. A meta-analysis of 8 studies found a low prevalence of biopsy positive GCA among diabetics. The authors suggested that DM may lower the risk of GCA. To our knowledge, the effect of DM on GCA has not been studied prospectively. Using the Medicare database, we followed historical patients prospectively through time to compare the incidence of GCA among patients with and without diabetes.

Methods:
A 5% sample of Medicare claims and enrollment data from 1994-2011 was analyzed. Patients with diabetes were defined as those with a diagnosis code of 250.xx. GCA was defined as 1) any subject who received a GCA diagnosis (ICD9 446.5) following a TAB (CPT 37609), or 2) any patient who received two GCA diagnoses (ICD9 446.5) within 180 days. A three-year look-back period during which a diagnosis of GCA was not observed was required for inclusion in the study. A combination of propensity score matching and competing-risk regression was used to assess the impact of DM on GCA. To optimize propensity score matching, patients under 68 years were excluded.

Results:
A total of 151,041 individuals with diabetes were matched to an equal number of controls. Mean study time was 67.39 months for diabetics and 68.11 months for controls. GCA was diagnosed among 1,116 patients with diabetes (0.73%) versus 465 (0.30%) controls. The risk of GCA diagnosis among patients with diabetes was increased by 100% (sub hazard ratio (SHR): 2.00; 95% confidence interval (CI): 1.78 2.25).

Conclusions:
Diabetes mellitus is not protective against GCA. The annual incidence of GCA diagnosis among individuals 68 and over was 9 in 10,000.

References:

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Practice Patterns Following Retinal Artery Occlusion

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Introduction:
Variability exists among physicians regarding the urgency of stroke workup following embolic retinal artery occlusion (RAO). Neither the American Academy of Ophthalmology (AAO) nor the American Academy of Neurology (AAN) has published recommendations regarding the initiation of emergent stroke evaluation for retinal artery occlusions. We surveyed both ophthalmologists and neurologists to compare their workups for embolic RAOs.

Methods:
Data were collected through a web-based, anonymous survey using Survey Monkey. Surveys were sent to all members of the North American Neuro-Ophthalmology Society, the AAN Stroke Section, the Minnesota Academy of Ophthalmology, and all medical and surgical vitreoretinal specialists registered on the AAO website. Data were analyzed using the Fisher exact test.

Results:
672 surveys were completed (466 ophthalmologists and 206 neurologists). Within 12 hours of RAO, most neurologists (71%) pursue hospital admission or prompt emergency room (ER) evaluation, while the majority of ophthalmologists (72%) pursue outpatient workup (p<0.0001). 24-48 hours following RAO, 44% of neurologists pursue inpatient or ER evaluation compared to 10% of ophthalmologists (p<0.0001). The vast majority (97%) of both neurologists and ophthalmologists pursue less urgent, outpatient stroke workup if RAO symptoms have been present for more than 7 days (p=0.61). Only 7% of respondents refer for intra-arterial tPA within 12 hours of RAO.

Conclusions:
There is a significant difference between neurologists and ophthalmologists regarding the urgency of stroke workup following embolic RAO. Neurologists promptly pursue higher acuity care, while most ophthalmologists order outpatient evaluations. Further research is needed to determine if there is a difference in clinical outcomes.

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Cataract Morphology Detected by Schiempflug Anterior Segment Analysis in Subjects with Pre-Clinical Alzheimer Dementia

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Introduction:
Conflicting reports exist describing the presence of β-amyloid and distribution of lens opacification in post-mortem cataracts in patients with Alzheimer disease [1, 2]. The purpose of this study was to quantitatively examine the morphology of cataracts in individuals with and without positive molecular biomarkers for Alzheimer disease (AD).

Methods:
Patients enrolled into the study were either AD biomarker positive or negative, with the former group at high risk for progression to cognitive impairment [3]. Biomarker positive individuals demonstrated amyloid-β (Aβ) in the cerebrospinal fluid (CSF Aβ42 > 440 pg/ml) and/or elevated Pittsburgh compound B (Pib) on positron emission tomography (PET) Aβ fibrillar imaging. Patients received an extended clinical and neuropsychological assessment to determine the presence of cognitive impairment. All patients underwent Scheimpflug anterior segment slit lamp photography. Scheimpflug biometric analysis, performed by investigators masked to biomarker status, was used to objectively quantify the thickness and density of the cortical and nuclear portion of the lens. Statistical analysis was performed to determine whether any significant difference in lens morphology existed between the CSF Aβ and Pib imaging biomarker positive and negative groups.

Results:
33 patients were enrolled, of whom 12 demonstrated positive biomarkers for Aβ by PET imaging or CSF analysis. 10 Aβ biomarker positive individuals did not show any evidence of cognitive impairment at the time of exam. Scheimpflug lens analysis demonstrated that no significant difference existed between the Aβ biomarker positive and negative groups in mean anterior-posterior thickness of the nuclear or cortical lens portions (P = 0.600, P= 0.125 respectively). Similarly, no significant difference was found between the Aβ biomarker positive and negative groups in nuclear or cortical lens opacification (P = 0.974, P= 0.453 respectively).

Conclusions:
Our results suggest that lens morphology in Alzheimer’s patients is non-specific, and may not be a useful biomarker predicting development of cognitive impairment in Alzheimer disease.

References:


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Demographics of ocular myasthenia gravis

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Introduction:
Among patients with generalized myasthenia gravis (GMG), women are more likely than men to present during early adulthood, with men typically developing GMG after 50 years of age [1, 2]. We investigated the incidence of ocular myasthenia gravis (OMG) by age, race and gender.

Methods:
In this multicenter (5 sites) cross-sectional study, we collected patients’ race, gender, and age at the time of diagnosis. OMG was defined as an autoimmune disorder causing ptosis and/or diplopia associated with acetylcholine receptor antibodies, typical electromyographic abnormalities, or response to acetylcholinesterase inhibitors. No patients had signs or symptoms of GMG. An a priori sample size calculation determined that 140 patients were required to accept that there was a ≤10-year difference in mean age (equivalence testing: power 90%, alpha 0.05). Robust Bayesian analysis and linear regression were applied to evaluate whether age differed by gender or race [3].

Results:
433 patients were included, of which 258 (60%) were men. Mean age among men was 57 years (standard deviation [SD]: 19) and 52 years (SD: 21) among women. The 95% credible interval (CI) (Bayesian equivalent of confidence interval) was 0.8-8.7 years for mean age and there was a 99.6% probability that the mean difference in age between genders was <10 years. Race was documented in 376 (68 (18%) non-white). Whites were 17.3 years older than non-whites at diagnosis (95% CI: 12.2-22.3 years; p<0.001) controlling for gender. There was no additive interaction of gender and race (p=0.74). Density plots showed a bimodal distribution for women peaking around 30 and 60 years. Men had a left skewed, unimodal age distribution peaking at age 70.

Conclusions:
The distribution of age at presentation in OMG is different between men and women, similar to GMG. Non-white patients tend to develop OMG at a younger age.

References:

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Unusual presentation of an isolated III Cranial Nerve palsy from brain metastasis

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Introduction:
Isolated 3rd cranial nerve (CN) palsy is a rare presentation of brain metastasis. It is more commonly associated with other neurologic conditions such as myasthenia (MG), diabetic neuropathy, multiple sclerosis (MS), posterior communicating artery aneurysm (PCOM) and trauma. Asymptomatic character or unspecific symptoms related to an occult malignancy often times make the diagnosis and work-up for a third nerve palsy challenging. Our case illustrates an isolated 3rd CN palsy from brain metastasis secondary to a poorly differentiated sarcomatoid lung carcinoma detected in a diagnostic process initiated by a neuro-ophthalmologic examination.

Methods:
This is a case report where extensive review of history, imaging and laboratory evaluation was performed.

Results:
A 63 year old right-handed Caucasian Female was admitted by neurology on 5/17/13 because of an acute onset of painless right (OD) ptosis. Her past medical history is significant for type 2 diabetes and hypertension. She denies recent head or neck trauma. Neurologic exam showed ptosis OD, dilated pupil (OD) unreactive to light with preserved consensual reflex. Intraocular pressure, funduscopy and the rest of neurologic exam were unremarkable. Initial work-up including MG panel, MS profile, central nervous system (CNS) infection and sarcoidosis were all unremarkable. MRI of the brain showed a homogenously enhancing mass in the right ventral midbrain. A CT scan of the chest and abdomen later showed metastatic disease involving the lungs, liver, bones and left adrenal gland. A core needle biopsy of the liver mass showed poorly differentiated sarcomatoid carcinoma.

Conclusions:
This case shows the possibility of an isolated 3rd cranial nerve palsy as a unique and exclusive manifestation of a brain metastasis. A thorough neuro-ophtalmologic examination is crucial in early detection of this life-threatening condition.

References:

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Occult Giant Cell Arteritis Manifesting with a Scalp Ulcer

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Introduction:
Giant cell arteritis (GCA) is a systemic inflammatory disorder of unknown etiology that affects medium and large sized arteries. It often presents with decreased vision or transient visual loss. Other typical manifestations include headache, jaw claudication, weight loss and scalp tenderness. Scalp ulceration in GCA is rare but may be a presenting sign and symptom. Elderly patients with new scalp ulcerations of no known etiology, even in the absence of other classic findings, should be evaluated for GCA.

Methods:
A case report.

Results:
An 83 year-old woman presented with a 3-week history of scalp tenderness that developed into an ulceration. She noted transient visual loss with occasional diplopia that had resolved. Recent echocardiogram and carotid ultrasound were normal. Erythrocyte sedimentation rate was normal at 16 mm/hr (0 - 40) as were platelets; C-reactive protein was elevated at 27.6 mg/L (0.0 to 4.9). She was referred for a temporal artery biopsy which was floridly positive for GCA including inflammatory cells and giant cells.

Conclusions:
Giant cell arteritis is a neuro-ophthalmologic emergency that may present to primary care, ophthalmology or dermatology offices. Although rare, scalp ulcerations in GCA are associated with greater visual loss and increased mortality than those patients without scalp ulcerations. Education and collaboration among physicians is important in order to prevent delay of diagnosis and permanent visual loss.

References:


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Fundus autofluorescence as a marker for retinal ischemia in a patient with giant cell arteritis.

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Introduction:
The ocular manifestations of giant cell arteritis are protean. Retinal venous ischemia is unusual though has been previously described. This is characterized by a unique pattern on fundus autofluorescence.

Methods:
We report on a case of a 67 year old male with biopsy proven Giant Cell Arteritis (GCA) who presented with classic symptoms including acute monocular vision loss proceeded by headaches, scalp tenderness and jaw claudication. Clinical signs included corrected vision loss to 6/18 with a dense afferent pupil defect. Retinal findings included numerous white lesions scattered through the left retina. Erythrocyte sedimentation rate was 95 (normal <35 [age-adjusted]) and C-reactive protein was 127 (normal <2).

Results:
Fundus autofluorescence revealed an unusual fern-like pattern in the posterior pole of the affected eye similar to that previously described in non–GCA related central retinal vein occlusion. This autofluorescence pattern resolved in parallel with his clinical symptoms and signs after treatment with high dose IV methylprednisolone that restored vision to 6/6 leaving only mild patchy peripheral field loss.

Conclusions:

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Applying laboratory data in temporal artery biopsy decisions

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Introduction:
Studies have described the sensitivity and specificity of acute phase reactants for predicting biopsy-proven giant cell arteritis (GCA).¹² The purpose of this study was to assess how well clinicians apply laboratory data to temporal artery biopsy (TAB) decisions.

Methods:
We retrospectively reviewed patient charts of all TABs performed at 9 institutions between January 1, 2007 and April 30, 2012. Data abstracted included: age at time of biopsy, sex, preoperative acute phase reactants including platelets, corticosteroid use, and tabulation of whether the biopsy was positive or negative. ESR was adjusted for patient age and sex. Patients were excluded if they were using steroids for more than 14 days in the 30 day period prior to the TAB. Multiple logistic regression was used to measure the association between all measured clinical variables and biopsy results. Because all patients in the study had a post-test probability high enough to warrant TAB, variables in the model that continue to predict a positive biopsy are being underutilized by clinicians in selecting patients for TAB. For example, if clinicians perfectly incorporated ESR information into biopsy decisions, ESR should not predict which biopsied patients would have a positive biopsy.

Results:
We identified 546 cases; 156 were excluded based on exclusion criteria and missing data, for a total of 390 cases (67.7% female) with a median age of 74.5 years (IQR: 67,81). 89 (23.%) were positive for GCA. After controlling for age, sex, and clustering within institutions, age (OR 1.05, p<0.0001), CRP (OR 1.89, p<0.038) and platelets (OR 1.01, p<0.0001) continue to predict a positive biopsy. ESR and sex did not.

Conclusions:
Clinicians are effectively utilizing the diagnostic information in ESR and sex and underutilizing CRP, platelets, and age in selecting patients to undergo temporal artery biopsy. A robust clinical risk prediction tool may improve patient selection for TAB.

References:

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The molecular and neuro-ophthalmological features of autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)

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Introduction:
The inherited ataxias and spastic paraplegias are genetically highly heterogeneous and reaching a confirmed molecular diagnosis remains challenging. Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a relatively rare subtype that was first described among French Canadian patients from Quebec presenting with a stereotypical triad of early-onset cerebellar ataxia, spastic paraplegia and peripheral neuropathy. Pathogenic mutations in the SACS gene were subsequently identified in these families. Although retinal hypermyelination was originally reported as a characteristic disease manifestation, the actual nature and frequency of these abnormal retinal findings in ARSACS has recently been disputed.

Methods:
Next-generation exome sequencing was used to investigate a cohort of 50 probands with suspected inherited ataxia and spastic paraplegia syndromes. A comprehensive neuro-ophthalmological examination, including high-resolution optic coherence tomography (OCT) imaging, was carried out on patients with confirmed pathogenic SACS mutations.

Results:
Pathogenic SACS mutations were identified in three probands and two additional affected family members were examined. Compared with patients from Quebec, our ARSACS cohort (n = 5) showed strikingly variable features with a delayed age of onset and a milder neurological phenotype. Eye movement abnormalities were common with ocular dysmetria and gaze-evoked nystagmus. None of our patients had evidence of retinal hypermyelination. However, retinal striations were observed around the optic discs in four patients with significant thickening of the peripapillary retinal nerve fiber layer (RNFL).

Conclusions:
Next-generation exome sequencing is a powerful diagnostic tool that is broadening the disease phenotype associated with specific mutations. Abnormal retinal thickening seems to be a common pathological feature among affected SACS mutation carriers. A dilated fundus examination and OCT imaging should therefore be considered in patients with unexplained multisystem neurological disease. When present, retinal striations and RNFL thickening raises the distinct possibility of ARSACS and SACS genetic screening should be considered.

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Pelizaeus-Merzbacher Disease Associated with Retinopathy. One Case Report.

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Introduction:
Pelizaeus-Merzbacher disease is an X-linked recessive neurological disorder with nystagmus, ataxia, spasticity and developmental delay. It is linked to a diffuse hypomyelination of the central nervous system due to mutations in the PLP1 gene with abnormal expression of the proteolipid membrane protein PLP in the central nervous system. Progression of clinical signs is related to age of onset of the disease. Initially, an irregular pendular nystagmus is always present without affecting visual function. Fundus appearance remains normal. Cortical flash visual evoked potentials (flash-VEPs) are typical for hypomyelination. Nystagmus may disappear between the age of 2 to 5 years while optic atrophy later develops.

Methods:
A 14-year-old boy presented with Pelizaeus-Merzbacher disease. He had been suffering from that condition for several years. At the time of examination, he was in a wheel chair but could stand up with difficulty and demonstrated an obvious psychomotor delay. He was subsequently shown to carry a mutation in the PLP1 gene on exon-5. There was no evidence of nystagmus or strabismus. His best corrected visual acuity was 2/10 OU. His fundi were normal but for a discreet optic disc pallor temporally. Flash- and pattern-ERGs, flash- and pattern-VEPs were recorded in order to better evaluate his visual function.

Results:
Surprisingly, rod and cone ERG responses were impaired while pattern-ERG, flash- and pattern-VEPs were non-detectable.

Conclusions:
These results suggest that both the photopic and scotopic retinal systems were deficient and that macular function was also altered (no pattern-ERG). These findings point to generalized retinopathy. To our knowledge, retinopathy had not been previously described in Pelizaeus-Merzbacher patients. In fact, it is our experience that the flash-ERG in Pelizaeus-Merzbacher patients is customarily reported as normal. As retinal fibers are not myelinated, the cause for this retinopathy remains to be clarified.

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Familial Neuromyelitis Optica in a Mother and Daughter: Case and Literature Review

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Introduction:
We describe cases of anti-aquaporin (AQP)-4 antibody-positive neuromyelitis optica in a mother and daughter, which is the second instance to our knowledge of a child manifesting the disease prior to the parent.

Methods:
Retrospective chart review and literature review.

Results:
A woman with onset of transverse myelitis at age 38 was eventually found to have a positive anti-AQP-4 antibody during work-up of recurrent symptoms. Subsequently she developed intermittent episodes of monocular vision loss with optic nerve involvement that were treated with IV solumedrol and Rituxan. Eighteen years after initial presentation, her 78-year-old mother with a history of recurrent urinary tract infections also developed monocular vision loss and the anti-AQP-4 antibody was positive. Although disease onset took place at different ages in the mother and daughter, the shared genetic lineage suggests a familial contribution to NMO and highlights the importance of family history during clinical evaluation.

Conclusions:
Genetic influence in the development of NMO is suggested by this family and several prior reports of familial NMO.

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A Round-About Diagnosis: How a Metastasis could do anything.

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Introduction:
A patient presented to the acute care clinic for second opinion regarding vision loss in the right eye to no light perception.

Methods:
Case presentation of a 64 year old Russian female who presented with acute vision loss followed by sequential ipsilateral CNIII palsy associated with galactorrhea and diabetes insipidus which led to a diagnosis of a metastatic breast cancer to the sellar region.

Results:
Age appropriate workup in a patient with acute vision loss with a lack of a positive review of systems but elevated serum markers for giant cell arteritis led to a delayed diagnosis of a metastasis to the pituitary region which was found only once the tumor extended along the optic nerve to cause CNIII dysfunction. After undergoing endonasal debulking and gamma knife surgery, she is doing well and maintaining vision in the left eye.

Conclusions:
When unable to elicit a review of systems, always look at other factors in patient's presentation: such as polydipsia/polyuria during clinic visits, biopsy of a "benign" breast lesion at outside facility, all may have clues for a systemic diagnosis to explain the unclear ocular findings.

References:


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Vision Loss and Ocular Movement Disorders in two young women after bariatric surgery.

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Introduction:
We present two cases of combined optic neuropathy and ocular movement disorders secondary to a dietary deficiency. A thorough medical history and neuro-ophthalmologic exam have enabled to list the most proper differential diagnoses and have an efficient work-up

Methods:
2 Case Reports.

Results:
Case 1: A 25 years old woman who had undergone sleeve gastrectomy had intractable vomiting and diarrhea diagnosed as pancreatitis. She then complained of a compressing headache, bilateral vision disturbances, hearing loss and tinnitus. Ocular examination revealed upbeat nystagmus, bilateral intermittent horizontal ophthalmoplegia, bilaterally decreased visual acuity with bilateral central scotomas. She had no pupillary dysfunction. Fundoscopic examination revealed bilateral swollen discs. Work-up revealed thiamine deficiency, supporting the diagnosis of Wernicke’s Encephalopathy (WE). She was treated with thiamine IV and subsequently improved vision. The nystagmus and bilateral disc edema were the last to improve.

Case 2: A 36 years old woman who had undergone several bariatric procedures with a prolonged, complicated recovery and had been previously treated with B-complex vitamins, complained of bilateral blurry vision. On exam she was found to have rotatory nystagmus and pale optic nerves. History suggested that she was not compliant with her oral vitamin regimen and vitamin B1 levels were found to be very low. IV treatment with thiamine and B12 IM had improved the nystagmus and the visual fields.

Conclusions:
Although in the past WE was associated mainly with heavy alcohol ingestion, in the last years, as bariatric surgery has become a common treatment procedure for morbid obesity, health practitioners involved in the management of these patients must consider WE in hyper-emetic patients, who show neurological deterioration. Early treatment can dramatically improve the patient's condition and prevent long term neurological sequel.

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Ophthalmic Presentation Of Giant Cell Arteritis In African Americans

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Introduction:
Giant cell arteritis (GCA) is considered to be rare in African Americans, although the true incidence of the disease in this population is unknown (1,2,3,4). Published data consists of case series that have primarily compared systemic features of GCA in African American patients to Caucasians (5). Details of ophtalmic involvement in African American patients have only been reported in the form of case reports and small case series (1,3). Our objective was to assess the ophtalmic and systemic presentations of GCA in African Americans and compare it to the published data from a larger series in Caucasians (6).

Methods:
Our retrospective study enrolled African American patients with ophtalmic involvement from GCA from seven centers seen from 1994 to 2013. Data on demographics, systemic and ophtalmic symptoms and signs, and laboratory values at presentation were entered into a database and compared to a published cohort of 85 Caucasian patients.

Results:
Our cohort of 23 African American patients did not differ significantly compared to the 85 Caucasian patients with regards to sex, age, ESR or CRP level. Headache (76% in African Americans vs. 45% in Caucasians, p-value 0.01), neck pain (53% vs. 13%, p-value <0.01), and anemia (41% vs. 14%, p-value 0.01) were more common in African Americans. Ocular symptoms and ocular ischemic lesions were largely similar between the two groups. Some notable differences included the prevalence of vision loss (78% of African Americans vs. 98% of Caucasians, p-value <0.01), eye pain (30% vs. 8%, p-value 0.01), and acute ischemic optic neuropathy (43% vs. 69%, p value 0.03).

Conclusions:
Aside from a few differences in systemic and ophtalmic presentation, giant cell arteritis in African Americans presents similarly to Caucasians and should be pursued as a diagnosis in the context of appropriate signs and symptoms to prevent permanent vision loss.

References:

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Neuroborreliosis And The Optic Nerve

Introduction:
Lyme disease is a spirochetal disease known to cause a variety of clinical manifestations including involvement of the optic nerves. Distinguishing optic nerve swelling from elevated intracranial pressure and optic neuritis can present a challenge to clinicians. We present a case illustrating each manifestation and review the literature to further explore the subtleties between optic nerve swelling from elevated intracranial pressure and optic neuritis in Lyme Disease. The main objective is to identify patterns, similarities, and differences in the presentation, treatment, and prognosis of these two entities.

Methods:
Two cases of Lyme disease are discussed, one presenting with intracranial hypertension and another with optic neuritis. After identifying search criteria, we performed a literature review of case reports in PubMed, Cochrane, and Medline databases to assess the similarities and differences among cases of Lyme disease affecting the optic nerve.

Results:
We describe two patients with different ocular presentations who were both found to have positive Lyme titers. We also review 24 cases reported in the English literature of optic neuritis and 19 cases of elevated intracranial pressure caused by Lyme disease. We determine that there is a large spectrum of neuro-ophthalmologic involvement. We tabulate the trends in ocular and systemic presentation, radiologic modalities, CSF findings, optic nerve assessment, treatment regimen, and visual outcomes. We encounter inconsistency in the use of terminology, particularly the use of “pseudotumor cerebri” as well as in criteria for diagnosing Lyme disease by serology.

Conclusions:
There is a broad spectrum in the presentation of optic nerve pathology in Lyme disease and no set of findings is solely associated with any single disease process. The trends we find have implications for more accurate diagnosis and future treatment of increased intracranial pressure and optic neuritis associated with Lyme disease.

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Teaching Ophthalmoscopy to Medical Students (TOTeMS) II: A one-year retention study

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Introduction:
Learning direct ophthalmoscopy is challenging, and medical students’ (MS) long-term retention of ophthalmoscopy skills is poor.¹ We previously demonstrated that MS performed more accurately and preferred using photographs than direct ophthalmoscopy to examine the ocular fundus.² We hypothesized that these differences would persist over time.

Methods:
One year after initial training, second-year MS were randomized and reevaluated on their ability to examine the ocular fundus using either fundus photographs or direct ophthalmoscopy on eye simulators.³ Positive and negative affect, preferences, and clinical experiences with ocular fundus examination were assessed.

Results:
107/119 students (90%) who participated in the original study completed this one-year retention study. Students answered 34/48 (71%) questions correctly using photographs and 31/48 (65%) correctly using ophthalmoscopy (p<.01). Both photograph and ophthalmoscopy groups answered five fewer questions correctly on average than one year prior (p<.001). Students rated photographs as “easier than ophthalmoscopy” (8/10 vs. 6/10, respectively; p<.001). Students’ positive affect scores were higher in the photograph group (26.5) than in the ophthalmoscopy group (23.2; p=.03). Students tested on simulators reported lower positive affect than one year ago (decrease of 6.4 points, p<0.001). Students’ self-reported median frequency of fundus examination over the preceding year was <10% (IQR 0-20%). Ocular fundus examination was not performed because of discomfort with the examination (38%), discouragement by their preceptor (20%), and insufficient time (15%). 79% of students felt uncomfortable with ophthalmoscopy, and 44% stated that they would not perform ophthalmoscopy during a general physical examination. 76% stated they would prefer using photographs instead of ophthalmoscope for fundus examination.

Conclusions:
Students preferred photographs for examining the ocular fundus and were more accurate using photographs vs. direct ophthalmoscopy one year after training. The increasing availability of non-mydriatic ocular fundus photography may allow more frequent and accurate examination of the ocular fundus by MS and non-ophthalmologists in many clinical settings.

References:

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Nonmydriatic ocular fundus photography among patients with focal neurologic deficits in an emergency department (ED).

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Introduction:
While several large cohort studies have associated ocular fundus abnormalities with the long-term risk of stroke, the value of ocular fundus examination in patients presenting with focal neurologic deficits, particularly suspected transient ischemic attack (TIA) and stroke, has not been evaluated. The ABCD2 score is widely used for the risk stratification of patients with suspected TIA, but does not include fundus findings. Our objective was to determine the frequency of and the predictive factors for abnormal ocular fundus findings among ED patients who presented with focal neurologic deficits.

Methods:
Cross-sectional study of prospectively enrolled adult patients presenting to our ED with a chief complaint of focal neurological deficits. Ocular fundus photographs were obtained using a non-mydriatic fundus camera. Demographic and neuro-imaging information were collected, including the ABCD2 score components. Two neuro-ophthalmologists independently reviewed photographs for acute retinopathic/vasculopathic findings (i.e., retinal hemorrhages, cotton wool spots, grade III/IV hypertensive retinopathy, and retinal vascular occlusions). The results were analyzed using univariate statistics and logistic regression modeling.

Results:
We included 257 patients (median age: 52 years, 63% women), among whom 81 (32%) had cerebrovascular disease (CVD; 22 strokes, 59 TIAs) and 17 (7%;95%CI:4-11%) had acute retinopathic/vasculopathic findings. Acute retinopathic/vasculopathic findings were associated with CVD among patients with focal neurologic deficits (odds ratio [OR]=3.4;95%CI:1.2-9.3;p=0.02), and a trend toward association remained after controlling for ABCD2 score and abnormal diffusion weighted imaging (DWI; OR=2.5;95%CI=0.8-7.2;p=0.10).

Conclusions:
Ocular fundus abnormalities were found in 7% of patients presenting with focal neurologic defects to our ED, and predicted CVD among these patients, probably even after accounting for ABCD2 score and DWI lesions. This suggests that inclusion of non-mydriatic ocular fundus photographs in the evaluation of patients with focal neurologic deficits could assist in the differentiation of high-risk CVD from other causes of focal neurologic deficits and warrants additional study.

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Ocular microvascular function in Cerebral Small Vessel Disease

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Introduction:
Cerebral small vessel disease (CSVD) is a common devastating neurological disorder that presents as progressive cognitive decline and gait difficulty. The cause and treatment of CSVD remain unclear largely due to the difficulty in studying the small cerebral vessels in vivo. Ocular microvasculature is similar as the vasculature in central nervous system anatomically and physiologically. The purpose of this project was to demonstrate the feasibility of imaging ocular microvascular function in patients with CSVD.

Methods:
A retinal function imager (RFI, Optical Imaging Ltd, Rehovot, Israel) was used to image the retina for measuring velocity of blood flow and to image the conjunctiva for creating noninvasive capillary-perfusion maps (nCPMs). Eight CSVD patients (average age 62.9 ±6.7, 6 females and 2 males) were imaged to measure retinal blood flow velocity. Seven of them were imaged to create conjunctival nCPMs. Custom software was used to segment the nCPMs and fractal analysis was used determine the microvascular density and complexity.

Results:
The average retinal venous velocity of CSVD patients was 2.4 ± 0.8 mm/s, which appeared lower than the published normality dataset with the same age range (~3.5 mm/s) (Burgansky-Eliash et al 2013). The nCPMs showed the conjunctival capillary network was loose and vessel tortuosity was obviously evident in 6 of 7 patients whose nCPMs were obtained. The fractal dimension of conjunctival nCPMs from 7 of these CSVD patients was 1.70 ± 0.05.

Conclusions:
This study demonstrated the feasibility of measuring retinal venous blood flow velocities and obtaining conjunctival nCPMs for fractal analysis in patients with CSVD. CSVD patients appeared to have decreased retinal venous velocity, which may indicate hypoperfusion. Possible conjunctival vasculopathies such as tortuosity and loose capillary network may warrant further studies.

References:

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Aetiology and Investigation of Adult Acquired Horner Syndrome

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Introduction:
In adult isolated Horner Syndrome (HS) there is a lack of evidence to help guide the physician as to what imaging study should be performed and in chronic cases, when we should scan. The aim of this study is to establish the current aetiology of adult HS and to analyse the utility of Radiology at a single neuroscience centre.

Methods:
A 5 year retrospective consecutive series identified HS cases from an electronic radiology card system and a case note review was then carried out. Isolated HS was defined as HS without additional neurological signs. Any cases of recurrent or bilateral HS were treated as one record for analysis purposes.

Results:
Seventy five HS cases (74 unilateral and 1 bilateral), with a mean age of 49.7 years (SD+/- 17yrs, range 18-87years), were identified. Forty-seven were clinically isolated, of these the commonest aetiology was undetermined cases (n=22) followed by Carotid dissection (n=11). Positive aetiology was found in 4 isolated HS cases that had no history of trauma or surgery, no reported headache, neck ache or pain: 2 carotid dissections, 1 pancoast tumour, and 1 C1 benign aneurysmal boney cyst. Positive aetiology was found in 3 isolated HS cases that presented with history of greater than 1 year: 2 had carotid dissection and 1 a cervical sympathetic paraganglioma.

Conclusions:
We present a contemporary aetiological spectrum for adult HS, with low incidence of undetermined cases. The study's findings suggest that an atraumatic non-painful isolated HS or a chronic history of isolated HS should not be treated as benign entities. Although no treatment would be warranted for carotid dissections at over 12 months; 2 recurrent cases of carotid dissection were found. This highlights the importance of investigating the patient to fully inform them and clinician in the event of recurrence. A prospective study is required to determine the "gold standard" imaging modality. We would currently recommend prompt imaging in all cases.

References:

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The Use of Low Vision Accessibility Features on the iPad/iPhone in Patients with Neuro-Ophthalmic Conditions

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Introduction:

iPads and iPhones have a number of low vision accessibility features including Siri Voice Assistant, Large Text, Zoom, Invert Colors, Voice Over, and Speech Selection. We studied the usage and preferences of low vision accessibility features on the iPhone and/or iPad in patients with neuro-ophthalmic conditions.

Methods:

Five low vision patients with neuro-ophthalmic conditions were selected and surveyed on their iPad/iPhone usage. Three subjects owned iPads, one owned an iPhone, and one owned both devices. Their mean age was 54.6 years, ranging from 38 to 72. The diagnoses represented were optic atrophy secondary to optic neuritis (2), non-arteritic anterior ischemic optic neuropathy (NAION)(2), and visual hemifield loss from surgical excision of a hemangiopericytoma (1).

Results:

Two of five (40%) patients ranked Siri Voice Assistant as the most beneficial feature. Both patients with NAION daily used the iPhone with Large Text. None of the five patients used Speak Selection on their device(s), but three of the five (60%) chose this function as the one they would use if they knew more about it. The patient with the worst VA utilized only auditory features and no magnification or contrast functions. None reported using low vision apps on their device(s). None of the subjects were strictly self-taught, most utilizing some combination of consumer and clinical training.

Conclusions:

Patients with neuro-ophthalmic conditions are using low vision accessibility features on their iPhone and iPad the majority of the time when operating these devices. Those not using these features are interested in learning more about them, but we as practitioners must do a better job of recommending appropriate features based on our patients’ visual impairments and goals.

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A Multi-Site Assessment of Neuro-Ophthalmology Education and Resident Attitudes toward Methods of Content Delivery

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Introduction:
Recent graduates of US and Canadian ophthalmology residencies report feeling inadequately prepared to manage patients with neuro-ophthalmologic disease. Active learning educational techniques have been shown to improve learning outcomes in other educational domains and could address this problem by increasing both knowledge retention and confidence of residents. We sought to determine resident confidence regarding neuro-ophthalmic topics and their attitudes toward alternate methods of education in preparation for designing an educational intervention.

Methods:
Semi-structured interviews with ophthalmology residents at a single center informed development of a 16-item survey regarding confidence with neuro-ophthalmic knowledge and attitudes toward possible alternative learning strategies. The survey was implemented online using Qualtrics Research Suite (Qualtrics Labs, Inc.). All ophthalmology residents from two university-based programs were invited to anonymously participate in the survey.

Results:
The overall response rate was 72.4% (21/29). Response rates varied by year of training (80% PGY-2, 100% PGY-3, 40% PGY-4). 47.6% and 57.1% were dissatisfied with their neuro-ophthalmic knowledge as it pertains to board examination and clinical practice, respectively. Ninety percent reported that they were interested in alternative uses of organized instructional time and were willing to spend a median of 1 hour (range 0-2) to prepare for each faculty-led active learning session. Over 50% of respondents expressed interest in case-based learning, faculty-led discussion, and open question sessions with faculty, with the last receiving the most interest.

Conclusions:
Surveyed residents reported dissatisfaction with their level of preparedness for board examinations and clinical practice in the field of neuro-ophthalmology, corroborating similar observations in recent residency graduates. Residents have overwhelmingly favorable attitudes toward active learning techniques and are willing to spend independent time preparing for them. The results of this survey will be used to design an educational intervention with the goal of improving resident confidence with and understanding of neuro-ophthalmic topics.

References:

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Posters

Anti-aquaporin-4 Antibodies without Optic Neuritis or Transverse Myelitis

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Introduction:
Neuromyelitis Optica is defined as a limited or atypical presentation of neurologic deficits associated with Anti-aquaporin-4(AQ4) antibodies. Classic syndromes relate to CNS locations that have a high density of AQ4 receptors. We report a case of biopsy-proven recurrent cerebral inflammation, absence of demyelination and positive AQ4 antibodies.

Methods:
Case Report

Results:
A 12-year-old girl presented in 2007 with headache and aphasia. MRI showed a left frontal mass. Brain biopsy showed inflammation. Her symptoms improved. Six months later, she developed CNIII palsy and cognitive decline. Brain MRI showed thalamic and midbrain lesions. CSF studies showed elevated IgG synthesis and no unique oligoclonal bands. Her symptoms resolved with intravenous steroids. In 2013, she presented with headache, ophthalmoplegia, and left facial droop. On examination, she had one-and-half syndrome, left facial droop, right hemiparesis. Her optic nerves were normal. MRI brain showed a space-occupying lesion in the entire pons and midbrain initially thought to reflect a CNS tumor. Her neurologic status quickly deteriorated to a locked-in state. She was treated with intravenous steroids, plasma exchange, and cyclophosphamide. Her laboratory results revealed positivity for NMO antibodies. CSF showed 28 WBCs, 100% lymphocytes, no oligoclonal bands, and elevated IgG synthase 9.8. She was discharged on azathioprine. While in a ventilator facility she was weaned from oxygen and regained the ability to walk.

Conclusions:
This is a case of a tumefactive recurrent inflammatory process of uncertain nature with biopsy proven cerebral inflammation but without demyelination. While this case demonstrated severe morbidity, the patient eventually improved with aggressive immunosuppression. The role of AQ4 antibodies in the pathogenesis of our patient’s recurrent CNS inflammation is unclear at this time. Aquaporin-4 antibody-positive cases that do not fit the strict criteria for NMO clinically have been reported. Our case is unique in that the locations do not have a high density of AQ4 receptors.

References:

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Poster 190

Visual fields with interpretation only – a preliminary evaluation

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Introduction:
Since 2009 the Ophthalmology Department at the Mayo Clinic has allowed outside departments, within Mayo, to order visual fields for interpretation without a complete eye examination. Departments approved to order this innovative form of visual field e-consult include Endocrinology, Neurology, Neurosurgery, the subdivision of brain rehabilitation unit in Physical Medicine and Rehabilitation, Radiation Oncology and surgeons performing blepharoplasties (Plastic Surgery and ENT). Each referring physician determines the appropriate patients for the field with an interpretation only. A standard 24-2 Visual Field is performed. The interpreting neuroophthalmologist reviews patient’s visual acuity and color vision, as collected by an ophthalmic technician, the indication for the test, any previous visual fields and all pertinent neuroimaging prior to concluding a finalized interpretation.

Methods:
Charts of patients who underwent a visual field (VF) interpretation without an eye exam as ordered by a non-ophthalmology department were reviewed between January 1, 2012 and December 31, 2012. Data was collected on the ordering department, indication, results, intracranial surgical intervention, and recommendation for complete ophthalmic exam. Blepharoplasty-associated ptosis VFs were excluded.

Results:
A total of 187 VFs without examination were reviewed. Endocrinology: 77 of 82 (94%) indicated for parasellar lesions. Neurology: 31 of 55 (56%) indicated for seizure-related pathology. Neurosurgery: 35 of 50 (70%) indicated for parasellar lesions with emphasis on pre/post-operative VF changes. Overall, 68 studies had prior VF available for comparison, 61 of which were evaluated as stable or improved. A complete eye exam was recommended in 4% of the VFs evaluated.

Conclusions:
A visual field study without a complete ophthalmic examination is a useful test modality for select departments and can be performed safely with minimal risk of overlooking ocular pathology, while adding to clinical efficiency. An effective means of communication when the interpreting neuro-ophthalmologist recommends a complete eye examination based on VF findings must be in place.

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Visual Field Rotation as Presumptive Evidence of Ocular Cyclodeviation

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Introduction:
Visual field rotation (VFR) is presumptive evidence of abnormal torsional eye position (cyclodeviation) and may occur in one eye or both eyes. It is most easily seen on careful Goldmann perimetry. VFR may occur in association with an ocular tilt reaction (OTR), or with third or fourth nerve palsies. We searched the registry of a large, single physician neuro-ophthalmic practice for cases of VFR and correlated perimetric findings.

Methods:
Retrospective case series; visual field defects were present in all eyes. Patients’ heads were kept vertical during Goldmann perimetry. Monocular patients and those with normal visual fields and only physiologic blind spot rotation were excluded.

Results:
Twelve subjects with VFR were identified. None had 3rd or 4th nerve palsies. Four subjects had conjugate, symmetric VFR in both eyes suggesting OTR. Eight subjects had dissociated VFR; six had monocular VFR and two had binocular VFR in opposing directions that implied excyclodeviation in each eye. When perimetry was repeated with both eyes open, VFR disappeared in all patients with dissociated rotations but not with conjugate VFR. In individual eyes, two of 16 eyes demonstrated incyclotorsion, six did not rotate, and eight showed excyclotorsion. Underlying pathology did not appear to coincide with VFR pattern. No subject with dissociated VFR reported diplopia.

Conclusions:
We identified two distinct patterns of VFR. Four of 12 subjects demonstrated conjugate rotation that did not correct with both eyes open. This pattern suggests an OTR. The remaining eight subjects demonstrated either monocular or oppositely-directed binocular rotation that corrected when fields were tested with both eyes open. This pattern suggests cyclophoria. When subjects are in a featureless perimetric background with one eye occluded, they receive no spatial cues and the eye may roll around the visual axis. Benign subclinical cyclophoria might thus be demonstrated during routine visual field testing.

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Bilateral Non-Arteritic Anterior Ischemic Optic Neuropathy in a Patient With a History of Diffuse Large B-cell lymphoma

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Introduction:
We describe a patient who presented with consecutive bilateral optic nerve head edema. Bilateral optic nerve head edema in a patient with a history of malignancy can represent a central nervous system (CNS) metastasis, and a systemic workup is warranted. This case demonstrates management of a rare presentation of consecutive bilateral non-arteritic ischemic optic neuropathy with crowded optic nerve heads.

Methods:
A 49-year-old gentleman presented with optic nerve head edema and a history of diffuse large B-cell lymphoma treated with 6 cycles of EPOCH-Rituximab. His vision was 20/30 OU and a 24-2 Humphrey visual field showed a full field OD and a dense inferior arcuate scotoma OS associated with disc edema. Two weeks later he presented with vision loss in the right eye and disc edema in both eyes. He had completed treatment 2 months prior to the onset of visual symptoms, and his only risk factor for ischemic optic neuropathy was crowded optic nerve heads.

Results:
A complete blood count and infectious workup for optic neuropathy were noncontributory. Magnetic resonance imaging of the brain and orbits was unremarkable, specifically without evidence of abnormal edema signal or enhancement along the optic pathway bilaterally. Several diagnostic lumbar punctures were negative for any malignant cells. Positron emission tomography/computed tomography scans performed near symptom onset and 7 months later described no findings to suggest residual or recurrent neoplastic disease. A diagnosis of consecutive, bilateral, non-arteritic ischemic optic neuropathy was made due to a negative systemic workup.

Conclusions:
Our case supports the notion that a crowded optic nerve head is a sufficient risk factor for consecutive bilateral non-arteritic ischemic optic neuropathy.

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Visual Recovery and Optical Coherence Tomography (OCT) Changes Following Treatment of Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) with Levodopa Alone or in Combination with Allopurinol and Tetracycline

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Introduction:
To determine the effectiveness of levodopa alone or in combination with allopurinol and tetracycline on visual acuity, visual field, and retinal nerve fiber layer (RNFL) thickness in eyes affected by NAION.

Methods:
Retrospective cohort study involving 33 eyes of 33 patients, from 119 consecutively evaluated patients with NAION. Patients evaluated within 45 days of NAION onset and who had at least one OCT within 1 year of NAION onset were enrolled. Patients had received treatment with levodopa alone (Levodopa only) or in combination with allopurinol and tetracycline (Levodopa combined). Best corrected visual acuity converted to logMAR, mean deviation (MD) threshold sensitivity on automated perimetry, and RNFL thickness on OCT were recorded. Primary outcome measures were changes in logMAR visual acuity, MD threshold sensitivity, and RNFL thickness within 1 year of NAION onset.

Results:
Among patients with visual acuity of 20/60 or worse, improvement by 3 or more lines was documented for 71% (5 of 7) of Levodopa only and 50% (4 of 8) of Levodopa combined participants. No patient had worsened visual acuity. There was no significant difference (p=0.9) between the change in visual acuity for Levodopa only (-0.4 logMAR) and Levodopa combined (-0.4 logMAR). There was no significant difference (p=0.9) between the change in MD threshold sensitivity for Levodopa only (1.79 dB) and Levodopa combined (1.54 dB). The average RNFL thickness at 5 months decreased by 23.6% for patients treated with levodopa, in contrast with previously published reports which documented decrease in average RNFL thickness of 35 to 42% for untreated patients.

Conclusions:
Treatment within 45 days of onset of NAION with levodopa alone or in combination with allopurinol and tetracycline improved visual acuity but not visual field. Levodopa may promote neuroprotection in NAION by decreasing retinal ganglion cell loss and subsequent RNFL thinning.

References:

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Trial Design for an International Phase 2 Study of the Efficacy, Safety and Pharmacokinetics of the Anti-LINGO-1 Monoclonal Antibody, BIIB033, in Subjects With a First Episode of Acute Optic Neuritis

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Introduction:
Acute optic neuritis (AON) is characterized by inflammatory injury to the optic nerve and is frequently the first manifestation of MS. In humans, ~20% of the nerve fiber layer is lost after an AON episode. LINGO-1 (leucine-rich repeats and immunoglobulin domain-containing neurite outgrowth inhibitor receptor-interacting protein-1) is a component of CNS signaling complexes that suppress axonal repair/remyelination. Blocking LINGO-1 improves remyelination in animal models, thereby providing a rationale for evaluating the anti-LINGO-1 monoclonal antibody, BIIB033 in a Phase 2 study of subjects with AON (RENEW).

Methods:
RENEW is being conducted at 44 centers in 11 countries in Australia, Canada and Europe to evaluate the efficacy, safety, and pharmacokinetics of BIIB033 in subjects with their first, unilateral AON episode. Eligible individuals (N=80; aged 18–55 y) are being randomized (1:1) to received intravenous infusions of BIIB033 (100 mg/kg) or placebo every 4 weeks for 20 weeks. The primary efficacy endpoint is the change in optic nerve conduction velocity at Week 24 for the affected eye from the baseline value for the unaffected eye, determined using full-field visual evoked potentials (FF-VEPs). Secondary endpoints include the change in thickness of the retinal nerve fiber layer and retinal ganglion cell layer/inner plexiform retinal layer, assessed by spectral domain optical coherence tomography and the change in low-contrast letter acuity using Sloan letter charts. Patient-reported vision-related quality of life is being measured using the 25-item National Eye Institute Visual Functioning Questionnaire. Safety and tolerability is being monitored via the incidence of adverse events (AEs) and serious AEs; population pharmacokinetics will be measured by serum concentrations of BIIB033 (ClinicalTrials.gov #NCT01721161).

Results:
Details of the study design for RENEW will be reported.

Conclusions:
RENEW is an international, Phase 2 study underway to examine the efficacy of BIIB033 in subjects with their first AON episode.

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Grant Support: None.
Asymptomatic Optic Neuritis in Neuromyelitis Optica and Multiple Sclerosis – a comparison.

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Introduction:
Chronic asymptomatic retrobulbar optic neuritis although rare has been reported in Multiple Sclerosis (MS)\textsuperscript{1,2,3}. We report two cases of asymptomatic chronic optic neuritis in MS and two cases in patients with Neuromyelitis Optica (NMO). Their clinical presentations as well as outcomes will be described and discussed.

Methods:
Retrospective case series

Results:
Two known MS patients and one with NMO had visual field abnormalities discovered during their routine follow-up visits. These were repeatable and progressive within a 2-3 week period. All were treated with pulsed steroid, two recovered vision while one did not. Another patient was found to have perception of light vision in one eye and optic atrophy at the time of diagnosis of NMO. No treatment was undertaken and vision has remained poor.

Conclusions:
Chronic asymptomatic retrobulbar optic neuritis is well documented in MS but can also occur in NMO. Vigilant follow-up is required to diagnose such cases. Other causes such as a compressive etiology should be excluded. Treatment with pulsed steroid may result in visual recovery and should be attempted. More studies should be undertaken to better understand the pathophysiology in these cases.

References:


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Retinal vessel diameter assessment in papilledema by semi-automated analysis of SLO images: feasibility and preliminary results

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Introduction:
Retinal blood vessel diameter changes are promising indirect markers for intra-cerebral and intra-optic nerve mechanical forces in idiopathic intracranial hypertension (IIH) because they are a consequence of compression of the ophthalmic artery and vein caused by the swollen optic nerve and elevated intracranial pressure. We report feasibility and preliminary results of retinal vessel diameter measurements using semi-automated image analysis of scanning laser ophthalmoscopic (SLO) images in eyes with pseudopapilledema and papilledema before and after treatment.

Methods:
A semi-automated customized image analysis software was used to measure the diameters of superior and inferior retinal arteries and veins on 21 SLO images of elevated optic discs. Measurements obtained by two observers were compared with each other and with manual measurements of the same vessels by the same observers. Retinal vein and artery diameters were compared between 6 papilledema and 5 pseudopapilledema subjects. Retinal vein and artery diameter changes were studied for 4 papilledema subjects following treatment for and resolution of papilledema.

Results:
Inter-rater reliability was 0.97 (Pearson correlation, r) for semi-automated measurements and 0.90 for manual measurements. Correlation between manual and semi-automated measurements was 0.85. Vein diameter for papilledema subjects was larger than for pseudopapilledema subjects (p=0.045, Mann-Whitney). Papilledema subjects had a decrease in vein diameter following treatment for and resolution of papilledema (p=0.043, Wilcoxon signed rank). Artery diameters were neither different between papilledema and pseudopapilledema groups, nor did they change following treatment.

Conclusions:
A novel methodology for semi-automated measurement of retinal artery and vein diameters from SLO images of elevated optic nerves is reliable and feasible. Vein diameters were larger in papilledema subjects before treatment compared with pseudopapilledema subjects. Vein diameters decreased in papilledema subjects following treatment. Further study is needed to determine the clinical utility of retinal vein diameter measurements as a marker for diagnosis and treatment of papilledema.

References:

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A Longitudinal Analysis of Stroke Risk Following Non-Arteritic Ischemic Optic Neuropathy

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Introduction:
Non-arteritic ischemic optic neuropathy (NAION) is the most common acute optic neuropathy in patients > 50 years old.1 The association between NAION and stroke is uncertain. Several small studies have shown no increase in stroke following NAION,2,3 while others have shown an increased stroke risk following NAION.4,5 Our goal was to determine if patients with NAION are at an increased long term risk of ischemic stroke and if that risk is independent of other known stroke risk factors.

Methods:
We used claims data from the OptumInsight Clininformatics Data Mart which contains records of all beneficiaries in a large managed care network in the United States who had some form of eyecare from 2001-2012. Inclusion criteria were ≥ 50 years old with continuous enrollment in the plan for ≥ 2 years. Incident NAION and ischemic stroke were identified by International Classification of Diseases-9 (ICD-9) codes. We excluded those with pre-existing stroke or NAION during their first 2 years in the plan, giant cell arteritis or optic neuritis. Unadjusted and adjusted Cox proportional hazards modeling were used to determine whether the development of NAION affected the risk of subsequent development of ischemic stroke. Models were adjusted for sociodemographic factors, medical, and ocular comorbidities.

Results:
Among the 1,930,194 enrollees who met the inclusion criteria, 2531 developed NAION (0.1%) and 50,699 (2.6%) experienced an incident ischemic stroke. After adjustment for covariates, individuals with NAION had a 162% increased hazard of developing ischemic stroke (adjusted HR 2.62, [95% CI 2.12-3.24]) relative to those who did not have a NAION.

Conclusions:
After accounting for comorbid medical conditions and other confounding factors, patients in our study with NAION had an increased risk of ischemic stroke. We recommend aggressive risk factor modification and counseling about signs and symptoms for ischemic stroke in patients with NAION.

References:


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Pseudoisochromatic plate testing: are we measuring color vision or something else?

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Introduction:
Color vision testing with pseudoisochromatic (PIP) plates [Hardy-Rand-Ritter (HRR), Ishihara] is a typical part of the neuro-ophthalmologic examination, and abnormal responses are often used as evidence of optic neuropathy. However, color disc arrangement tests such as the Farnsworth D-15 are the gold standard for detecting and classifying color vision deficits. The aim of this study was to determine if apparent color vision deficits on HRR and Ishihara plate testing represent truly aberrant color vision or indicate a decrement of other psychovisual parameters.

Methods:
Forty-seven subjects (age 18-65) were recruited prospectively from an outpatient clinic. The study group included patients diagnosed with optic neuropathy (n=23), retinal dystrophy (n=3) and dry eye syndrome (n=1), and controls (n=20). Individuals with Va<20/200 or with congenital color blindness were excluded. All subjects underwent a comprehensive eye examination including visual acuity, color-vision and contrast sensitivity testing. Color vision was assessed using HRR and Ishihara PIP plates and Farnsworth D-15 hue discrimination test. Contrast sensitivity was measured using Pelli-Robson contrast sensitivity charts.

Results:
HRR score and contrast sensitivity (CS) were correlated (Kendall’s correlation=0.31, p<0.001), with no relationship between HRR score and Farnsworth D-15 score (Kendall’s correlation=0.06, p=0.250). On multivariate analysis, CS (β=8.36, p<0.001) and visual acuity (β=1.92 p=0.025) both showed association with HRR scores. Ishihara score weakly correlated with CS (Kendall’s correlation=0.16, p=0.016) but did not correlate with Farnsworth D-15 score (Kendall's correlation=0.04, p=0.363). HRR score had a stronger relationship with CS than did the Ishihara score (p=0.014).

Conclusions:
Both Ishihara and HRR PIP testing appear to measure contrast sensitivity in a visual acuity-dependent manner; they do not accurately assess color vision. HRR is a more sensitive measure of contrast sensitivity deficits than is the Ishihara PIP set.

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A Retrospective Study of Chronic Relapsing Inflammatory Optic Neuropathy (CRION)

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Introduction:
CRION is a poorly understood disease leading to recurrent inflammation of the optic nerve. Very little is known about etiopathogenesis, course and outcome of this rare entity. We aim to review the demographics, clinical course, diagnostic workup, treatment and visual outcome in patients with CRION seen at our institute.

Methods:
Clinic charts of patients with CRION who met the following criteria were reviewed- One episode of optic neuritis (ON) and at least 1 relapse- Absence of known causes of ON including neuromyelitis optica (NMO)- Absence of demyelinating disease (white matter lesions on MRI brain and additional neurological deficits)- Demonstrable response to immunosuppressive treatment with relapse on withdrawal or dose reduction.

Results:
Thirteen patients (9 females, 4 males; age range: 15 to 69 years) with CRION seen between July 2010 and June 2013 were included. Twelve patients had bilateral ON (11 sequential; 1 simultaneous) and 1 unilateral. Disease activity ranged from 8 months to 34 years. Relapse rates ranged from 1 to 30. Final visual acuity (VA) was better than 20/40 in 64% eyes; 20% had severe visual loss (20/200 or worse) including 3 with no light perception. 43% eyes had severe visual field loss (>-15dB) while 60% eyes demonstrated retinal nerve fiber thickness (RNFLT) <75µm, which was independent of relapse rate. CSF abnormalities included mononuclear pleocytosis (1 patient) and elevated protein (1 patient). Non-specific serological marker elevation included anti-thyroid antibodies (1 patient) and ANA (2 patients). There was no predictable response to any of the treatment modalities- steroids (12 patients), methotrexate (2 patients), intravenous immunoglobulin (2 patients), combination (1 patients) and no therapy (4 patients).

Conclusions:
CRION appears to be a heterogeneous autoimmune disease that results in significant retinal nerve fiber loss and poor visual outcomes in more than a third of affected eyes.

References:

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Visual function and retinal nerve fiber layer thickness in Neuromyelitis optica: a longitudinal and comparative study

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Introduction:
Longitudinal studies in multiple sclerosis (MS) show that visual function decreases as a function of time and is correlated with a thickening of the retinal nerve fiber layer (RNFL) measured by optical coherence tomography (OCT). We determined the outcome of visual acuity and RNFL thickness in Neuromyelitis optica (NMO) in the lack of clinical relapse.

Methods:
Patients underwent high and low-contrast visual acuity (2.5%, 1.25%), frequency doubling technology perimetry (FDTP) and OCT measurement of RNFL thickness at baseline and at least a year later.

Results:
Among 42 patients with ≥ 1 year follow-up, 15 (30 eyes) were diagnosed with NMO and 27 (53 eyes) with MS. While every assessment in NMO eyes did not show any decrease, MS eyes without history of optic neuritis (ON) showed a worsening of 1.25% low contrast visual acuity (-4.81; p=0.04) and FDT median deviation (-1.85; p=0.039). Furthermore, the whole MS eyes exhibited a significant loss of RNFL thickness (-4.56 μm; p<0.0001).

Conclusions:
While visual function in NMO patient remain stable, progressive RNFL thinning occurs as a function of time in patients with MS, even in the absence of ON, and is associated with clinically significant visual loss. These findings are consistent with sub-clinical axonal loss in MS and the absence of chronic inflammation in NMO. Consequently, NMO therapeutic strategies would have been limited to the acute relapses treatment and prevention. Neuroprotection would not have any effectiveness in this disease.

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Eye movement perimetry for evaluation of visual field loss in patients with glaucoma versus recovered optic neuritis

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Introduction:
We have developed an eye-movement based perimetry technique that evaluates two novel response measures, saccadic eye movement latency and accuracy, in addition to visual threshold.1 We aimed to determine if this technique demonstrates abnormalities in the latency or accuracy of saccadic eye movements made to peripheral visual stimuli, or visual threshold, in patients with optic neuropathy due to glaucoma or prior optic neuritis.

Methods:
We tested 28 age-matched normal control subjects, 19 patients with glaucoma, and 12 patients with a prior history of optic neuritis (with good visual recovery) for detection of briefly-flashed peripheral visual stimuli of parametrically varied size. In patients, test locations corresponded to areas of normal sensitivity (+2 to -2dB), mild visual loss (-3 to -6dB), or moderate visual loss (-7 to -16dB) based on standard automated perimetry (Humphrey 24-2 SITA-standard). Subjects were instructed to look toward any perceived visual stimuli as quickly as possible and their eye movements were recorded with an EyeLink 1000 system; no manual response was required. Visual thresholds were estimated by fitting frequency-of-seeing curves to response data. We evaluated for group-level differences in latency, amplitude, and visual threshold for test locations of normal sensitivity, mild visual loss, and moderate visual loss.

Results:
Patients in both groups had higher visual thresholds and less accurate responses than normal controls at all test locations. Response latencies were not significantly different from normal controls at any test location in glaucoma or optic neuritis patients. In both patient groups, visual threshold was higher than for controls at test locations corresponding to areas of normal sensitivity on standard automated perimetry.

Conclusions:
Eye movement perimetry can be used to detect visual field loss from optic neuropathy, but may be more sensitive than SAP for detecting mild loss. Abnormal response accuracy might help to identify visual field loss.2

References:


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Abnormal Electroretinogram findings in a patient with Neuromyelitis Optica Spectrum Disorder

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Introduction:
Neuromyelitis optica (NMO) is a demyelinating disorder that can cause bilateral optic neuritis and transverse myelitis in the setting of antibodies to aquaporin-4. Though some reports of retinal autoantibodies and abnormalities in electroretinogram (ERG) have been reported in multiple sclerosis, these findings have yet to be described in neuromyelitis optica. We report a case of NMO with ERG abnormalities.

Methods:
Retrospective review of one patient with a diagnosis of neuromyelitis optica spectrum disorder. Physical examination, visual fields, fluorescein angiography, ICG angiography and serial ERGs were reviewed.

Results:
A 60 year old female with a history of hypothyroid and hypertension presented with decreased vision in both eyes for over 6 weeks. Visual acuity on presentation was 20/40 OD, counting fingers at 2 feet OS. Ocular exam showed poorly reactive pupils bilaterally but the remainder of the exam including optic nerve exam was unremarkable. Formal visual field examination revealed bilateral superior altitudinal defects most dense in the left eye. Fluorescein and ICG angiography were unremarkable. Electroretinogram noted decreased scotopic, photopic, and flicker response in the left eye when compared to the right eye. Both eyes had a diminished response overall. MRI of the brain was notable for abnormal T2 signal changes of the prechiasmiatic segments of both optic nerves and the left lateral optic chiasm. Aquaporin-4 antibody testing was positive. MRI of the cervical spine was unremarkable. Patient was diagnosed with NMO spectrum disorder. The patient was treated with high dose steroids and over a few weeks the visual field abnormalities resolved. The ERG also gradually returned to normal with treatment. She continues to be relapse and symptom free for the last 12 months.

Conclusions:
This case suggests that NMO spectrum disorder can include retinopathy that has not been previously reported. Further investigation is necessary to investigate how the NMO antibody causes an autoimmune retinopathy.

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Retrospective Analysis Of Nutritional Optic Neuropathy

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Introduction:
Nutritional optic neuropathy is a multifactorial disease, where nutritional deficiency associated with toxic factors such as tobacco and alcohol lead to mitochondrial dysfunction and consequently to optic nerve damage. Apart from the so-called Cuban Epidemic Optic Neuropathy, literature reports are vague and sporadic. In view of the frequency of this disease in our hospital and the absence of treatment protocols, comes this report in order to systematize the study and treatment of this disease.

Methods:
A Retrospective review was performed of patients diagnosed with nutritional optic neuropathy in our hospital between August 2011 to June 2013.

Results:
Twenty-one patients were included, 18 (86%) males. Mean age at diagnosis was 45 years, and 57% was between 40-60 years. Heavy smokers (62%), Heavy drinkers (81%). (Average alcohol consumption 250 gr/day) Cocaine (23%) Poor diet (without proteins) (100%) Association with Leber (9,5%) Vitamin deficiency was not found. Initial visual acuity was poor (57% <0,1) Visual acuity was stable in patients without treatment. Visual acuity improved in patients with treatment. Ishihara test did not improve in any patient. Main findings in Fundus: first visit: Normal. Month: temporal pallor. Final visit: general pallor. Visual field alteration was found in all patients. Cecocentral scotomas was found in (65%) patients. OCT in initial states was not remarkable, and decreased fiber layers at advanced states was the main finding.

Conclusions:
It is widely accepted that nutritional optic neuropathy is rare, but we believe that it is misdiagnosed. Our retrospective analysis of nutritional optic neuropathy revealed that vitamin supplement is effective in the outcome of visual acuity. We protocolize vitamin treatment due to the limited literature and researches. Further evaluation of these cases may yield useful information about the pathogenesis and the relationship between genetic, smoke, alcohol, drugs and poor diet of this disorder also standardizing treatment.

References:

Financial Disclosures: The authors had no disclosures.

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25-hydroxyvitamin D levels in optic neuritis and demyelinating disorders. Relation to paraclinical findings and demographic characteristics

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Introduction:
The importance of vitamin-D in preventing multiple sclerosis (MS) and reducing disease severity in MS is becoming increasingly accepted. The study examines 25-hydroxyvitamin-D (25HVITD) levels in acute optic neuritis (ON) patients compared to levels in MS patients. 25HVITD levels as a predictor for paraclinical findings (MRI and CSF findings) and risk of RRMS in ON is estimated.

Methods:
A cross-sectional study of 25HVITD in ON (n=130) and MS (n=787) with retrospective follow-up of the ON patients. Mean 25HVITD differences and differences in prevalence of 25HVITD deficiency (<50nmol/L) between ON and MS and differences between subgroups of ON patients (two-sample t-test, Mann Whitney, chi-square) were assessed. Associations between 25HVITD levels, paraclinical findings and demographic characteristics in ON patients (Spearman and logistic regression) and differences in hazards of MS (log rank test) were assessed. Mean 25HVITD difference between ON patients with high>

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The socioeconomic consequences of optic neuritis with and without multiple sclerosis: a controlled national study.

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Introduction:
Optic neuritis (ON) often precedes multiple sclerosis (MS). MS is associated with a significant socioeconomic burden. However, the burden of ON with and without MS before and after its diagnosis has never been calculated.

Methods:
Using complete national records from the Danish National Patient Registry (1998-2006), we identified 1677 patients with ON and compared them with 6708 randomly selected citizens matched for age, sex and geography. A societal perspective is taken towards the cost analyses. Costs included in the analysis are those of the health sector, including all contacts with primary and secondary sectors, and the use and costs of drugs. Productivity losses included labour supply and income. All social transfer payments were also calculated.

Results:
Patients with ON had higher rates of contact with healthcare services, medication use and income from employment, all of which incurred a higher socioeconomic cost. Employed patients had lower income than control subjects. The total annual excess costs relative to matched controls were €3501 for ON patients and €9215 for patients with a dual diagnosis of ON and MS. The ON and ON+MS patients received an annual mean excess social transfer income of €1175 and €4619. ON/ON+MS patients presented social and economic consequences up to 8 years before diagnosis, and these increased after the diagnosis was established.

Conclusions:
ON, especially if combined with a diagnosis of MS, has a significant socioeconomic consequence for the individual patient and for society. Productivity losses are a far more important economic factor than health sector costs.

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Introduction:
Non-arteritic ischemic optic neuropathy (NAION) is a common neuroophthalmic disorder. A second episode of NAION in the fellow eye occurs in 15-35% of patients. Doppler OCT studies have demonstrated a reduction in blood flow in the anterior lamina circulation in patients with NAION. Pentoxifylline is a medication with a long history of use in peripheral vascular disease and has been shown to have a rheological benefit from increased red blood cell compliance. We sought to determine if pentoxifylline improved central retinal artery derived blood flow by Doppler OCT in patients with NAION.

Methods:
Nine eyes of five patients with NAION were examined with Doppler OCT. All patients were on pentoxifylline, 3 patients had bilateral NAION. Doppler OCT was performed using high-resolution Fourier domain-OCT scans and post-acquisition blood flow calculations using a previously published technique.

Results:
The average blood flow in the eye with NAION was 29 µl/min. The average blood flow in the fellow eye of patients with unilateral NAION was 52 µl/min. In four eyes with a purely altitudinal field loss the blood flow in the affected heminerve was 9 and 17 in the unaffected heminerve.

Conclusions:
When compared to normative data pentoxifylline caused a small increase in the retinal blood flow in the fellow eye of patients with unilateral NAION (NAION 52, normal 45). A similar increase was not seen in the affected eye (NAION 29, Normal 28). This may represent an effect of pentoxifylline on retinal blood flow that may help protect the fellow eye from a second episode of NAION. This data is part of an ongoing study looking at the effects of pentoxifylline on retinal blood flow.

References:

Financial Disclosures: The authors had no disclosures.

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Characterizing the Pathobiological Mechanisms of Binocular Acuity Summation versus Inhibition in MS: Central Adaptation or Not?

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Introduction:
Research has shown that the 'fellow' unaffected eye, and its afferent visual pathway, in patients with unilateral optic neuritis, can exhibit physiologic changes which synchronize the arrival of visual information within the cortex. This 'temporal reorganization', if confirmed, would represent an important central adaptation for visual processing, with implications for binocular fusion and stereopsis. Recent visual evoked potential studies show prolonged latency in visual cortical responses in both the optic neuritis eye and fellow 'adapting eye.' Detailed analysis revealed a delay in 'time to peak' of the cortical response in the adapting eye, as opposed to a delay in 'time to onset' in the optic neuritis eye. A similar process of central adaptation, may explain the phenomena of binocular summation and inhibition, observed in patients with asymmetric monocular visual acuities. The aim of our study is to analyze the structural and functional measures of the anterior visual system in MS patients exhibiting binocular summation versus inhibition, to elucidate the pathobiological underpinnings that differentiate these distinctive processes. Additional studies on the influence of body temperature and potassium channel modulation with 4-aminopyridine will be conducted.

Methods:
In this cross sectional, observational study, high and low-contrast acuities were assessed binocularly and monocularly in Multiple Sclerosis patients and healthy controls. Retinal architecture was analyzed using spectral domain optical coherence tomography and scanning laser polarimetry. Functional assessments included Humphrey automated perimetry, multifocal visual evoked potentials, multifocal electroretinogram and pupillary light reflex responses.

Results:
We will present the findings of our ‘structure-function’ investigation, on the different mechanisms underlying binocular low contrast acuity summation and inhibition in MS.

Conclusions:
Central adaptive processes may account for temporal reorganization, and synchronized arrival of visual information within cortex, of MS patients exhibiting binocular acuity summation. Alternately, binocular acuity inhibition signifies the presence of bona fide, and distinctive MS-associated pathological changes (albeit on an occult basis), affecting the fellow ‘unaffected’ eye.

References:


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Clinico-Pathological Correlation of the Optic Neuropathy in Familial Dysautonomia

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Introduction:
We have demonstrated that Familial Dysautonomia (FD) or Riley Day syndrome is associated with a specific optic neuropathy that resembles other mitochondrial optic neuropathies. In this study we provide histopathologic evidence that mitochondrial dysfunction occurs in the optic nerves of FD patients.

Methods:
The eyes of three patients with FD, two of whom had neuro-ophthalmic examination including OCT. were obtained at autopsy. Anatomo-pathological study, including special immunohistochemistry stains for neurofilaments, melanopsin ganglion cells and mitochondrial COX protein was obtained.

Results:
Clinical and OCT findings indicated RNFL loss mainly in the papillomacular bundle. Histologic sections of the optic nerve showed axon loss in the papillomacular bundle best seen with neurofilament immunohistochemistry. Melanopsin-containing ganglion cells were preserved. COX stain showed increased accumulation of mitochondria in the pre-laminar optic nerve.

Conclusions:
Pathologic changes and clinical findings indicate that it is possible that the genetic abnormality associated with FD may affect other genes involved mitochondrial protein function or transport leading to the type of optic neuropathy that is seen in other hereditary optic neuropathies. These findings may have implications regarding the molecular biology of familial dysautonomia.

References:

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Safety and effect of rituximab treatment in pediatric demyelinating disease

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Introduction:
Rituximab is a B-cell therapy that reduces relapse rate in adult demyelinating diseases, but there is limited knowledge of clinical treatment experience in pediatric neuromyelitis optica (NMO) and multiple sclerosis (MS). Demyelinating diseases in children can have high morbidity, especially in children with NMO with optic neuritis causing rapid progression to blindness and incomplete or no recovery from steroids, plasmapheresis and intravenous immunoglobulin therapy. Our study investigates the safety and effect of rituximab in children with NMO and MS.

Methods:
This is a retrospective case series of 11 patients with pediatric NMO and MS seen at a specialty referral center for pediatric demyelinating disease who received at least one rituximab infusion between September 2005 and September 2013. Each patient was infused 375mg/m² (max of 1,000mg) twice with a 2-week interval between the infusions. Outcomes based on Expanded Disability Status Scale (EDSS), relapse rate and visual acuity more than 6 months after the first infusion were investigated. Adverse reactions were monitored.

Results:
8 children with NMO, 2 with relapsing-remitting MS and 1 with primary progressive MS were studied (median EDSS 4.0, range 2.0-9.0). Of the children with NMO, the best unilateral visual acuity at presentation was 20/30 or better in 3, 20/70 in 1 and 20/200 or worse in 4. 82% (n=9) had reduction of relapse rate and stabilization or improvement in EDSS and visual acuity. There were no serious infections. Infusion reactions were reported in 3 patients and managed successfully in subsequent infusions with increased pre-treatment medications and use of slower infusion rates. Rituximab was not discontinued in any child due to side effects, however 18% (n=2) discontinued treatment due to disease progression.

Conclusions:
The use of rituximab in our pediatric NMO and MS cohort was safe and effective.

References:

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Poster 211

Retro bulbar optic neuropathy and Bing-Neel syndrome

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Introduction:
Bing-Neel syndrome is an extremely rare neurologic complication of Waldenström macroglobulinemia (WM) that was first described in 1936. It is associated with central nervous system infiltration by neoplastic lymphoplasmacytoid and plasma cells with or without cerebrospinal fluid (CSF)hyperglobulinemia.

Methods:
We report a case of a 60-year-old white man. In 2010 he presents a para paresia with extended medullary lesion (T1-T9). In 2011 he presents a right retro bulbar optic neuropathy. A DEVIC syndrom is evoked. He was diagnosed with Bing-Neel syndrome based on presence of monoclonal dysglobulinemia (kappa Ig M) and Kappa Bence Jones proteinury. In addition, a review of Bing-Neel syndrome in literature was performed.

Results:
Our patient underwent successful treatment with intrathecal and intra venous chemotherapy. He has been in clinical and pathologic remission. Based on our literature review, we also summarize and discuss clinical manifestations, diagnosis, and treatment options for Bing-Neel syndrome.

Conclusions:
Bing-Neel syndrome is a rare and potentially treatable complication of WM. Patients with a history of WM presenting optical symptoms should be evaluated for possible Bing-Neel syndrome.

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Compressive Optic Neuropathy Due To A Suprasellar Arachnoid Cyst Presenting With Cupping and Lack Of Optic Disc Pallor

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Introduction:
Cupping without optic disc pallor, although infrequent, may be the initial presentation of a compressive optic neuropathy.\(^1\),\(^2\),\(^3\) Histologically, the cupping in compressive optic neuropathy has been shown to correlate with axonal loss rather than glial atrophy as is typically seen in glaucoma.\(^1\),\(^4\) Our patient demonstrated normal retinal nerve fiber layer measurements, generally accepted as a measure of axonal integrity\(^5\) suggesting an alternate mechanism of optic disc cupping. This case report highlights the importance of visual field testing in the differentiation of glaucomatous versus non-glaucomatous optic neuropathies presenting with optic disc cupping alone.

Methods:
Case report

Results:
57-year old African-American female presented with sudden onset of painless vision loss in the left eye. Ophthalmologic exam revealed a left optic neuropathy with decreased visual acuity, dyschromatopsia, a left afferent pupillary defect (APD), bitemporal hemianopia and left optic disc cupping without pallor. Optical coherence tomography demonstrated normal retinal nerve fiber layer bilaterally. Neuroimaging revealed a suprasellar arachnoid cyst and pterional craniotomy was performed for cyst fenestration. Post-operatively she had complete resolution of her left optic neuropathy and bitemporal visual field defects.

Conclusions:
Optic disc pallor has been shown to be specific for non-glaucomatous optic neuropathy;\(^5\),\(^7\) though not a sensitive finding of early compressive lesions.\(^2\),\(^6\),\(^8\) The pathophysiology of optic disc cupping without pallor due to compressive lesions is unknown. The only clinical histopathologic case described presented with optic disc cupping and pallor in the setting of a long-standing compressive lesion and showed axonal loss and “collapse of glial columns”.\(^4\) The mechanism may be different in early compressive optic neuropathy as reflected by our patient’s normal retinal nerve fiber layer. Bitemporal visual field defects, as seen in our case, can be invaluable in differentiating a compressive etiology from glaucomatous optic neuropathy in the absence of optic disc pallor.\(^3\),\(^6\)

References:

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Excavation of the optic nerve: a characteristic form of the evolution towards optic atrophy in methanol poisoning.

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Introduction:
Methanol is an industrial-use product. Methanol ingestion may be accidental, with suicidal intent or as a substitute for ethyl alcohol when it is not affordable. After methanol poisoning it has been observed a permanent loss of vision in 11-18% of patients. Other neurological abnormalities caused by methanol include: confusion, coma and putaminal necrosis. Optic atrophy after methanol exposure is evident within 30-60 days. In some patients without knowing exactly why atrophy occurs mimicking glaucomatous cupping.

Methods:
We present 16 patients with methanol poisoning. We describe the clinical features in all of them (visual acuity, results of MRI of the brain and orbits, pupillary reaction and fundus features). None of them were seen in the acute phase of intoxication. All patients were evaluated by the neuro-ophthalmology section in stable clinical phase.

Results:
In all of them there is a characteristic loss of pupillary reaction to light with pupil dilation. In 12 of them (75%) there is optic atrophy with prominent optic nerve excavation (> 0.8 cup to disc ratio). In 4 patients (25%) there was putaminal necrosis.

Conclusions:
When the optic nerve atrophy evolves, can do it basically taking two patterns: an optic atrophy in which gliosis predominates occupying the prelaminar space where axons disappear; or producing a complete removal of prelaminar axons and astrocyte glial tissue, being visible the cribriform plate. We postulate that the excavation observed in some patients exposed to acute methanol poisoning is caused by acute and prominent toxicity on axons in the prelaminar and laminar sector as well as an impairment of prelaminar astrocytic glial cells and retrolaminar oligodendrocytes. This would cause a disappearance of cells and axons in the retrolaminar space leading to an excavation feature in some patients. This phenomenon may be more common than previously described in the literature.

References:

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Ocular vascular features in mitochondrial optic neuropathies

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Introduction:
To investigate the vascular dysfunction in Leber hereditary optic neuropathy (LHON). With different techniques we evaluated: (i) vascular dysfunction in asymptomatic (cLHON), acute (aLHON) and chronic (chLHON) stages of the disease, comparing LHON patients with healthy controls; (ii) vascular setting in dominant optic atrophy (DOA), comparing DOA patients with controls.

Methods:
We investigated 6 cLHON, 2 aLHON, 8 chLHON patients and 6 DOA patients. All patients underwent a complete ophthalmologic examination including EDI-OCT (enhanced depth imaging-optical coherence tomography). Color Doppler imaging (CDI) was performed by 6 LHON patients and 4 DOA patients. Three LHON patients and 3 DOA patients ended the Retinal Vessel Analyzer exam. The healthy control groups were composed by 10 subjects for EDI-OCT and CDI and 6 subjects for RVA.

Results:
Macular choroidal thickness was significantly reduced in both aLHON and chLHON. In DOA patients we also observed a reduction of choroidal thickness reaching statistical significance only in 1500 temporal and SF measurements compared with healthy controls. The functional values obtained with CDI showed a general increase of peak systolic velocity (PSV) in aLHON and a subsequent reduction in the chronic phase of the disease.

Conclusions:
The present study revealed a structural damage of posterior vessels in LHON, probably related to the microangiopathy affecting LHON in addition to the possible non-specific correlation with the occurrence of optic atrophy, considering the reduction observed also in DOA. The result is compatible with the stroke-like hypothesis, followed by reduction of microangiopathy, once the optic nerve atrophy becomes established. The information gained by this approach will be also instrumental to assess the outcome of currently used therapies for mitochondrial optic neuropathies.

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Assessment of color vision in MS using a smartphone platform

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Introduction:
Smartphone-based assessments may improve monitoring of patients with multiple sclerosis (MS).

Methods:
We designed a custom application suite consisting of 20 tests of color vision, attention, dexterity, cognition, and quality of life. We enrolled patients with MS and their cohabitating partners as control pairs. Each subject received an Android HTC Sensation 4G smartphone. During the 1-year study, subjects accessed the study application daily to complete a quasi-randomly assigned test.

Results:
43 subject pairs were enrolled. 75% of MS patients and 40% of non-MS cohabitants were female. The median age was 34.5 (range 21-52) in MS patients and 38 (range 18-55) in non-MS cohabitants. There was an 87.5% patient retention rate and 72% compliance rate. Interim analysis was performed for 38 subject pairs that completed the color vision test weekly for at least 4 months. This task requires the subject to view 9 separate pseudoisochromatic images monocularly and to type in the perceived number. Using a threshold of 8/9 correct responses, 81% of tests for MS patients and 94% of tests for controls were performed accurately. Nine MS subjects had color vision deficits in one or both eyes. In affected eyes (n=13), the mean accuracy was 54% (SD±33.43), while the accuracy in paired controls was 99% (SD±1.46). Color vision performance modestly correlated with results from the Impact of Visual Impairment Scale.

Conclusions:
We captured high-frequency data from MS patients using a battery of assessments on a smartphone platform. Analysis of color vision test data identified eyes with poor color performance and found that those eyes demonstrated greater variance. These data illustrate the potential of smartphone-based applications to (1) gather clinically relevant data in a natural setting and (2) capture longitudinal data that may be sensitive to small but clinically meaningful changes.


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Cyanocobalamin is a Superoxide Anion Scavenger and Neuroprotectant in Neuronal Cells

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Introduction:
Vitamin B12 deficiency can cause an optic neuropathy characterized by bilateral centrocecal scotomas. The mechanism for this is not well understood. In 2009, another group demonstrated that vitamin B12 scavenges superoxide as effectively as superoxide dismutase (SOD). Our prior work showed that retinal ganglion cells (RGC) axotomy induced a burst of superoxide that then led to RGC death. We hypothesized that superoxide scavenging by cyanocobalamin, the most abundant vitamin B12 vitamer, would be neuroprotective, and studied this in vitro and in vivo.

Methods:
Superoxide reacts with hydroethidine to produce a fluorescent product, 2-hydroxyethidium. Superoxide scavenging by cyanocobalamin in a cell-free system was measured with a fluorescent microplate reader. Superoxide scavenging in 661W cells was assessed in vitro by fluorescent microscopy. Neuroprotection against menadione was evaluated by calcein-AM/propidium iodide assay. An optic nerve transection model in Long-Evans rats was used to study superoxide scavenging and neuroprotection in vivo, with visualization of retrograde-labelled RGCs by confocal scanning laser ophthalmoscopy.

Results:
Cyanocobalamin at concentrations of 10 μM and 100 μM reduced the rate of superoxide generation by 34% and 79% in cell-free assays. In menadione-treated 661W cells, cyanocobalamin concentrations above 10 nM scavenged superoxide anion similar to cells treated with pegylated-SOD. Cyanocobalamin at concentrations of 100 μM and 1 mM reduced 661W cell death from menadione by 20% and 32%, respectively. In rats with unilateral optic nerve transection, a single intravitreal dose of 667 μM cyanocobalamin significantly reduced the number of 2-hydroxyethidium–positive RGCs and also increased RGC survival.

Conclusions:
These data suggest that vitamin B12 may be an endogenous neuroprotectant, which could cause RGC death by a superoxide-dependent mechanism when depleted in nutritional deficiency. Vitamin B12 could potentially be used to slow progression of RGC death in patients with optic neuropathies characterized by overproduction of superoxide.

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Understanding Optic Neuritis from Murine Models of Multiple Sclerosis

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Introduction:
The availability of a good animal model is critical for understanding MS and developing therapies to control the disease. The primary experimental MS animal model has been the experimental autoimmune encephalomyelitis (EAE) model. Another model of viral induced CNS demyelination was recently published, based on ocular infection with a recombinant HSV-1 constitutively expressing murine IL-2 (HSV-IL-2).

Methods:
Study design: experimental animal research approved by IACUC committee. We used six-week old female C57BL/6 mice and compared MOG35–55, MBP35–47, and PLP190–209 models of EAE with our viral-induced MS model, using clinical and histo-pathologic data to assess demyelination (LFB), inflammation (HE) and immune cells infiltration (FACS). We also looked at the possibility of blocking optic nerve (ON) demyelination using IFN-beta, IL-4 and IL-12p70.

Results:
Mice ocularly infected with HSV-IL-2 showed a significant delay of VEPs compared with mice infected with control viruses. Mice with viral-induced and MOG-induced inflammatory demyelinating disease demonstrated similar pattern and distributions of demyelination in their ON, brain and spinal cord. In contrast, no demyelination was detected in ON of MBP- and PLP-injected mice. Inflammatory score in ON of MOG group was significantly higher than PLP, MBP and HSV-IL-2 groups. Except for ON in MOG group, inflammatory responses did not correlate with severity of demyelination. Mice injected with IFN-β DNA showed no ON demyelination in both MOG and HSV-IL-2 models. While HSV-IL-12p70 protected HSV-IL-2 infected mice from optic neuritis, ON demyelination, clinical severity and mortality increased in MOG group infected with HSV-IL-12p70.

Conclusions:
HSV-IL-2 ocularly infected mice behave like MOG-injected in terms of optic neuritis and MS clinical and pathological characteristics. In MBP and PLP animal models of MS, ON demyelination was not histo-pathologically described. Therefore, MOG and HSV-IL-2 models are better animal models for studying ON demyelination.

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Bilateral Disc Swelling in Renal Failure; Hypertensive Optic Neuropathy or Papilloedema?

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Introduction:
Both hypertensive optic neuropathy and papilloedema present with bilateral disc swelling, normal visual acuity and colour vision in the acute stage. We present a patient with chronic renal failure, elevated blood pressure and bilateral disc swelling. Although initially diagnosed with malignant hypertension and hypertensive optic neuropathy, neuro-ophthalmological evaluation indicated papilloedema and lumbar puncture confirmed idiopathic intracranial hypertension (IIH). We will show photos to differentiate the clinical features of these two life- and sight-threatening conditions. We also review literature on the etiology of disc swelling in patients with renal failure and postulate on the mechanism of IIH in patients with renal failure.

Methods:
Retrospective case report

Results:
A 29 year old female with no past medical history presented to the emergency department complaining of mild bilateral blurring of vision. On examination, visual acuity, colour vision and confrontational visual fields were normal. Her blood pressure however was elevated at 237/112 mmHg and her creatinine was elevated at 1115umol/L. Humphrey visual field however revealed bilateral generalized depression and fundal examination revealed bilateral disc swelling. On detailed questioning, she had no headaches, double vision or tinnitus to suggest increased intracranial pressure. Despite this, increased intracranial pressure was suspected due to clinical signs which will be discussed. Magnetic resonance imaging including venography was normal and lumbar puncture revealed an opening pressure greater than 50 cm water with a diagnosis of IIH.

Conclusions:
Patients in chronic renal failure can present with disc swelling due to several causes, namely hypertensive optic neuropathy, anterior ischaemic optic neuropathy as well as IIH. It is important to recognize and differentiate these conditions so that appropriate treatment can be instituted. In addition, further studies should be undertaken to understand the pathophysiology of this condition.

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Huge anterior cranial fossa Neurenteric Cyst With Unusual Ocular Presenting symptoms : A Case Report

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Introduction:
To describe a case of anterior cranial fossa neurenteric cyst in adult patient

Methods:
A 47-year-old healthy Thai male presented with esotropia for 1 year and gradually decreased vision in the past 6 months. He denied ocular pain, nausea, vomiting and headache. His visual acuity was counting finger 2 feet in the right eye and hand motion in the left eye. Eye examinations revealed temporal pallor of both optic discs, decreased corneal sensation and marked limitation of abduction in the left eye. The Krimsky test showed esotropia 90 PD. The findings were otherwise unremarkable. Blood hormonal test results were within normal limit. Orbital MRI depicted a large lobulated cystic mass, 7.1* 8.0* 7.5 cm. involves sellar, suprasellar, anterior cranial fossa region and bilateral small size optic nerves. Mass effect on inferior frontal lobe, medial temporal lobe, pons, midbrain, optic nerves, optic chiasm, optic tract, hypothalamus, as well as cavernous sinuses is observed. Aspiration of the cyst was done by endoscopic transphenoidal approach and incisional biopsy was done at aspirated cyst wall.

Results:
Pathologic examination showed fragments of fibrous cyst wall, lined with non-keratinized stratified squamous epithelium. In occasional areas, ciliated simple columnar epithelium is noted in top of the squamous epithelium, compatible with endodermal cyst.

Conclusions:
Neuroenteric cysts are rare, congenital, benign lesions lined by mucin-secreting columnar epithelium reminiscent of intestinal tract. These cysts tend to be found in the spine, rare in intracranial location. Intracranial lesion typically found in posterior fossa. We report the large anterior fossa neurenteric cyst case presented with bilateral optic atrophy, unilateral fifth (ophthalmic branch) and sixth cranial nerve palsy without other systemic symptoms. The unusual presentation may cause misdiagnosis and improper initial investigation. Therefore, we should keep in mind of this rare disease with unusual presentation.

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Optic Neuropathy due to Intracranial Dolichoectasia– A Case Series

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Introduction:
Dolichoectasia, also known as dilatative arteriopathy, comes from the greek words dolichos (elongated) and ectasia (dilated). Several proposed mechanisms of injury causing cranial neuropathies due to dolichoectasia include: direct compression of the nerve, impaired circulation by direct compression of smaller feeder vessels, obliteration of nutrient vessels derived from the diseased artery, and emboli. Visual pathway compression by internal carotid artery and vertebrobasilar dolichoectasia has been reported. We describe three patients with compressive optic neuropathy due to supraclinoid ICA dolichoectasia, and a fourth patient with transient blood pressure spikes and associated left homonymous hemianopia thought to be due to VBD.

Methods:
Chart review and descriptive case reports of four patients referred to neuro-ophthalmology for visual field abnormalities found to have intracranial dolichoectasia. Commonalities reported and neuro-imaging presented.

Results:
Four patients presented in their 7th-8th decade with a history of hypertension and unexplained visual field abnormalities. Three patients were found to have decreased color vision, as well as unilateral relative afferent papillary defect, increased cup to disc ratio, optic nerve pallor, visual field defect and MR evidence of optic nerve compression by a dolichoectatic supraclinoid internal carotid artery. The third patient reported episodic left homonymous hemianopsia with transiently increased blood pressure found to have right optic tract compression by a dolichoectatic posterior cerebral artery.

Conclusions:
All four cases describe compressive optic neuropathy. Intracranial dolichoectasia can be a cause of optic neuropathy and must be considered when evaluating patients with a history of hypertension and/or atherosclerosis. The use of high resolution MR imaging can play an important role in diagnosis and treatment. We report the only case to our knowledge of blood pressure associated homonymous hemianopsia due to vertebrobasilar dolichoectasia.

References:


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Visual Outcomes in Pediatric Optic Neuritis

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Introduction:
Despite well-established differences between optic neuritis in children and adults, pediatric treatment protocols and visual outcome data is often derived from adult studies. The purpose of this study was to describe clinical features and visual outcomes of a large cohort of pediatric patients with optic neuritis.

Methods:
Retrospective, single-center study of all patients with first-episode optic neuritis and at least 3 months of follow-up over a 10-year period (2002-2012).

Results:
Of the 59 pediatric patients with presented with first episode optic neuritis, 47 had at least 3 months follow-up and 37 had at least 1 year of follow-up. Mean age was 12.3 years old, 74% were female, 45% had bilateral involvement and 47% developed an underlying diagnosis (36% MS, 6% ADEM, 4% NMO). A large majority of the patients (94%) received systemic treatment (85% steroids, 9% multimodal). At 3 months, 64% of the patients were 20/20 or better and 89% were 20/40 or better. At 1 year, 78% of the patients were 20/20 or better and 86% were 20/40 or better. The only factor associated with a poor visual outcome at 1 year (defined as a visual acuity of <20/40) was a visual acuity of less than 20/20 at the 3-month visit (p = 0.03). Other factors such as bilateral disease, optic nerve edema, treatment and visual acuity at presentation were not significantly associated with a poor visual outcome at 1 year.

Conclusions:
In this large cohort of pediatric patients with optic neuritis, the majority of patients regained normal vision and visual outcomes overall were quite similar to the Optic Neuritis Treatment Trial (ONTT). Future studies of pediatric optic neuritis should focus on long-term visual outcomes and a randomized trial is needed to evaluate the risks and benefits of treatment.

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Compressive Optic Neuropathy Secondary To Sphenoid Sinus Aspergillosis

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Introduction:
Compressive optic neuropathy as an initial presentation of fungal sinusitis is a rare but important occurrence. We report a case of compressive optic neuropathy in an immunocompetent patient secondary to sphenoid sinus aspergillosis and an ONODI cell.

Methods:
Clinical presentation, radiological and histopathological data are reviewed and discussed.

Results:
A 63-year-old Chinese man presented with acute painless blurring of vision of his right eye. Significant past medical history included diabetes mellitus. He had bitemporal headache but was otherwise constitutionally well. Best-corrected visual acuity was 20/400 and 20/20 in his right and left eyes respectively. A right relative afferent pupillary defect was present, associated with reduced colour vision and diminished light perception and red desaturation. Fundal examination revealed a right temporal optic disc pallor. There were no signs of orbital apex or cavernous sinus syndromes. Computed tomography of the brain and orbits revealed an enhancing irregular soft tissue mass in the right sphenoid sinus, associated with bony erosion of the roof and posterior superior orbit wall. Magnetic resonance imaging demonstrated that the right optic nerve was inseparable from the soft tissue mass at the orbital apex and canal. The patient underwent emergency endoscopic bilateral sphenoidotomy. The right optic nerve was seen within an ODONI cell. The right sphenoid sinus mucosa was thickened with yellow green pus seen. A fungal ball was removed. Fungal cultures grew Aspergillus fumigatus. Histopathology of the biopsied mucosa confirmed invasive sinus aspergillosis. Postoperatively, the right eye vision improved to 20/40, with resolution of the headache. The patient completed a course of systemic voriconazole and methylprednisolone.

Conclusions:
Fungal sphenoid sinusitis is difficult to diagnose and treat due to its nonspecific symptoms. Hence ophthalmologists should have a high index of suspicion. An early diagnosis with timely aggressive surgical resection and appropriate anti fungal treatment is important to prevent permanent visual loss.

References:


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Acute Optic Neuropathy Is Not Associated with Posttraumatic Stress Disorder contrary to Rhegmatogenous Retinal Detachment

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Introduction:
Posttraumatic stress disorder (PTSD) is an anxiety disorder that may develop as a consequence of ocular insult. The burden of PTSD can be high and cause functioning disability. We studied the prevalence and risk factors of PTSD in an acute optic neuropathy (AON) cohort, and compared these findings with those reported on patients following surgery for rhegmatogenous retinal detachment (RRD).

Methods:
A prospective consecutive observational study of 171 AON patients and 366 patients who underwent surgery for RRD. Study patients were screened for the existence of PTSD symptoms via telephone survey, and those positively identified as having PTSD underwent a structured psychiatric interview.

Results:
None of the 171 AON patients was diagnosed with PTSD, as opposed to 9 out of 366 patients (2.5%) in RRD patients (P = .063). No significant differences were found in visual acuity at presentation and last follow-up visit between the two groups (logMAR 0.73 ± 0.80 for the RRD group and logMAR 0.36 ± 0.45 for the AON group, P ≥ .29). All of the RRD patients underwent surgery compared to none of the AON patients (P < .001), and 58 (34%) of the AON patients were administered steroids during the acute phase compared to none of the RRD patients (P < .001). Past history of trauma emerged as being a risk factor for the development of PTSD (P = .004). There were no statistical group differences in the 25-Item National Eye Institute Visual Function Questionnaire scores.

Conclusions:
PTSD tended to be associated with RRD but not with AON. It may result from the smaller number of AON patients in our study or from the third AON patients treated with corticosteroids in the acute phase. There are data suggesting that glucocorticoids given exogenously in proximity to the traumatic event may serve to prevent the development of PTSD.

References:


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Fabry Disease with Anterior Ischemic Optic Neuropathy

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Introduction:
Fabry disease is a X-linked inherited lysosomal storage disease due to the absence or reduction of α-galactosidase A activity. Anterior ischemic optic neuropathy (AION) has rarely been reported in Fabry disease. Herein we report a case with bilateral sequential AION.

Methods:
case report

Results:
A 14-year-old boy suffered from sudden loss of vision OS 3 days after mountain climbing. BCVA was 6/6 OD and HM/20cm OS. Slitlamp revealed faint nebula of superficial cornea and subtle lens opacity OU. There was a markedly pale swelling of the left optic disc, accompanied with tortuosity of retinal vessels OU. FAG revealed markedly delayed filling of left optic disc and choroid. Visual field was full OD and totally obscured OS. CT scan revealed an enlarged left intraconal optic nerve with contrast enhancement. He received methylprednisolone pulse therapy, but his vision remained CF/10cm. Another attack occurred in the right eye 7 months later. BCVA dropped from 6/5 to CF/30cm OD within 24 hours after a scheduled MRI examination. FAG revealed filling defect in right optic disc. Steroid pulse therapy was given immediately with systemic urokinase, coenzyme Q10 and L-arginine. Two days later, his vision did not improve and then hyperbaric oxygen (HBO) was used. His vision recovered to 6/7.5 OD on the next morning after HBO therapy.

Conclusions:
Fabry disease should be suspected by the characteristic corneal verticillata, spoke-like cataract, and conjunctival/retinal vessel tortuosities. The diagnosis could be confirmed with enzyme level measurement or genetic analysis. Enzyme replacement therapy with recombinant human α-galactosidase A has been shown safe and effective. Hyperbaric oxygen therapy could be beneficial in Fabry patient with ischemic vasculopathy.

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Pituicytoma – A Case Report

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Introduction:
Pituicytomas are very rare but benign tumors that arise from the neurohypophysis and only around 60 cases have been described in the literature so far. Misdiagnosis as pituitary adenoma is common due to the lack of distinguishing clinical or radiological features.

Case Description: We present a 49 year old male patient with sexual dysfunction, hair loss and low plasma testosterone levels. Pre-operative Humphrey visual field showed a 24-2 pattern deviation plot demonstrating essentially normal visual field in the left eye (left) and mild temporal depression obeying the vertical meridian in the right eye consistent with subtle chiasmal syndrome (right). No other neurological deficits were present. Subsequent MRI of the brain demonstrated an isointense lesion with homogenous enhancement, located immediately posterosuperior to the diaphragm sella and posterior to the pituitary stalk in the posterior suprasellar cistern. Lesion was located slightly eccentric to the right and measured 1.4 x 1 x 1.2 cm. Differential diagnosis included primary hypothalamic glioma, choristoma, or inflammatory/infectious etiologies such as hypophysitis or sarcoidosis. The lesion was biopsied using a transplanum transclinoial approach and pathological analysis showed a spindle shaped tumor with S100 and GFAP positivity and low positivity for Ki-67, therefore diagnosis of pituicytoma was made. The patient declined any further treatment such as gross total resection or radiation therapy and is therefore under close clinical follow up.

Conclusions:
Pituicytomas are benign and usually slow growing tumors and are part of differential diagnosis for suprasellar lesions. Complete surgical resection is usually curative, however cases have been described that were treated with stereotactic radiation or fractionated radiotherapy, but this therapeutic approach remains controversial.

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Optical Coherence Tomography upon Presentation of Non-Arteritic Anterior Ischemic Optic Neuropathy: Patterns of Edema and Atrophy in Acute and Subacute Disease.

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Introduction:
Non-arteritic anterior ischemic optic neuropathy (NAION) is characterized by acute onset of vision loss with optic disc edema secondary to hypoperfusion of the nerve head. The disc appearance evolves over time from edema to atrophy.¹ Sectors of atrophy correspond well with areas of visual field loss.² We have observed in practice that, acutely, sectors of optic disc edema do not always correlate with areas of visual field loss. The purpose of this study is to characterize visual field deficits in relation to areas of optic disc edema within the first 30 days of vision loss.

Methods:
A retrospective review of patients evaluated for NAION was conducted. Criteria for inclusion were clinical diagnosis of NAION, Humphrey Visual Fields (HVF) and spectral domain OCT within 30 days of onset of vision loss. Unaffected fellow eyes served as controls. Data were analyzed by comparing mean deviation hemifields on HVF to corresponding sectors of the retinal nerve fiber layer (RNFL) on OCT.³ Correlation between OCT and HVF was categorized as (1) matching edema, (2) diffuse edema or (3) paradoxical edema. OCT were also analyzed for concurrent atrophy in the RNFL or macula.

Results:
17 NAION eyes of 15 subjects were included. 8 eyes demonstrated matching edema. 5 eyes demonstrated diffuse edema which was more extensive than expected. 4 eyes demonstrated paradoxical edema. Some element of atrophy in the RNFL or macula was noted in every eye with paradoxical edema, as opposed to other groups. There was no significant difference between groups based on time from onset.

Conclusions:
In the acute to subacute stages of NAION, areas of visual field loss do not consistently correlate with sectors of optic disc edema. However, at the time of presentation, OCT does provide useful information about the state of the optic nerve in its progression from edema to atrophy.

References:


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Management dilemmas for optic nerve glioma with proptosis and visual loss in children

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Introduction:
Optic nerve (ON) gliomas account for 4% of orbital tumors in children. They can be located purely within the orbit or extend to involve the chiasm. Exophthalmos and loss of visual acuity are uncommon presenting features. Here we present 4 cases of optic nerve glioma with proptosis and severe visual loss and their management.

Methods:
A retrospective study of cases with unilateral ON glioma. Cases with NF 1 were excluded. Four cases were presented with proptosis and poor vision, aged 9 months, 1, 11 and 12 years old.

Results:
We present 4 cases with proptosis and visual loss at presentation. Neuroimaging at presentation showed a large mass involving the optic nerve in all cases, and extending to the chiasm in 1. Biopsy was performed in 3 cases confirming the diagnosis. All 4 were treated by conventional chemotherapy. No change was observed during follow up MRI in 3 patients, but in 1 child the orbital mass increased with involvement of the chiasm and optic tract. This patient with radiographic progression was age >10 and eventually received radiation. No child regained any vision in the affected eye and vision in the unaffected eye remained normal. Resection of the tumor was performed in 1 patient. Follow up ranges from 1-6 years and is continuing for these patients.

Conclusions:
In children with monocular severe visual loss and proptosis treatment has no effect on vision in the affected eye. Treatment provided no cosmetic benefit. The unaffected eye remained healthy whatever the treatment was. Chemotherapy, radiation and resection were of limited visual and cosmetic benefit in our cases and have attendant side effects. We need to try to achieve consensus regarding management of these cases.

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Acquired monocular nystagmus is a common initial presenting sign of a chiasmal glioma in young children

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Introduction:
To retrospectively investigate the incidence of nystagmus at presentation of chiasmatic-hypothalamic glioma (CHG) in children.

Methods:
Files of 35 patients with CHG followed-up in our Center from 2001-2013 and were reviewed for demographic, clinical, radiological findings and outcome. Thirteen patients with NF1 were excluded being diagnosed by routine MRI screening. Four others had incomplete records and one had only mild pre-chiasmatic thickening. The remaining 17 children, with measurable CHG, were included; 8 boys, 9 girls, age 3.2\textpm{}3.0 years old, mean follow-up of 8.0\textpm{}5.8 years. Seven underwent partial resection/biopsy; 14 were treated by chemotherapy: 5 with good radiographic response, 3 stable, and 6 deteriorated under treatment. The size of the CHG ranged from 10x6 to 62X29 mm.

Results:
Of the 17 patients with CHG, 12 were less than 2 years old at diagnosis. Eight of these 12 had monocular nystagmus at diagnosis. No child older than 2 years at diagnosis presented with monocular nystagmus. Of the 8 with monocular nystagmus, two had bilateral poor vision, 4 had unilateral visual loss and 2 had good vision (in one of whom the nystagmus was attributed to esotropia). The mass ranged in size from 25x25 to 45x59 mm. On completion of follow-up in these 8 children, both of those with good vision (2) deteriorated, the others already had bilateral (2) or monocular severe (4) visual loss. 5 had RAPD, 2 homonymous field defect, 3 had strabismus.

Conclusions:
Monocular nystagmus is a common presenting sign in CHG in children under 2 years old. This is a subtle clinical sign but has a very narrow differential diagnosis in this age group. The presence of monocular nystagmus in a young child should raise early suspicion of a chiasmatic tumor and prompt rapid referral for imaging studies. Visual prognosis in this age group is moderate to poor.

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DNMT1 mutations are associated with a complex phenotype including optic atrophy, deafness, narcolepsy with cataplexy and peripheral neuropathy.

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Introduction:
DNMT1 is a DNAmethyltransferase involved in maintenance of DNA methylation patterns. DNMT1 mutations have been linked to two distinct autosomal dominant neurodegenerative diseases: hereditary sensory and autonomic neuropathy with dementia and hearing loss type IE (HSAN IE) and autosomal dominant cerebellar ataxia, deafness and narcolepsy (ADCA-DN).

Methods:
We report on the extensive phenotypic characterization of five Italian patients from four unrelated families with HSAN IE (3 patients) and ADCA-DN (2 patients) phenotypes. Patients underwent genetic analysis of DNMT1 gene, ophthalmological studies including optical coherence tomography, neurophysiological tests investigating sleep, auditory functions, peripheral nervous system, brain MRI, cerebrospinal fluid hypocretin-1, Tau and 14-3-3 proteins measurement, skin, muscular and sural nerve biopsies.

Results:
Exome and direct sequencing studies disclosed two different point mutations affecting exon 21 of DNMT1 gene in both ADCA-DN patients, a novel heterozygous point mutation in exon 20 in two affected HSAN IE siblings, and a trinucleotide deletion in exon 20 in the latter HSAN IE patient. Phenotypic characterization pinpoint that ADCA-DN and HSAN IE represent two discrete clinical entities belonging to the same disease spectrum, with variable degree of overlap. Common symptoms and features observed in both phenotypes included optic neuropathy, previously not reported in HSAN IE, deafness, narcolepsy with or without cataplexy with low or normal cerebrospinal fluid hypocretin-1 respectively, large and small fibers polyneuropathy.

Conclusions:
Overall, the two syndromes share more characteristics than previously recognized. The clinical features are thought to originate from nuclear and possibly mitochondrial genomes dimethylation with involvement of multiple pathways. Optic atrophy is common to both and may be related to mitochondrial dysfunction. HSAN IE and ADCA-DN are two extreme phenotypic manifestations of a DNMT1 methylopathy.

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Acute Vision Loss and Choroidal Filling Delay in the Absence of Temporal Arteritis

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Introduction:
Fluorescein angiography (FA) demonstrating delayed or absent choroidal perfusion may serve to distinguish temporal arteritis (TA) from alternative diagnoses. We examined choroidal filling patterns and abnormalities in TA suspects who were ultimately found to have alternative diagnoses.

Methods:
A search of the medical record of two neuro-ophthalmologists (CMM and GVS) found 7 patients with acute vision loss concerning for TA and evidence of choroidal filling abnormalities on FA. The history, exam, acute phase reactant testing, and duration of follow-up were reviewed. The FA performed at the time of patient presentation was reviewed for choroidal and retinal filling abnormalities. Choroidal filling time was defined as the time span from when dye first appeared in the choroid to complete choroidal filling.

Results:
7 patients referred for possible TA (71.4% men, mean age 66.1 years) were identified for inclusion in the study. The mean choroidal filling time was 19.4 seconds with range from 8.95 to 55.5 seconds. 3 out of 7 patients demonstrated an elevated ESR or CRP. 5 out of 7 patients had temporal artery biopsies performed without pathological evidence for giant cell arteritis (GCA); the two other patients did not require a biopsy to rule out TA. 5 out of 7 patients were diagnosed with non-arteritic ischemic optic neuropathy, 1 with migraine with visual aura, and 1 with idiopathic chorioretinal vasospasm. Mean follow-up time was 38.8 months with range from 2.33 to 57.5 months. Patients showed no evidence of progression of symptoms.

Conclusions:
Prior literature suggests prolonged choroidal filling delay (greater than 20 seconds) is strongly predictive of TA. Two patients in our series demonstrated markedly delayed choroidal filling in the absence of TA. Delayed choroidal filling is suggestive of TA when profound and in the correct clinical context, but is not pathognomonic.

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Visual Outcome After Endoscopic Endonasal Surgery In Pediatric Craniopharyngioma

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Introduction:
Although the expanded endonasal approach (EEA) has been utilized for years in the treatment of craniopharyngioma, there is a paucity of literature regarding visual outcomes in children. This study details postoperative visual outcomes in this population.

Methods:
A retrospective chart review was performed on patients with an initial diagnosis of craniopharyngioma at age less than 20 years between July 1999 to May 2011. Visual acuity, color vision, visual field and optic nerve abnormalities were noted preoperatively, immediately postoperatively and during extended follow-up.

Results:
Fourteen patients were included in this series. Average preoperative acuity was logMAR 0.080 (Snellen equivalent 20/25) in the better eye and logMAR 0.362 (20/46) in the worse eye. At long-term follow-up, average postoperative visual acuity was logMAR 0.061 (20/23) in the better eye and logMAR 0.264 (20/36) in the worse eye. Average age at surgery was 8.9 years (range 1.9-16.4). Eight patients had documented decrease in either visual acuity or visual field prior to surgery, six of whom improved postoperatively, and two of whom maintained their preoperative function. Four were normal before surgery, and remained so after surgery. Two patients had only postoperative data available, and these were normal. Two CN III and 2 CN VI palsies occurred over the course of this series, 75% of which resolved completely (one oculomotor palsy recovered somewhat). Of the 11 patients who had preoperative visual field testing, 8 presented with field defects, most commonly a bitemporal hemianopsia. Of those patients, 5 returned to normal fields over long-term follow-up. Color vision was reduced at presentation in 7 patients; all were stable or improved postoperatively.

Conclusions:
In children, as in adults, EEA for most types of craniopharyngioma allows for excellent visual preservation and most often for improvement in visual function. No pediatric patient has lost vision as a result of surgery.

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Vasospastic Amaurosis Fugax Secondary to Ophthalmic Artery Vasospasm

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Introduction:
To describe what we believe to be the first case of amaurosis fugax secondary to ophthalmic artery vasospasm.

Methods:
A 49-year old female was referred for recurrent transient left eye visual loss. The episodes had started two months earlier and were near complete loss of vision lasting five minutes occurring between one and fifteen times per day. Review of systems was negative and past medical history included migraines and mitral valve prolapse. During the examination, the patient had an attack of visual loss leading to no light perception. Retinal photos were captured both before and after the episode. Retinal perfusion was sluggish as evidenced by tram-track appearance of arterioles with segmental constriction. A RAPD was present during this time. Following resolution of the attack, the optic disc and arterioles appeared normal. Autoimmune, hematologic and infectious workup were negative. Neuroimaging including CT angiogram, MRI orbits/brain, echocardiogram and transcranial Doppler were negative. OCT measured the RNFL at 97 microns in the right eye and 100 microns in the left eye. Humphrey visual fields showed scattered areas of depression inferiorly that resolved completely at follow up. A fluorescein angiogram was performed and the left eye displayed a prominent vertical watershed area in the choroidal circulation with prolonged filling suggesting a wider territory involvement than the central retinal artery raising suspicion for ophthalmic artery involvement.

Results:
A presumptive diagnosis of vasospastic amaurosis fugax was made and the patient was started on Nifedipine XL 60 mg once daily. Very shortly after, the patient reported her episodes of visual loss had completely resolved. She has no recurrence of her symptoms at follow up.

Conclusions:
Although vasospasm of the central retinal artery has been described, there are no descriptions of ophthalmic artery vasospasm. The condition responded well to the mainstay of calcium channel blockers used in vasospasm

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Progression of optic atrophy in traumatic optic neuropathy documented by optical coherence tomography (OCT) and fundus photography: Progression of retrograde neuronal degeneration

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Introduction:
We evaluated the progression of optic atrophy in traumatic optic neuropathy by retinal nerve fiber layer thinning on Optical Coherence Tomography (OCT) and by progression of optic disc pallor on fundus photography. This study is expected to provide useful information about progression of retrograde neuronal degeneration.

Methods:
Nine patients who were diagnosed with TON and whose visual acuity were below count finger were included. Retinal nerve fiber layer thickness (RNFL) was evaluated by spectral domain OCT and optic disc pallor evaluated by fundus photography serially. More than 10 μm of decrease in RNFL thickness in each quadrant was defined to be significant change. The appearance of optic disc pallor on fundus photography was defined by agreement of three ophthalmologists.

Results:
The significant decrease of RNFL thickness was apparent by 2 weeks after trauma in most of subjects (6/9), and by 4 weeks in all subjects. The mean detection time was 2.6±1.0 weeks. The mean decrease of RNFL thickness was 9.9% at this point. The disc pallor was apparent by 4 week in all subjects. The mean detection time was 3.3±1.0 weeks after trauma. Detection of optic atrophy was earlier by OCT compared to fundus photography in 44.4% (4/9), and it was same in 44.4% (4/9).

Conclusions:
In traumatic optic neuropathy, optic atrophy is apparent from 2 week to 4 weeks after trauma on OCT. OCT is considered to early detection modality in case of retrobulbar origin optic atrophy. We think this study provide useful information about progression of retrograde neuronal degeneration.

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Poster 235

Post-vaccination Bilateral Retrobulbar Optic Neuritis with Leptomeningeal Enhancement in Magnetic Resonance Imaging

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Introduction:
To report a case of idiopathic retrobulbar optic neuritis with leptomeningeal enhancement in Magnetic Resonance Imaging (MRI) after influenza vaccination

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

Results:
A 23-year-old woman presented with three days history of blurred vision and eye movement pain in the right. She was healthy, came from India recently and received influenza vaccination a few weeks ago. She had no history of febrile sickness, sick contact or exposure to animal or bugs. Neuro-ophthalmologic examination showed decreased visual acuity, color vision and relative afferent pupillary defect and optic disc swelling in the right eye. MRI brain and orbit with and without gadolinium showed enhancement of the right retrobulbar optic nerve and right hemispheric leptomeninges. Serologic studies showed increased ESR, CRP, mildly elevated IgG (112.7) and low vitamin D, however ANA, ANCA, Anti-Ro/La, C3/C4, aquaporin 4, vitamin B1, B6, B12, E were normal and Lyme, Syphilis, HIV, Bartonella, Brucella, Tuberculosis screen were negative. Cerebrospinal fluid study showed leukocytosis but normal range of protein, glucose, and negative CMV, EBV, HSV, VZV, mycobacterium, fungus culture. Chest computed tomography angiography was normal. PET scan showed no lesion outside brain and eye. MRI brain with and without gadolinium was repeated for involvement of the left eye and showed new abnormal enhancement of the left optic nerve. The patient underwent meningeal and brain biopsy which showed a reactive inflammatory process without evidence of neoplasm, granulomas, or vasculitis. Her vision improved on discharge without receiving systemic corticosteroid.

Conclusions:
It can be postulated as an immune mediated, idiopathic bilateral retrobulbar optic neuritis with leptomeningeal enhancement which developed after vaccination. The case showed involvement of bilateral optic nerves in asymmetric pattern and leptomeninges and started improving in a week after symptom occurrence without systemic corticosteroid.

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**Poster 236**

**ERG and OCT Findings in Herpes Zoster Optic Neuritis – A Case Report**

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**Introduction:**
This case report aims to describe retinal morphological and functional changes after unilateral Herpes Zoster optic neuritis (HZON) in a 66 year old, immunocompetent patient.

**Methods:**
Patient was evaluated 1 and 4 months after onset of symptoms. Examinations included color and red free (RF) retinography, fundus autofluorescence (FAF), spectral-domain optical coherence tomography (sOCT), (RF, FAF and sOCT: HRA Heidelberg Engineering). Visual acuity, pupilar reflex were tested, and full-field and multifocal electroretinography (ERG, and mfERG) were recorded according to ISCEV standards (Espion E2; Diagnosys LLC).

**Results:**
Fundus examination at 1 month revealed optic nerve diffusely paled. Evaluation of peripapillary retinal nerve fiber layer (RNFL) thickness with OCT showed nearly normal values (general thickness = 79 µm) at 1 month, but with massive loss of RNFL at 4 months (45 µm). In contrast, perimacular RNFL showed reduced at 1 month. Photopic full-field ERG demonstrates b-wave, 30-Hz flicker, and oscillatory potentials amplitude reduction. Of interest is the massive reduction observed for the photopic negative response (PhNR), at 1 month.

**Conclusions:**
Structural and functional retinal alterations might be already seen before RNFL loss, as soon as 1 month after initial clinical presentation in HZON.

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Aquaporin-4 Antibody-Positive Optic Neuritis In Thai Patients

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Introduction:
To determine the demographic data, clinical features, and short-term visual outcomes of Thai optic neuritis patients with seropositive aquaporin-4 (AQP4) antibody/NMO-IgG.

Methods:
The records of all patients with optic neuritis, seen during January 2010 to December 2012 at a tertiary care center in Bangkok, Thailand were reviewed. Eighteen patients with seropositive AQP4 antibody were included into this study.

Results:
Of 18 patients, 15 (83%) were female and 3 (17%) were male. Mean age at onset was 36 years, ranged from 15 to 57 years. Thirteen (72%) patients had bilateral involvement and 5 (28%) had unilateral involvement. In bilateral group, 10 (77%) had bilateral sequential visual loss and 3 (23%) had bilateral simultaneous visual loss. Of 31 eyes, 24 (77%) had severe visual loss (acuity less than 20/200) at initial presentation. All of patients were given with high dose intravenous methylprednisolone and subsequent long-term oral corticosteroid and immunosuppressive agents. Final visual acuity ranged from 20/20 to no light perception. Twenty-four eyes (77%) showed improvement of their visual acuity. Sixteen eyes (52%) achieved a final visual acuity of 20/40 or better. The visual acuity remained unchanged in 4 of 5 eyes presenting with no light perception. During the average 41-month follow-up, 4 patients developed transverse myelitis. The comparison between NMO and non-NMO optic neuritis will be discussed.

Conclusions:
AQP4 antibody-positive optic neuritis in Thai patients had poor presenting visual acuity with high rate of visual recovery after treatment. The initial visual acuity of no light perception suggests a poor visual outcome.

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A Case of Bilateral Optic Disc Edema and Periphlebitis Preceding Cerebral Vasculitis in a patient with Systemic Lupus Erythematosus

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Introduction:
Ophthalmic manifestations of Systemic Lupus Erythematosus (SLE) are common and diverse. Optic nerve involvement occurs in 1% of patients with SLE, most frequently presenting as optic neuritis or inflammatory optic neuropathy (1). We describe a case of bilateral optic disc edema and periphlebitis which preceded the onset of retinal and cerebral vasculitis.

Methods:
Case Report

Results:
A twenty-five year old woman with a history of SLE on low-dose Prednisone, Azathioprine, and Hydroxychloroquine presented with headaches and fevers for two months. She had preserved visual acuity (20/20 OU), normal colour vision, and no RAPD, but was found to have bilateral optic disc edema, peripapillary hemorrhages OD, and mildly enlarged blind spots. Investigations revealed an elevated CSF protein (547mg/L), opening pressure of 22cm H2O, unremarkable CT venogram and MRI, reduced C3 and C4, and elevated inflammatory markers. Fluorescein angiography confirmed late leakage from the right optic nerve and a focus of periphlebitis. She received treatment with intravenous Methyprednisolone followed by tapering oral steroids. One week later, she presented with paresthesias in both legs and urinary urgency and received a second course of IV Methylprednisolone. Shortly after initiating treatment, she noted a sudden reduction in vision in her right eye and was discovered to have a right RAPD, and retinal vasculitis with cotton-wool spots, and retinal hemorrhages within the posterior pole OD. One day later, she developed right-sided arm and leg weakness and slurred speech. MRI demonstrated an infarct of the left cerebral peduncle consistent with cerebral vasculitis.

Conclusions:
We describe a patient with SLE who presented with bilateral optic disc edema, peripapillary hemorrhages, and periphlebitis suggestive of optic disc vasculitis. Additional episodes of retinal and cerebral ischemia suggest that patients with SLE who are found to have optic nerve involvement should be followed closely for neurologic sequelae of vasculitis.

References:

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Orbital Magnetic Resonance Imaging at 3.0 Tesla in a Patient with Toxoplasma Optic Papillitis and Neuroretinitis

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**Introduction:**
Toxoplasma optic papillitis is a rare cause of optic neuropathy reported in immunocompromised and immunocompetent patients. High resolution MRI scanning performed early can be pivotal in differentiating NAION from inflammatory, infectious and demyelinating optic neuropathies.

**Methods:**
Case Report.

**Results:**
We report a 52-year-old male who presents with acute optic neuropathy. There were multiple vascular risk factors including diabetes, hypertension, and hyper-homocysteinemia and non-prescription drug use for erectile dysfunction. The patient has a history of progressive visual loss OS, associated with low-grade orbital pain. Eight weeks prior to the onset of visual loss, the patient had a diarrheal illness lasting 6 weeks, accompanied by 20-pound weight loss. His examination was 20/20 OD and 20/60-2 OS. Fundoscopic examination showed hyperemic disc edema. Humphrey Visual Field OS showed dense inferior and superonasal altitudinal visual field defects. Optical coherence tomography showed mean retinal nerve fiber layer thickness OS at 483 microns. Initially it was our impression that the patient has NAION OS. Brain MRI (3.0 Tesla) did not show any white matter lesions indicative of demyelinating disease or microvascular ischemic changes. Orbital MRI showed prominent enlargement and focal intense gadolinium enhancement of the left optic nerve head consistent with optic papillitis. Diffusion-weighted imaging showed corresponding restricted diffusion of the optic nerve head. Subsequently, his follow up examination showed a new macular star OS. Laboratory studies revealed normal ESR and ACE levels. HIV, antiphospholipid antibody, Lyme disease, and Bartonella tests were normal. Additional laboratory studies were performed including Toxoplasma IgG titer which was markedly elevated at >500 IU/ml (normal <0.9 IU/ml).

**Conclusions:**
This patient presented with features typical of NAION. However, due to the robust enhancement of the optic papilla and development of a macular star, we were able to establish a diagnosis of toxoplasma optic papillitis and neuroretinitis.

**References:**

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Laser-induced Optic Neuropathy as A Model to Study Neuro-protection

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Introduction:
Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) is believed to result from insufficient blood flow to the optic nerve head. However, the precise mechanism of ischemia remains unclear. A successful experimental animal model would help us better understand the pathophysiology of the disease. The purpose of our study is to develop a novel version of the photodynamic model of rodent optic neuropathy currently used, which will give us results with high reproducibility.

Methods:
Laser-induced optic neuropathy was induced in Brown Norway rats by intraperitoneal injection of mesoporphyrin IX, followed by application of 532nm diode-laser. Fluorescein angiography (FA), spectral domain optical coherence tomography (SD-OCT) and visual evoked potentials (VEP) were performed at different time points. Immunohistochemistry was used to monitor apoptotic cell death (TUNEL assay), cell survival (Neuronal Nuclei antigen) and macrophage infiltration (CD68+ cells), while ELISA was performed to determine changes in inflammatory cytokine levels.

Results:
FA showed early disc staining and late leakage, while SD-OCT allowed visualization of optic nerve edema and accumulation of subretinal fluid. The TUNEL+ cells were significantly elevated from the first day after laser application (p <0.01) and peaked one week later (p <0.01). Similarly, increased recruitment of CD68+ cells observed on day 7 (p = 0.014) was indicative of macrophage infiltration, while the inflammatory cytokines examined were upregulated at different timepoints. Finally, the VEPs were suggestive of the functional impairment observed after induction of optic neuropathy.

Conclusions:
Photodynamic therapy with Mesoporphyrin IX leads to macroscopic, histologic and physiologic findings similar to those seen in other rodent models of optic neuropathy. The longer half-life of Mesoporphyrin IX and the ease of intraperitoneal injections result in highly reproducible outcomes. Improving the consistency of an experimental model can lead to increased understanding of the pathophysiology of the disorder examined and more accurate detection of changes induced by neuroprotective agents.

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Optic Nerve Head Meningocele

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Introduction:
Optic nerve head meningocele (ONHM) also known as dural ectasia of the optic nerve sheath is rare. It is reported in patients with neurofibromatosis type 1 [1], but can also be idiopathic. ONHM can cause optic nerve dysfunction [2], cystoid macular edema, acquired hyperopia and choroidal folds [3, 4].

Methods:
An 82 year old male patient was referred for a pressure-like feeling and blurring of vision in the left eye of one year duration. On examination best corrected visual acuity was 20/20 OU and color vision 13/13 Ishihara plates OU. There was a relative afferent pupillary defect in the left eye. The left optic disc appeared hyperemic and mildly elevated with indistinct margins. The blood vessels over the left disc were not obscured and there were no hemorrhages or exudates. There was a subtle macular edema, a few choroidal folds and tortuosity of the retinal vessels in the left eye. The right optic disc was normal. 24-2 threshold Humphrey visual fields were normal. There were no skin lesions suggestive of neurofibromatosis.

Results:
MRI of the brain and orbits showed enlarged left optic nerve sheath with prominence of the CSF around the normal appearing optic nerve without evidence of orbital masses. CSF opening pressure was normal and so were the constituents of the CSF. Based on these findings a diagnosis of ONHM was made.

Conclusions:
The combination of macular edema, chorioretinal folds, and optic nerve dysfunction can be seen in patients with ONHM. The natural course of this entity is not clearly known due to the rarity of the condition, but progressive visual loss can happen [2] which underscores the importance on early recognition. Carbonic anhydrase inhibitor has been tried in ONHM [5]. In severe cases, optic nerve decompression may halt the progression of the visual loss [5].

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
The Case of the Vanishing Optic Disc Capillary Hemangioma

Ahmara G. Ross¹, Tarek A Shazly¹, Hazem Samy¹, Gabrielle R Bonhomme¹

¹Dept. of Ophthalmology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA, ²UF Health Eye Center, Gainesville, FL, USA

Introduction:
Capillary hemangiomas of the optic disc are endophytic or exophytic vascular hamartomas that may arise from the optic nerve. These congenital hereditary lesions may be associated with central nervous system diseases such as von Hippel–Lindau disease (VHL).

Methods:
Case report and review of literature.

Results:
A 71-year-old female with past medical history of hypertension presented in October of 2008 with an asymptomatic right optic nerve mass. Her visual acuity refracted to 20/20 in each eye. On examination, her disc was large, sloped with a cup/disc ratio of 0.8, and a small, pink, elevated, vascular mass arising from the nasal optic nerve rim, partially obscuring the cup. She denied any visual or neurological symptoms. Her optical coherence tomography (OCT) demonstrated normal retinal nerve fiber layer thickness bilaterally. Automated visual field testing detected a subtle right nasal field defect. Documentary disc photos were obtained. Fluorescein angiography exhibited normal choroidal and arterial filling without leakage from the mass, and late staining of the nasal side of the mass. Brain Magnetic Resonance Imaging (MRI) was normal, other than a small, left temporal horn cyst. The diagnosis of optic disc capillary hemangioma was made. She has been examined at regular intervals for 5 years with stable clinical findings, visual fields, and OCT scans. Given her prominent cupping, she has been monitored by Glaucoma service as well, with stable IOP and optic nerve exam. In 2013, on routine follow up, her hemangioma became nearly indistinguishable from the disc rim, without any detectable vascular patterns. She denies any changes in her medications (atenolol, valsartan and spironolactone) since 2008.

Conclusions:
Review of the literature reveals only 3 cases reporting spontaneous regression of optic disc capillary hemangioma. The mechanism and etiology of the tumour regression remains unknown.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Poster 243

Tracking the Course of Giant Cell Arteritis: Symptoms or Labs?

Harris Sultan¹, Chia-Ling Kuo, David Waitzman

University of Connecticut Health Center, Farmington, CT, USA

Introduction:
The standard of treatment for giant cell arteritis (GCA) consists of IV steroids followed by one year of oral steroids. The literature asserts that 30-50% of patients will relapse in disease during the course of their steroid taper, at which point the patient’s steroid dose would be increased and symptoms or lab values will resolve. The rheumatologic and neuro-ophthalmologic literature differ with regards to the treatment for giant cell arteritis. Rheumatologists consider a relapse to be symptom-based, while neuro-ophthalmologists use laboratory values to define relapse. This study aims to reconcile these differences.

Methods:
Retrospective repeated measures-analysis was performed on 17 biopsy positive GCA-patients (28 eyes) for progression of visual loss. Patient symptoms included visual loss, headache, jaw claudication, blurred visions, diplopia, temporal artery tenderness, and evidence of polymyalgia rheumatica (PMR). Laboratory values were erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The visual acuity is presented as the LogMar equivalent of Snellen and the visual fields were tracked using the Pattern Standard Deviation (PSD).

Results:
Twenty-eight eyes were followed for an average of 161 weeks. One-hundred percent of patients relapsed in disease, presenting with the aforementioned symptoms or elevations in laboratory values. Mean time to first relapse was 36 weeks with an average dose of prednisone at 12mg. Linear mixed effects models were used to correlate symptoms and laboratory values with visual outcomes. In one set of eyes, patient labs tracked with LogMar values (p=0.002) while in the contralateral eye, patient symptoms tracked with the PSD values (p=0.02). When we reversed the eyes, the LogMar values trended with labs, and the PSD values with symptoms, but did not reach statistical significance (p=0.078, p=0.19, respectively).

Conclusions:
Our data suggests that both laboratory values AND patient symptoms should be utilized to decide the course and duration of treatment for individual patients.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Traumatic optic neuropathy by pellet. Three cases.

Thierry David¹², Edel M. Finke¹², Pierre L. Sustronck¹²

¹Centre Hospitalier Universitaire de Guadeloupe, Pointe-à-Pitre, Guadeloupe, ²UFR médecine Antilles-Guyane, Pointe-à-Pitre, Guadeloupe

Introduction:
The optic nerve wounds by shot are rare in the eye trauma.

Methods:
We report three cases of patients who had presented severe ocular wounds with optic nerve injuries. The first case is about a 44 year-old man who had received shoots of hunting gun in both eyes. The second and the third cases are about a 36 year-old man and a 16 year-old girl who had received a gunshot in their left eyes. At the first examination, the patients could only hardly see bright in the touched eyes. In emergency the perforans wounds were stiched for these three patients.

Results:
The eye tomography showed for the first patient an explosion of the right eye, and air into the left eye. For the three patients, there were also a shot in every optic nerve canal. The echography of eyes found a bruise of the posterior pole in two eyes and a retinal detachment in the two others eyes. The visual evoked potential of the eyes with shot in the optic nerve canal were flat and the latency of the wave P 100 increased as well that the amplitude of it decreased. For every patient an intravenous antibiotic therapy and bolus of one gram per day for three days of methylprednisolone were realized. A retinal surgery was performed for patients who had retinal breaks associated with retinal detachment. No improvement of the visual acuity was observed at the end of all treatments. All the affected eyes presented at the end of care a negative bright perception.

Conclusions:
Traumatic optic neuropathy by pellet is rare and its prognosis is unmistakably poor. No treatment gave evidence of its efficiency for a visual recovery even a small one.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Chiasm glioblastoma with multifocal spread

J. Alexander Fraser¹,², Christopher J. Watling¹, Lee Cyn Ang³

¹Dept. of Clinical Neurological Sciences (Neurology), Western University, London, ON, Canada, ²Dept. of Ophthalmology, Western University, London, ON, Canada, ³Dept. of Pathology, Western University, London, ON, Canada

Introduction:
Isolated enhancing chiasm mass lesions pose a diagnostic challenge. An aggressive diagnostic approach is justified when an aggressive disease process is suspected.

Methods:
Review of a case of optic chiasm glioblastoma with multifocal spread

Results:
A 78 year old woman presented twenty days after the onset of rapidly progressive painless vision loss in the right eye. Past medical history, medications, social history and family history were noncontributory. Her visual acuity was count fingers OD and 20/30 OS. There was a dense right RAPD. Dilated funduscopic examination was normal. The remainder of the clinical examination was unremarkable. Visual field analysis showed a dense right junctional scotoma. An MRI showed enlargement and enhancement of the optic chiasm but no other intracranial abnormality of note. The differential diagnosis included lymphoma, glioblastoma, sarcoidosis, tuberculosis, and Langerhans histiocytosis. Routine bloodwork and CSF analysis were unremarkable. CT chest/abdomen/pelvis was unremarkable. We proposed an urgent chiasm biopsy, but the patient declined. In the absence of more directed treatment, she was therefore started on empiric dexamethasone, which stabilized her vision for several weeks. Her CSF ACE, AFB, mycobacterium culture, C&S, and cytology ultimately returned negative. Gallium scan was normal. Serum ACE was negative. Serial MRIs showed only minimal improvement in chiasm enhancement and bulk. 2.5 months later, she developed new brain lesions. Biopsy confirmed a diagnosis of glioblastoma. She was treated with radiotherapy and temozolomide, but ultimately died of multifocal glioblastoma several months later.

Conclusions:
Chiasm glioblastoma can mimic much more common inflammatory lesions on MRI. It is extremely aggressive, and must be diagnosed and treated before it invades adjacent structures (hypothalamus, brain, third ventricle). Progression is typically inexorable, however, with loss of all vision in a matter of weeks and death within 6-12 months. Early diagnosis via biopsy may delay this morbidity and mortality.

References:

Financial Disclosures: The authors had no disclosures.

Grant Support: None.
Although initially designed to provide a structural biomarker for “intra-ocular diseases” such as diabetic retinopathy, macular degeneration, and glaucoma, optical coherence tomography [OCT] has undergone exponential growth in neuro-ophthalmology for clinical evaluations, single center clinical research projects, and multi-centered national and international clinical trials. How has OCT found its way into neuro-ophthalmology?

Starting with a brief review of the history of this technology and the status of the current devices, this symposium will: 1) Provide practical information in a didactic format so that practicing neuro-ophthalmologists can understand normal OCT structures; 2) Differentiate papilledema from optic disc drusen, distinguish maculopathy from optic neuropathy; and 3) Be able to evaluate the immense amount of data generated by OCT for clinical trials and how to interpret the results, clinically and statistically. The “pipeline” for future optic nerve and retinal imaging technologies will also be discussed.

Finally, a series of cases will be presented in a CPC format in which OCT provided critical data for the diagnosis and management of complex clinical situations.

This course is designed to procure the following desirable physician attributes: Patient care, medical knowledge, practice based learning and improvement.
Idiopathic intracranial hypertension (IIH) is a disease of overweight women in the childbearing years, characterized by elevated intracranial pressure of unknown cause. We have completed enrollment and six month follow-up for the NORDIC IIH Treatment Trial (IIHTT), a multicenter, randomized, double-masked, placebo-controlled study designed to determine if acetazolamide can reduce or reverse visual loss in IIH subjects with mild visual loss that are enrolled in a low sodium, weight-loss program. A secondary objective is to identify genetic risk factors for IIH by comparing IIH subjects and controls. We will be performing primary outcome analyses in summer 2013. We will report the methods, analysis of baseline data and the sixth month primary and secondary outcomes.

At the conclusion of this symposium, the attendees should be able to: 1) Understand the methods of the IIHTT; 2) Understand the subject characteristics at baseline; and 3) Learn the primary and secondary outcomes and how to apply these outcomes to their practice.

This course is designed to procure the following desirable physician attributes: patient care; medical knowledge.
Bilateral cecocentral scotomas are distinctive visual field defects seen in remarkably few optic neuropathies. The most common in this group include Leber hereditary optic neuropathy, toxic optic neuropathies, and vitamin B12 deficiency, raising the question of what they have in common, what is their shared pathophysiology, and how does that pathophysiology lead to the distinctive visual field defect. Evidence from the bench and the bedside will be presented in an attempt to answer these questions, and in the process suggest a mechanism to explain some of the peculiarities of the onset, progression, and reversibility of one of the group.

At the conclusion of this program, participants should be able to: 1) Improve the understanding of diseases associated with cecocentral scotomas; 2) Gain an appreciation of mechanisms causing death of retinal ganglion cells in optic neuropathies; and 3) Learn some of the causes of toxic optic neuropathies.

This course is designed to procure the following desirable physician attributes: medical knowledge; employ evidence-based practice.

Hypothesis-driven clinical trials often arise from clinical observations. Whether planning to report your own case series or reading reports in the literature, certain clinical research principles must be considered to avoid making potentially erroneous conclusions. Although the topics will be broadly applicable to all types of clinical research, we will primarily discuss common issues in the concept, design, analysis, and interpretation of observational studies. The course is directed toward practicing physicians in academic medicine and private practice, as well as trainees, with limited or no background/experience in clinical research. Examples from the literature will be used.

At the conclusion of this program, participants should be able to: 1) Determine whether retrospective observations merit reporting and further investigation; 2) Design a basic prospective observational study; 3) Identify different types of observational studies; and 4) Understand basic statistical concepts in observational research: a. Name common sources of bias and confounding in clinical research studies b. Identify the correct statistical test(s) for a given analysis c. Explain randomness and the importance of using measures of variation d. Distinguish standard error from standard deviation e. Differentiate description, inference, and prediction f. Define a p-value and understand its (un)importance.
1:30 p.m. – 4:30 p.m.  Smartphones and Gadgets: How to Practice Neuro-Ophthalmology

Anywhere in the 21st Century [3 CME]

Presenters: Y. Joyce Liao, MD, PhD and Thomas Hwang, MD, PhD

Smartphones and portable electronic devices have become ubiquitous and are emerging as the latest tools in the practice of medicine. In this symposium, we will describe ways we can incorporate portable devices into everyday clinical practice with special focus on:

1) Taking high quality anterior and posterior segment photographs using smartphones and inexpensive adapters to enhance lighting and magnification;
2) Building your own eye movement and pupil recording set-up;
3) Internet resources for vision assessment and telemedicine, including secure exchange and storage of images and videos;
4) A round table discussion on the use of portable devices to enhance clinical care and education and the potential issues of incorporating portable devices in clinical practice.

At the conclusion of this program, participants should be able to:

1) Learn about the basic techniques and assistive devices to take good images and videos using portable devices;
2) Understand the internet resources for neuro-ophthalmic examination and to exchange information in a secured fashion;
3) Recognize the benefits and challenges of telemedicine for patients and clinicians.

4:30 p.m. – 5:30 p.m.  Abstract Committee Meeting

Board Room

4:30 p.m. – 5:30 p.m.  International Relations Committee Meeting

Parrot

6:45 p.m. – 12:00 a.m.  Annual NANOS Reception and Banquet

Event is casual. Please wear comfortable shoes as the banquet will take place in the rainforest.

Buses depart El Yunque Foyer at 6:45 p.m. – Buses will return as they fill. Due to the location and minimal parking, driving separately is strongly discouraged.
**OCT TECHNOLOGIES: WHICH MACHINE DO YOU WANT TO OWN?**

Fiona Costello, MD, FRCP
*University of Calgary
Calgary, CA*

**LEARNING OBJECTIVES**

1. To discuss the various spectral-domain optical coherence tomography (SD-OCT) machines and techniques currently commercially available.
2. To review emerging advances in SD-OCT that may impact the management of ophthalmic and neuro-ophthalmic disorders in the future.

**CME QUESTIONS**

1. Name one advantage of SD-OCT over prior time domain OCT (TD-OCT) technology.
2. Name three important categories to consider when deciding which SD-OCT machine you want to own.

**KEYWORDS**

1. Optical coherence tomography
2. Spectral domain
3. Retinal nerve fiber layer
4. Ganglion cell layer
5. Emerging techniques

**INTRODUCTION**

Optical coherence tomography (OCT) has evolved over the past decade to become one of the most important ancillary tests in ophthalmic practice. This non-invasive ocular imaging technique provides high-resolution, cross-sectional images of the retinal nerve fiber layer (RNFL), macular volume (MV), ganglion cell layer (GCL), and optic nerve head [1, 2]. With OCT, we can learn much about axonal-neuronal integrity in the anterior aspect of the afferent visual pathway. Spectral domain OCT (SD-OCT) techniques provide an axial resolution in the range of 5 to 7 microns (μm), thus images derived from SD-OCT have been likened to an in-vivo ‘optical biopsy’ of the retina [1]. Optical coherence tomography uses light from a broadband source, which is divided into a reference and a sample beam, to obtain a reflectivity versus depth profile of the retina [1, 2]. The light waves are backscattered from the retina to interfere with the reference beam, and this interference pattern is used to measure light echoes [1, 2]. Initially, time-domain detection (TD-OCT) was the technique employed by commercially available OCT systems. Previous TD-OCT systems featured scan rates of 400 A-scans per second with an axial resolution of approximately 8 to 10μm in tissue [1]. In 2006, the first commercially available spectral domain (also known as Fourier domain) OCT (SD-OCT) system was introduced [1]. In contrast to TD-OCT, SD-OCT employs detection of the light echoes simultaneously by measuring the interference spectrum, using an interferometer with a high-speed spectrometer. This technique provides scan rates of 20,000–52,000 A-scans per second to achieve a resolution of 5 to 7μm [1]. This is approximately 50-fold faster than the previous generations of TD-OCT [2].

**OPTICAL COHERENCE TOMOGRAPHY—WHAT IS OUT THERE?**

Currently, there are several different SD-OCT machines available on the market (Table 1). The decision regarding which machine to buy should take into account a variety of factors including: the main purpose of the machine (research versus clinical), the setting (neuro-ophthalmic versus general ophthalmic practice), cost, space, and the ability to build upon existing platforms with future software developments. The cautious consumer should also consider hardware, image quality, and software issues.

**Hardware:** When choosing a SD-OCT for purchase there are several hardware specifications to keep in mind including the light source, the speed of the image sensor, and the instrument’s non-OCT imaging capabilities [3]. The quality of the axial resolution is determined by the light source in the OCT machine, such that broader bandwidth sources produce better results. Recent progress in the field of broadband super-luminescent diodes has made high resolution imaging (5 to 7μm) with SD-OCT more affordable. As advanced super-luminescent diodes and laser technologies become cheaper, commercial ultra-high resolution (approximating 2 to 3μm) machines will emerge as options to consider [3].

In addition to axial resolution, image acquisition speed is another important hardware specification to keep in mind.
Some SD-OCT machines enable 3D retinal reconstructions. The fast scanning speeds that facilitate this feature should translate into more efficient patient flow, improved patient comfort, reduced opportunity for disruptive eye movements, and increased opportunities for the machine to control noise [3]. That said, enhanced speed may affect image quality, particularly in patients with anterior segment abnormalities. Therefore, when evaluating the performance of a given OCT machine, it is important to think above and beyond the demonstration images, and review the quality of the more rapidly acquired 3D-OCT images, which will better reflect the data that will be collected in a routine clinical setting [3].

Several commercially available OCT instruments allow for “upgrade” options, such as the line-scanning laser ophthalmoscope, fluorescein angiography, indocyanine green, auto-fluorescence, and microperimetry. These “combo” packages present potential advantages and disadvantages to the consumer. More specifically, the upgraded features may allow comparisons between OCT and non-OCT images that may assist diagnostic or management decision-making. Yet, combining too many critical functions into a single machine can become problematic if the device breaks down, or if patients requiring only OCT scans are delayed by patients receiving time-consuming angiography and/or microperimetry studies [3].

Other important hardware factors to consider include the ergonomics of the device as well as the service and support reputation of the manufacturer. Instruments that are difficult to use or repair may introduce more problems than advantages to your practice.

**Image Quality:** Spectral domain OCT machines have a “sweet spot” of maximum sensitivity, and by extension, image quality that resides either on the vitreous or the choroid side of the retina [3]. For this reason, prior to capture, the operator using the machine may need to select which tissue to image with higher sensitivity (inner retina or choroid) and then keep the patient’s eye in a position that maximizes this signal. Some SD-OCT machines may be more susceptible than prior TD-OCT devices to disruptions caused by media opacities and corneal disease. In these situations, increased “noise” may obscure subtle features including sub-retinal fluid and make it difficult to distinguish pathological findings from normal tissue structures. It is therefore important to look for devices that consistently produce a brighter signal in the outer retinal layers as compared to the vitreous. Since grayscale images may hide the “speckles” that signify vitreous tissue and mask noise problems, pseudo-color images should be employed to assess the quality of the vitreous signal and to expose potential problems that can be masked with grayscale images [3].

**Software:** The large datasets acquired by SD-OCT instruments allow for several capabilities. Dense 3D-OCT scans produce maps that can be aligned with non-OCT imaging modalities such as color fundus imaging. Any well-designed SD-OCT instrument should include point-to-point registration capabilities that allow users to identify areas either in the OCT or non-OCT image and see the corresponding point of interest [3]. With proper software, the same point in the fundus can be compared between visits despite issues with fixation, thus improving the reproducibility of longitudinal clinical measurements [3]. Yet, all of these advanced capabilities come at a price. In order for an SD-OCT device to perform effective inter-visit alignment or produce good 3D reconstructions, it must account for eye movements that occur during image acquisition. Thankfully, effective eye-tracking software can help correct this problem. Therefore, when evaluating SD-OCT machines, it is wise to evaluate 3D reconstructions and inter-visit comparisons to demonstrate registration problems. This requires ergonomic software that can be easily operated by the clinic staff. Furthermore, it would be optimal for SD-OCT machines to have the capacity to integrate robust network support software, so that large files can be transferred efficiently and rapidly across local networks directly to patient-care areas [3]. Finally, clinicians interested in using SD-OCT for optic neuropathy monitoring or screening should select an instrument that includes support for large databases.

In summary, when deciding which SD-OCT machine might best suit your practice, it would be best to look for high-resolution 3D-OCT devices with rapid scanning speeds and good accessory imaging, which are manufactured by a company with a reputation for service and support. When considering software features, look for a machine with an easy-to-use, ergonomic software interface, integrated network support, and large normative databases. Ideally, the device you choose should correct for eye movements during OCT acquisition to improve the accuracy of inter-visit and inter-modality image alignment. Finally, if engaged in multi-centre research studies it is noteworthy that measurements and protocols are not interchangeable between technologies. Therefore, for the purposes of multi-centre research studies the same OCT models with common software should be utilized for longitudinal data collection.
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<th>Machine</th>
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<th>Product Description</th>
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<tr>
<td>CIRRUS™ HD-OCT 5000 and 500</td>
<td>Carl Zeiss Meditec</td>
<td>The Cirrus™ HD-OCT 5000 is described as “the clinical powerhouse” for an advanced care practice, whereas the 500 model is an “essential” technology for a comprehensive ophthalmic practice.</td>
<td>FCirrus™ compares retinal measurements from prior visits to recent visits to generate a thickness map, aided by a retinal tracking system (FastTrac™). This feature helps to reduce eye motion artifacts, provide precise macular thickness measurements, and enable advanced retinal pigment epithelial (RPE) analysis. Glaucoma applications include retinal nerve fiber layer (RNFL), optic nerve head (ONH), ganglion layer, and angle analyses. Specialized software (Guided Progression Analysis™) makes it possible to determine change for RNFL and optic nerve head parameters. State of the art technology ensures the Early Treatment Diabetic Retinopathy Study (ETDRS) and ganglion cell + inner plexiform layer measurements are centered on the fovea (FoveaFinder™). The RNFL, macular thickness, and optic disc measurements have been validated, showing excellent repeatability and accurate segmentation. The ONH algorithm is designed to measure the neuro-retinal rim while accounting for tilted discs, disruptions to the retinal pigment epithelium, and other pathology. There is an automatic means of centering the 3.4 mm diameter peripapillary RNFL calculation (AutoCenter™), which is not operator dependent. The Cirrus™ HD-OCT technology allows expanded capabilities to share data between instruments and review stations.</td>
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SPECTRALIS® HRA+OCT

Heidelberg Engineering

The platform includes multiple models at various price points. The so-called “workhorse” is the SPECTRALIS® OCT, an economical, easy-to-use version with one-touch preset scan patterns. Additional models built upon this base platform allow clinicians to tailor a system to the evolving needs of their practice. Using an upgradeable platform approach SPECTRALIS® has enhanced the role of SD-OCT by integrating it with confocal scanning laser ophthalmoscopy (cSLO). Different SPECTRALIS® models include: OCT, OCTPlus with Multicolor™, HRA, FA+OCT, HRA + OCT, OCTPlus with BluePeak™, OCT with BluePeak™.

The advantages of cSLO over traditional fundus photography include: improved image quality, small depth of focus, suppression of scattered light, increased patient comfort (less bright light exposure), 3D imaging capability, video capability, and effective imaging of patients who fail to dilate well. The specialized (TruTrack™) eye tracking system reduces eye motion artifact and ensures point-to-point correlations between OCT and fundus images without post-processing of the data. This technology (TruTrack™) also minimizes operator variability in follow-up scans (AutoRescan™) adding precision to measuring changes in RNFL values over time. The Heidelberg Noise Reduction™ option provides enhanced image detail. The non-invasive blue laser autofluorescence (BluePeak™) imaging takes advantage of the natural fluorescent properties of lipofuscin to capture fundus auto-fluorescence (FAF) images, providing structural and metabolic information about the retina. Deeper retinal structures are imaged with the Enhanced Depth Imaging (EDI) feature, which provides detailed views of choroid and lamina cribrosa. The SPECTRALIS® Anterior Segment Module offers image acquisition of the cornea, sclera and the anterior chamber angle, providing a detailed view of the anterior segment. Infrared Reflectance (IR) imaging provides a variant of fundus photography that uses infrared light rather than white light for illumination. This provides several advantages including: reduced light exposure and decreased patient sensitivity, improved penetration through unclear media, and enhanced visualization of epiretinal membranes and cystoid macular edema compared to fundus photography and red-free imaging. Foveal-to-Disc Alignment technology (FoDi™) tracks and aligns circle scans to improve the accuracy of RNFL scans, by overcoming effects of head tilt and eye rotation. The Region Finder™ software allows the instrument to quantify and track dark areas on BluePeak images. SPECTRALIS® MultiColor™ imaging delivers high contrast, detailed images even in difficult patients including those with cataracts or nystagmus. SPECTRALIS® confocal scanning laser ophthalmoscope (cSLO) with Blue Reflectance imaging uses blue light to illuminate the retina. This wavelength accentuates the visibility of blood vessels and enhances the contrast of certain structures on the surface of the retina, making them easier to see relative to white light illuminated images. The SPECTRALIS® cSLO technology enhances fluorescein angiography (FA) by increasing the signal-to-noise ratio and blocking out-of-focus and scattered light. SPECTRALIS® FA can be combined with indocyanine green angiography (ICGA) to view retinal and choroidal blood flow. The Widefield imaging feature allows a broader view of the retina beyond the macula. The Non-Contact Ultra-Widefield Angiography module offers the widest view of the retina with a one shot view, making it possible to detect peripheral changes of interest. This feature can be combined with fluorescein and indocyanine green techniques, either individually or together. The machines use the Heidelberg Eye Explorer (HEYEX™) software platform and database to store patient information and images. Image acquisition and analysis is controlled by HEYEX™ plug-in software modules that are specific to each device. Network connections between devices allow access to the common HEYEX™ database.
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<th>Device</th>
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<tr>
<td>iVue ® SD-OCT</td>
<td>Optovue, Inc</td>
<td>The iVue® is described as the most compact SD-OCT system.</td>
<td>This machine is designed to be very easy and fast, and includes a convenient footswitch control and touch screen on the scanner head. Anterior Segment imaging provides visualization and measurement of the angle and the cornea. Corneal thickness is offered as a full 6x6mm pachymetry map with minimum thickness marker, in addition to a user-defined corneal point thickness. Additional features include: ganglion layer thickness imaging with ganglion cell complex upgrade, and 3D “En Face” analysis upgrade. The iVue® SD-OCT is available with a 21.5 inch screen or with the optional laptop configuration for maximum portability. Color-coded retinal thickness mapping enables segmenting of the inner, outer, and full retina with over-layered ETDRS thickness values.</td>
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<tr>
<td>3D OCT 2000</td>
<td>Topcon Medical Systems</td>
<td>This is the first SD-OCT to incorporate a high resolution fundus camera and a color touch screen display in a compact, space saving design.</td>
<td>It is possible to obtain dynamic viewing of data, with 3D, 2D, and fundus images simultaneously (FastMap™ software). Moreover, users can determine the location of the OCT image within the fundus image (Pin-Point™ Registration). Serial examinations may be viewed and compared. The EyeRoute® Image Management System provides access to images.</td>
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<tr>
<td>OCT/SLO Combination Imaging System</td>
<td>Optos, Inc.</td>
<td>The OCT SLO system combines SD OCT imaging with a confocal scanning laser ophthalmoscope (SLO) in one instrument</td>
<td>The confocal scanning laser ophthalmoscope provides high-resolution images and retinal tracking before, during, and after the OCT scan. The SLO “Lock and Track” function ensures that follow-up scans are obtained from the same location in an operator independent fashion. The SLO confocal fundus image and the OCT image are generated through the same optics and are pixel-to-pixel correspondent, ensuring precise OCT registration. Furthermore, 3D topographies can be aligned to the SLO image to compensate for rotation and shift. The “Auto – Compare” features allows automatic comparison of multiple topographic maps taken over time including retinal thickness. With Optos’ “Viewer Software” any clinician can view the system database from a remote computer or laptop, including OCT scans, 3D topography scans, RNFL scans, and optic nerve views.</td>
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<tr>
<td>SD-OCT Copernicus</td>
<td>Optopol/Canon Incorporated</td>
<td>SOCT Copernicus HR is a SD-OCT with Ultrahigh resolution (3 microns).</td>
<td>Ultrahigh scanning speed (52000 A scans/sec) shortens data collecting and improves the comfort of examination for both patient and operator. The SOCT Copernicus HR Glaucoma Module allows for the detection and management of glaucoma. The tool tracks progression with time. Software features include retina and RNFL volume maps, optic nerve head analysis, 3D visualization, and traction visualization. The Disc Damage Likelihood Scale (DDLS) provides a novel way to analyze the optic nerve. Instead of a cup/disc (c/d) ratio, a rim/disc (r/d) ratio and the nerve size is measured. This method is reported to be superior than any other reporting measure because it eliminates the effects of disc size, and provides more weightage to the neuroretinal rim damage. The anterior segment module allows cornea and anterior imaging with a resolution of 3 microns. The new advanced 3D module allows visualization of 3D reconstructions. SOCT images can be stored in the central area and be accessible from different locations.</td>
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CONSIDERING THE BELLS AND WHISTLES:

When purchasing a SD-OCT machine there are several specific software features to weigh in the balance so that you will get the “best bang for your buck” from your investment:

Retinal Sector Analysis: Retinal axons of some retinal sectors are more vulnerable than others in certain disease states. Therefore, quantitative analysis of retinal sectors allows for sensitive detection of axonal loss in all regions [7].

Retinal Nerve Fiber Layer Thickness and Reflectivity Maps: Using individual circular RNFL scans at the optic-nerve to accurately localize focal and peripheral loss of retinal axons is challenging. One possible approach is the development of RNFL thickness maps. An integrative approach combining polarizing sensitive OCT data with RNFL thickness maps may help predict the topography of RNFL loss in neuro-ophthalmic diseases [7].

Retinal Layer Segmentation Algorithms: With the introduction of SD-OCT, RNFL image quality allows for segmentation and quantification of individual layers. Therefore, new segmentation algorithms for quantitative analyses of individual retinal layers may facilitate better tracking of progression in neuro-ophthalmic diseases [7].

Fluorescence Labeling: As an example, fluorescence labeling of a protein that binds to a key component initiating apoptosis enables real-time in-vivo monitoring of retinal ganglion cell apoptosis. Detection of this phenomenon provides a promising surrogate outcome for neuro-protective treatment strategies in glaucoma, dementia, and potentially multiple sclerosis [7].

Optical Coherence Microscopy and Action Potentials: With optical coherence microscopy, the structural assessment of action potentials has become a reality. Functional imaging of the human retina in vivo may allow us to investigate whether axonal dysfunction precedes retinal GCL or RNFL loss in different disease states [7].

Choroidal Imaging: Most commercially available SD-OCT systems can be used to evaluate choroidal thickness [1]. The method used for choroidal thickness analysis involves manual measurements taken perpendicularly from the outer edge of the RPE to the inner sclera (choroid–sclera junction) using the software within the system [1].

Color Imaging: Multicolor imaging delivers high contrast, detailed images, even in patients with cataracts or nystagmus. The image clarity and detail is highly improved, and can increase sensitivity in the detection of pathology in the posterior pole.

Future Directions: Emerging Applications of OCT

Advancements in OCT technology continue to evolve at a rapid pace. These developments may or may not impact your clinical practice at the present time, but could change how ophthalmic and neuro-ophthalmic diseases are tracked and measured in the future.

Ultra-High Resolution OCT: UHR-OCT utilizes an ultra-broadband with light sources to provide axial resolutions approximating 2 to 3µm, which reveals retinal morphology in high detail. Yet because this technology requires femtosecond lasers and expensive light sources, it has not been widely used as a commercially available OCT system for clinical settings [8].

Mobile Spectral-domain OCT: Interferometric-based imaging systems such as SD-OCT have been traditionally viewed as stationary table-top tools for examining alert adult patients. The commercialization of mobile SD-OCT systems may expand the application spectrum to allow analysis of subjects manifesting significant motion, including adult and pediatric patients groups. The first commercialized mobile SD-OCT scanner (Bioptrigen Inc., Research Triangle Park, NC) provides a light hand-held imaging probe that can be maneuvered independently. This technique may be used in the imaging of small animal eyes in the research setting. Other applications for this technique include evaluating foveal architecture in pediatric ocular albinism, and the extent of retinal pathology accrued from shaken-baby syndrome [8].

Spectral-domain OCT for Intraoperative Use in Vitreoretinal Surgery: Vitreoretinal surgeons have long relied upon the optical stereo microscope to visualize the surgical field. Even with recent design improvements, there are limitations to intraoperative visualization and accurate localization with this approach [8]. Current imaging modalities do not provide real-time cross-sectional images of the change in location of a surgical instrument relative to tissue, or of tissue deformation during surgery. This feedback may be important in judging whether to continue a specific maneuver. A SD-OCT surgical microscope could potentially provide a base for significant advances in ocular surgery and other branches of microsurgical intervention. Moreover, this imaging modality may also be useful for sub-retinal drug-delivery applications [8].

Functional/Targeted SD-OCT Imaging: Unlike many other medical imaging modalities with functional adjuncts, such as computed tomography (CT) and magnetic resonance imaging (MRI), ophthalmic use of SD-OCT has been restricted to structural imaging [8]. Two new functional SD-OCT imaging modalities are emerging with a wide spectrum of potential diagnostic applications:

a) Doppler Spectral-domain OCT for Blood-flow Imaging: Doppler OCT technology was first developed using TD-OCT systems and was later utilized for retinal flow analysis [8]. However, the slow data acquisition coupled with patient head motion restricted the reliability of the data. In SD-OCT systems, Doppler flow velocities are acquired much more quickly, and recent extensions to Doppler SD-OCT are enabling complete 3D mapping of the retinal vasculature for the first time, with potential applications in monitoring...
diabetic retinopathy and other blinding diseases with a vascular component [8]. In multiple sclerosis, peri-vasculitis is believed to lead to extravascular hyaline deposits in a process referred to as “vascular sheathing”. These changes may lead to increased rigidity of retinal vasculature and, by extension, rapid pulse propagation from the posterior (choroidal) to the anterior (retinal vasculature) circulation [7]. This hypothesis could potentially be investigated by combination of SD-OCT with Doppler velocity measures. This technique is non-invasive and allows for accurate topographic localization of retinal blood vessels [7].

b) Polarization-Sensitive OCT: Polarization-sensitive SD-OCT (PS-OCT) yields depth resolved information about any light polarization changing properties of the sample related to tissue birefringence [7, 8]. The birefringence of the RNFL is related to the structure of neurofilaments and microtubules. Studies have shown that the birefringence of the RNFL is not constant, but varies by a factor of three around the optic-nerve head, with higher values reported in the superior and inferior quadrants, and lower values in the nasal and temporal quadrants. This property distinguishes the RNFL from other retinal structures, which are either polarization preserving (eg, photoreceptor layer) or polarization scrambling/depolarizing (eg, retinal pigmented epithelium) [8]. Because changes to the axonal cytoskeleton such as neurofilament compactness, phosphorylation, and stoichiometry can precede axonal loss, there might be an opportunity to detect early stages of axonal pathology in diseases like multiple sclerosis with PS-OCT [7]. From a general ophthalmic standpoint, PS-SD-OCT is a promising tool for AMD evaluation, in which tracking RPE degeneration and dislocation is of interest [8].

**Longer Wavelength and Swept Source Technology:** For adequate analysis of choroidal thickness and volume in healthy and diseased states, the clarity of the choroid–sclera interface is important. This can be achieved by increasing the depth of tissue penetration using a longer wavelength of incident light centered near 1050 nm, so that attenuation from scattering can be reduced [1]. The acquisition of scans is much faster in swept source OCT (SS-OCT), when compared with the SD-OCT systems. The SS-OCT systems have axial scan rates of up to 100 000–236 000 A-scans per second, which is 5 to 10 times that of the SD-OCT systems [1]. Therefore data can be acquired much faster and volumetric assessment of the choroid is also feasible [1]. As longer-wavelength OCT systems including SS-OCT become available, the visualization of choroid–sclera interface is expected to improve [1]. Therefore, volumetric analysis of the choroid, as well as that of the various pathological features such as choroidal neovascularization and subretinal/intraretinal fluid, may be possible [1]. Such a volumetric analysis is expected to help with monitoring the progression of diseases such as wet AMD, and diabetic retinopathy, as well as assessment of the response to treatments such as anti-VEGF agents, laser photocoagulation and PDT [1].

**En-face imaging:** En-face imaging, allows the clinician to visualize 3D data in a fundus projection. Using this technique, particular retinal and/or choroidal layers at a given depth are projected onto an en-face view. Although cross-sectional images (B-scans) have helped delineate pathological features in retinal diseases, the microstructural changes and morphology of the retinal and choroidal vasculature are difficult to evaluate using B-scans [1]. This is expected to improve as en-face imaging provides further detail about the subtle pathological features in the retina and choroid in diseased states [1]. In addition, the involvement of the specific vascular layers of the choroid in different diseases such as AMD, diabetic retinopathy and inherited retinal dystrophies is expected to be unveiled in further detail using this technique [1].

**CONCLUSION**

The evolution of OCT technology has provided a quantifiable means of capturing structural changes in axonal and retinal integrity which can be paired with functional outcomes to follow various neuro-ophthalmic disorders. Future improvements in both hardware and software techniques should further advance the clinician’s ability to assess and manage their patients.

**CME ANSWERS**

1. Spectral-domain OCT provides scan rates of 20,000–52,000 A-scans per second and a resolution of 5–7µm. This is approximately 50-fold faster than the previous generation of TD-OCT, which provided an average image resolution of 8-10µm.

2. Hardware, image quality, and software.
REFERENCES

OCT IN PAPILLEDEMA:
WHAT AM I MISSING?

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University of Iowa, Hospitals & Clinics and Veterans Administration
Iowa City, IA

LEARNING OBJECTIVES

1. The attendee will be able to describe the problems with subjective grading of papilledema by ophthalmoscopy or digital photography.
2. The attendee will be able to describe the OCT features that have been shown to vary continuously with the severity of papilledema.
3. The attendee will be able to describe OCT related features that can explain decrease in visual acuity in papilledema.

CME QUESTIONS

1. Which of the following describe the main drawbacks of using a subjective grading scale for quantifying papilledema:
   a. Inter-observer disagreement in Frisen grading of papilledema
   b. Intra-observer repeat variability in Frisen grading of papilledema
   c. It does not provide a continuous scale assessment of papilledema
   d. all of the above

2. Which of the following OCT based features is the most robust and least subject to software segmentation artifact for quantifying the severity of papilledema:
   a. Displacement of Bruch’s membrane
   b. Disc volume
   c. Total retinal peripapillary thickness
   d. Retinal peripapillary nerve fiber layer thickness (RNFL)

3. Which of the following is not considered a typical cause of acute decrease in visual acuity in papilledema:
   a. Neurosensory retinal detachment encompassing the fovea
   b. Choroidal folds
   c. Loss of photoreceptors
   d. Loss of retinal ganglion cells

KEYWORDS

1. Papilledema
2. Optical coherence tomography (OCT)
3. Retinal nerve fiber layer (RNFL)

INTRODUCTION

To the experienced neuro-ophthalmologist, the most relevant question is: Do we really need an imaging modality such as optical coherence tomography (OCT) to evaluate papilledema? Most clinicians feel that careful ophthalmoscopy or digital fundus photography is more than adequate for diagnosing the presence of papilledema, determining its severity and deciding on whether it has changed over time. After all, this is what has been done for years, so why do we need something more? The need for "something more" derives from a number of studies, including the multicenter NIH-sponsored Idiopathic Intracranial Pressure Treatment Trial (IIHTT):

- Inter-observer agreement on grading the severity of papilledema is poor among expert observers, even using well-defined criteria such as the Frisen scale, whether this is done using ophthalmoscopy or by grading of digital fundus photographs (1-3).
- Non-expert clinicians often find it difficult to properly view the optic nerve using ophthalmoscopy and to accurately interpret digital fundus photographs when using non-mydriatic retinal cameras at the point of care. This can lead to failure to diagnose papilledema in non-ophthalmologic care settings such as emergency rooms, family practice offices, neurology clinics, or neurosurgery clinics and may delay treatment, which can result in vision loss.
- Distinguishing papilledema from pseudopapilledema is difficult when obvious surface drusen are not present. Buried drusen, when un-calcified, may not be readily apparent using funduscopy, ultrasound, optical coherence tomography, or Computed Tomographic (CT) scans.
- It is often difficult to determine whether a reduction in optic nerve edema is due solely to improvement in the status of the nerve or whether this represents concomitant loss of axons and viable retinal ganglion cells, leading to a poor visual outcome. More timely advancement of treatment would occur if loss of neurons could be diagnosed at an earlier stage of evaluation while optic disc edema is still present.
An important (and reachable) long-term goal is to provide a portable, low cost retinal imaging device with embedded software that would not require expertise for acquiring and making a diagnosis of papilledema or other optic nerve pathology. Ultimately, generation of an automated report providing diagnostic probability at the point of care and at the time of image acquisition is needed which would bypass the need for a telemedicine reading center. Use of such a device would be adopted in clinical settings lacking easy access to ophthalmologists and neuro-ophthalmologists, such as in emergency rooms, family practice offices, neurology and neurosurgery clinics and inpatient units.

The following summary will outline and define the critical need for new imaging modalities such as OCT and image analysis aimed at providing tools for improved diagnosis of papilledema, differentiating papilledema from pseudopapilledema and other causes of optic nerve edema, and for identifying early signs of retinal nerve loss in order to optimize treatment and prevent vision loss.

DIAGNOSIS AND GRADING OF SEVERITY OF PAPILLEDEMA BASED ON FUNDUS FEATURES: ARE WE GOOD ENOUGH?
Many clinicians are confident in their ability to accurately diagnose and grade the severity of papilledema and most use the accepted standard of the Frisen grading scale (1). However, even in the original report by Frisen, there was intra-observer variability in grading of photographs on repeat testing, whether the grading was done by a medical student, resident or expert (Figure 1). Significant variability among experts in grading papilledema from digital fundus photographs has also been established in our own studies (2), as shown in Figure 2 and in the study by Sinclair et al (3), shown in Figure 3.

Figure 1: Reproducibility for three difference observers, who staged the same fundus photographs for disc swelling on two separate occasions. Each dot represents one photograph. The diagonals represent identity of stage numbers on test and re-test. First graph is for medical students, second graph is for ophthalmology residents and third graph is for expert specialist neuro-ophthalmologists. From Frisen L. Swelling of the optic nerve head: a staging scheme. J Neurol Neurosurg Psychiatry. 1982 Jan;45(1):13-18

Figure 2: Four neuro-ophthalmology experts (3 from Iowa and the 4th was Lars Frisen) independently graded papilledema based on criteria outlined in the Frisen scale. Disagreement within one grade scale was common (43% of cases) and there were even cases where there were 2 or more grade scale difference between experts (3.6% of cases) at the higher grades. Modified after Scott CJ, Kardon RH, Lee AG, Frisen L, Wall M. Diagnosis and grading of papilledema in patients with raised intracranial pressure using optical coherence tomography vs clinical expert assessment using a clinical staging scale. Arch Ophthalmol. 2010 Jun;128(6):705-11.

Frisen Grade Variability Between Experts
Based on availability and cost in a telemedicine setting, the imaging modality to be used could be flexible and selected for a given patient. These two imaging modalities. The imaging modality to supersede the non-continuous Frisen scale) using either features with OCT based features, so that quantification of papilledema on a continuous scale could be made to a continuous scale based upon OCT measurements of the peripapillary retina for quantifying elevation of the nerve head above that plane, especially in higher grades of papilledema. Even in glaucomatous optic neuropathy, there was disagreement as to what portion of the retina was best suited for a reference plane that was not affected by the pathology under evaluation. Also, the availability of HRT was not widespread; only some academic institutions had the resources and interest to acquire the instrumentation for evaluating the optic nerve and retina using confocal laser microscopy. Scanning laser polarimetry (SLP), which also predated OCT, was gaining use for glaucoma evaluation and was based on changes in the retardation of reflected polarized light from the retinal nerve fiber layer that contained regularly oriented microtubules and microfilaments which could modify polarized light passing through it. Reports of its use for showing thickening of the retinal nerve fiber layer in papilledema were initially negative or only showed mild thickening (8,9); there was very little change in retardation of polarized light by axoplasmic flow stasis, since in most cases the organization of the microfilament substructure was unaffected. However, SLP did reveal axon loss, similar to its use in glaucoma (8-10).

Unlike HRT, OCT provided information on retinal thickening, and in particular, peripapillary thickening of the retinal nerve fiber layer (RNFL) in papilledema without the need for a reference plane (11-21. Also, since OCT was based on actual thickness of the retinal layers, it complimented SLP, which primarily demonstrated loss of microtubule and microfilament organization within the axon bundles. However, it was soon noticed that in the presence of moderate to severe papilledema (Frisen Grade 3 or above), substantial thickening of the peripapillary retinal nerve fiber layer would often cause the software algorithm that was used for determining the RNFL borders to fail in over a third of the cases (2), causing inaccurate reporting of RNFL thickness. A significant improvement in the quantification of papilledema was realized by segmenting the total retinal thickness (TRT) in the same peripapillary scan, since the inner and outer borders of the retina can be more readily defined by automated software in the presence of moderate to severe papilledema. The total retinal thickness was found to highly correlate with the RNFL thickness in eyes where the algorithm did not fail. Automated software segmentation of the retinal layers using a 3D graph-based approach has significantly improved upon the accuracy of defining the thickness of the retinal

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**Figure 3**: Cross tabulation of the Frisen grades assigned to the optic disc photographs by each pair of reviewers. Complete agreement between the reviewers is shaded in yellow. The red shading indicates disagreement between the reviewers in assigning a Frisen grade. From (supplement on-line) Sinclair AJ, Burdon MA, Nightingale PG, Matthews TD, Jacks A, Lawden M, Sivaguru A, Gaskin BJ, Rauz S, Clarke CE, Ball AK. Rating papilloedema: an evaluation of the Frisen classification in idiopathic intracranial hypertension. J Neurol. 2012 Jul;259(7):1406-12.

These studies give us pause in relying upon humans (including experts) to accurately and reliably diagnose and grade papilledema. Efforts to refine and provide even more specific criteria for each Frisen scale may help to improve reliability between observers. Since the Frisen scale consists of 6 grades (0-5) that are non-continuous, a further improvement would be to devise a continuous grading scale, based on structural features, that could be objectively quantified by computerized image analysis of fundus images. We have shown that quantitative analysis of digital fundus images is a promising approach (4) and features that incorporate sharpness of the disc border, texture of the retinal nerve fiber layer and discontinuity of blood vessels can be used by a machine classifier to assign a Frisen grade to a disc photograph (4). The next step would be to map features from digital fundus photography to a continuous scale based upon OCT measurements of papilledema such as disc volume or thickness of the peripapillary retina (5,6). This would associate fundus photo features with OCT based features, so that quantification of papilledema on a continuous scale could be made (superseding the non-continuous Frisen scale) using either of these two imaging modalities. The imaging modality to be used could be flexible and selected for a given patient based on availability and cost in a telemedicine setting where the patient enters the medical system.

**TOWARDS A CONTINUOUS SCALE QUANTIFICATION OF PAPILLEDEMA SEVERITY (RETINAL NERVE FIBER LAYER, TOTAL RETINAL THICKNESS, AND DISC VOLUME)**

When time domain OCT first came on the scene around 2001, there had already been attempts at quantifying papilledema using confocal microscopy with Heidelberg Retinal Tomography (HRT) and scanning laser polarimetry. HRT appeared promising (7), but was limited by the difficulty in defining an appropriate “reference plane” in the peripapillary retina for quantifying elevation of the nerve head above that plane, especially in higher grades of papilledema. Even in glaucomatous optic neuropathy, there was disagreement as to what portion of the retina was best suited for a reference plane that was not affected by the pathology under evaluation. Also, the availability of HRT was not widespread; only some academic institutions had the resources and interest to acquire the instrumentation for evaluating the optic nerve and retina using confocal laser microscopy. Scanning laser polarimetry (SLP), which also predated OCT, was gaining use for glaucoma evaluation and was based on changes in the retardation of reflected polarized light from the retinal nerve fiber layer that contained regularly oriented microtubules and microfilaments which could modify polarized light passing through it. Reports of its use for showing thickening of the retinal nerve fiber layer in papilledema were initially negative or only showed mild thickening (8,9); there was very little change in retardation of polarized light by axoplasmic flow stasis, since in most cases the organization of the microfilament substructure was unaffected. However, SLP did reveal axon loss, similar to its use in glaucoma (8-10).

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layers in papilledema (6), resulting in much fewer algorithm failures. In this approach, the entire surface of each retinal layer is determined within the scan volume using all of the surrounding 3D features in the OCT scan and not just the features in each individual B scan. We have further utilized this approach to segment the volume of the optic disc, which highly correlates with the RNFL, total retinal thickness and Frisen grade of papilledema (Figure 4) in patients with raised intracranial pressure (6).

ADVANCED FEATURE ANALYSIS OF THE DISC USING DIGITAL FUNDUS PHOTOGRAPHY AND OCT

The ability to accurately derive an OCT-based, continuous measurement of papilledema (for example, total disc volume, as explained in the previous section) provides an objective means of quantifying the severity of papilledema. The next step forward is to map other OCT and fundus-based features to a continuous scale of disc volume, which highly correlates with the RNFL, total retinal thickness and Frisen grade of papilledema (Figure 4) in patients with raised intracranial pressure (6).

Another OCT-based feature, which provides additional information about the direction of force vectors at the optic disc in papilledema, is the deformation of Bruch’s membrane surrounding the neural canal due to a pressure differential between the retrobulbar optic nerve and vitreous cavity (Figure 6). The shape characteristics of Bruch’s membrane in this area, in terms of the degree of angling towards the vitreous, can help in the monitoring of the force differential over time as the intracranial pressure changes and may also help to differentiate papilledema from other causes of optic disc edema or pseudopapilledema (23,24). This angle can vary to some degree within normal eyes without papilledema. The
The ability to differentiate true papilledema due to raised intracranial pressure from other forms of optic disc edema or pseudopapilledema is crucial.

Figure 5: Computerized image analysis features of fundus photos that are specific for papilledema and its degree of severity include, from left to right, texture ("entropy") of the peripapillary retina (with insert), degree of definition of the disc border, vessel discontinuity index (VDI) due to obscuration of retinal vessels by edematous overlying retinal nerve fiber layer, 3D disc volume derived from stereo pairs of disc photographs. From, Eccegaray S, Zamora G, Yu H, Luo W, Soliz P, Kardon R. Automated Analysis of Optic Nerve Images for Detection and Staging of Papilledema. Invest Ophthalmol Vis Sci. 2011 Aug 23

A change in the angle from positive to less positive following treatment or after lumbar puncture would also enforce a suspicion of papilledema and would verify a treatment effect (Dr. Pat Sibony, personal communication). Newer generation OCT instruments with enhanced depth penetration and longer wavelength light (exceeding 1micron) provide even greater resolution of deeper structures, such as Bruch’s membrane, even in the presence of optic disc edema.

Figure 6: Left panel of OCT of disc tissue in a patient with papilledema, showing the upward angling and displacement of Bruch’s membrane (red arrows) in the right and left eyes. Right panel of change in displacement of Bruch’s membrane in the same eye before and after treatment of raised intracranial pressure. From, Kupersmith MJ, Sibony P, Mandel G, Durbin M, Kardon RH. Optical coherence tomography of the swollen optic nerve head: deformation of the peripapillary retinal pigment epithelium layer in papilledema. Invest Ophthalmol Vis Sci. 2011 Aug 22;52(9):6558-64.
DIFFERENTIATING PAPILLEDEMA FROM PSEUDOPAPILLEDEMA USING OCT

The ability to differentiate true papilledema due to raised intracranial pressure from other forms of optic disc edema or from pseudopapilledema can be challenging, particularly when the degree of edema is not severe (i.e. Frisen grade 1 or 2). When calcified optic disc drusen are located superficially, the diagnosis is relatively easy and can be made with careful ophthalmoscopic observation. When calcified drusen are deep and buried under the surface, then clinical observation may be equivocal and the use of autofluorescence (a modality offered on OCT instruments that use a blue scanning laser), ultrasound, or observation of CT scans of the optic nerve have been useful. Features on OCT have been used to differentiate papilledema from pseudopapilledema (25-33), including calcified drusen, which have been visualized on OCT scans through the nerve head as shown in Figure 7. Sometimes calcified drusen and their shadows, visualized on OCT, are not easy to distinguish from larger, superficial blood vessels. Non-calcified drusen are not usually visualized, as they are presumed not to exhibit a significant difference in reflectivity from surrounding disc tissue. Often a patient with pseudopapilledema (with or without calcified drusen), may show visual field loss. In these eyes, the retinal nerve fiber layer may appear thickened in some areas, presumably due to axoplasmic flow stasis, and thin in other areas, corresponding to locations of visual field loss. Another OCT approach to differentiating papilledema from pseudopapilledema is based on defining topographical shape characteristics of the elevated nerve head. In this approach, a machine classifier is used to define shape characteristics that are more likely to be associated with true papilledema and those characteristics that are more likely to be associated with pseudopapilledema. As outlined in the previous section, shape characteristics of Bruch’s membrane may also help in differentiating papilledema from pseudopapilledema and other forms of optic disc edema not due to raised intracranial pressure.

WHY IS MY PATIENT WITH PAPILLEDEMA LOSING VISION? DIFFERENTIATION OF VISUAL LOSS DUE TO OPTIC NEUROPATHY VS MACULOPATHY (FLUID AND SURFACE WRINKLING)

When a patient with papilledema has best corrected vision of 20/25 or worse, then there is a concern for whether this may be caused by optic neuropathy, requiring more aggressive treatment that may have an urgency associated with it or whether it may be due to a more benign, reversible macular abnormality such as subfoveal fluid or choroidal folds. The more benign outer retinal causes are relatively easy to diagnose with OCT and can help resolve the uncertainty rather quickly. The most obvious sign that can be easily discerned with OCT is a neurosensory retinal detachment from peripapillary fluid between the retina pigment epithelium and photoreceptors that tracks into the fovea (34,35). On OCT B scans, the fluid appears dark and low reflective. The macular thickness is greater than surrounding areas without fluid on the color OCT thickness plot and the probability plot shows the area with fluid to be significantly thicker than age matched normative data (Figure 8). Decrease in vision due to fluid under the fovea is largely reversible and should not be considered a cause of vision loss requiring urgent management and may be treated with weight loss and acetazolamide. However, rarely, with chronic papilledema, a subretinal neovascular membrane in the peripapillary retina may form and cause fluid that will not go away unless treated more definitively with either intravitreal anti-VEGF agents or laser treatment to the peripapillary area in the location of the membrane. Another outer retinal cause of decreased visual acuity is choroidal folds caused by distortion of the posterior globe by abnormal amounts of fluid under pressure in the subarachnoid space surrounding the optic nerve as it exits the globe. Choroidal folds can be recognized in OCT B scans, in the infrared fundus image, or on digital photography and fundus exam. The folds may contribute to metamorphopsia and are often reversible with successful resolution of papilledema, but not always.

Figure 7: A very large, coalescing druse imaged in several SD-OCT modalities. a, Fundus photo with two vertical markers placed on either side of the druse, obtained with 3D Disc scan on Topcon 3D-OCT 2000. b, Low-resolution SD-OCT image, obtained on same 3D Disc scan. c, High-resolution image, obtained with 7-Line Raster on Topcon 3D-OCT 2000. d, High-resolution (5-Line Raster) image, obtained with Zeiss Cirrus. HD-OCT. From Slotnick S, Sherman J. Buried disc drusen have hypo-reflective appearance on SD-OCT. Optom Vis Sci. 2012 May;89(5):E704-8.
Figure 8: OCT example of a papilledema associated with a neurosensory retinal detachment between the left optic nerve and the fovea. Top is the macula total retinal thickness plot showing the elevation in the area of the fluid (arrows). Bottom left is one B scan through the detachment area showing the fluid (dark reflective layer) between the pigmented epithelium and the photoreceptors (arrow). At right is the 3D macula thickness plot showing the elevation in the area of the detachment with fluid (arrow).

Most neuro-ophthalmologists would agree that perhaps the most important cause of reduced visual acuity in papilledema is from optic neuropathy, which can progress to profound visual loss. Once diagnosed, progressive optic neuropathy requires more aggressive, urgent treatment to attempt to minimize the degree functional and structural deficit and restore any reversible component of vision.

A decline of visual acuity in the absence of macular fluid or folds is usually the most obvious sign of progressive optic neuropathy in this setting. Since the retinal nerve fiber layer is thickened in papilledema, a reduction in its thickness, assessed by OCT, may be difficult to interpret and could represent either a reduction in disc edema due to improvement or due to axon loss (36-38). We have shown that imaging early signs of axon loss in the presence of papilledema can be revealed by using scanning laser polarimetry (10). Since scanning laser polarimetry is sensitive to disorganization of axon microtubules and microfilaments, which may be one of the earliest signs of axon disruption. However, this technology has become somewhat obsolete and was superseded by OCT for optic disc edema. OCT algorithms that take advantage of 3D information instead of just 2D information from single B scans are better suited to overcome this problem (6). The working assumption is that thinning of the GCL-IPL will reveal early signs of progressive optic neuropathy in the presence of papilledema. This will undoubtedly be the focus of studies in the near future to understand the usefulness of GCL-IPL thickness in the evaluation and monitoring of papilledema.

As an alternative, assessment of ganglion cell loss by OCT in the setting of papilledema may be suitable for early detection of neuron loss in order to identify patients in need of more aggressive treatment. Since optic disc edema and axon swelling does not appear to directly affect the retinal ganglion cell layer thickness, allowing it to be an effective tool for the early diagnosis of progressive optic neuropathy. However, commercial algorithms for segmenting the ganglion cell-inner plexiform layer complex (GCL-IPL layer) were designed for normal and glaucoma eyes and often fail in the presence of optic disc edema. OCT algorithms that take advantage of 3D information instead of just 2D information from single B scans are better suited to overcome this problem (6). The working assumption is that thinning of the GCL-IPL will reveal early signs of progressive optic neuropathy in the presence of papilledema. This will undoubtedly be the focus of studies in the near future to understand the usefulness of GCL-IPL thickness in the evaluation and monitoring of papilledema.

Another recent development in OCT which has possible relevance to understanding the pathogenesis of visual loss in papilledema due to ischemia relates to the visualization of optic nerve capillaries and capillary blood flow. Using phase contrast OCT it is now possible to visualize capillaries and quantify flow within a capillary bed without the use of contrast agents (39). An example of OCT derived capillary flow in the normal and glaucomatous optic nerve head is shown in Figure 9.
Figure 9: Disc photographs (A, C) and en face OCT angiograms (B, D) of the ONH in representative normal (A, B) and preperimetric glaucoma (PPG) subjects (C, D). Both examples are from left eyes. In (B) and (D) the solid circles indicate the whole discs, and the dash circles indicate the temporal ellipses. A dense microvascular network was visible on the OCT angiography of the normal disc (B). This network was greatly attenuated in the glaucomatous disc (D). From Jia Y, Morrison JC, Tokayer J, Tan O, Lombardi L, Baumann B, Lu CD, Choi W, Fujimoto JG, Huang D. Quantitative OCT angiography of optic nerve head blood flow. Biomed Opt Express. 2012 Dec 1;3(12):3127-37.

CME ANSWERS

1. d
2. b
3. c

REFERENCES


LEARNING OBJECTIVES

1. Understand how optical coherence tomography (OCT) was introduced into clinical trials and other research in neuro-ophthalmology as structural correlate to functional outcomes.

2. Learn how evolving OCT techniques, including retinal layer segmentation, have enabled the afferent visual pathway to become a model for testing new therapies in neuro-ophthalmologic disease.

3. Examine our current knowledge of OCT measures of retinal nerve fiber layer (RNFL), and macular thickness in the context of what is average or “expected” for disease-free persons and for eyes of patients with multiple sclerosis (MS) with and without a history of acute optic neuritis. Participants will understand the potential roles and limitations of OCT in clinical practice based on clinical trial data.

CME QUESTIONS

1. Neuronal loss that occurs following acute optic neuritis (ON) is best represented by which of the following OCT measurements:
   a. retinal nerve fiber layer (RNFL) thickness
   b. ganglion cell layer (GCL) + inner plexiform layer (IPL) thickness
   c. outer nuclear layer
   d. photoreceptor layer

2. The anterior visual pathway is an ideal model for testing new therapies in MS because of:
   a. unique structure-function correlations
   b. common occurrence of visual involvement
   c. non-invasive testing methods such as OCT
   d. all of the above are correct

3. The visual function test most often included in MS clinical trials is:
   a. contrast sensitivity
   b. low-contrast letter acuity
   c. HRR color plate testing
   d. computerized static perimetry

KEYWORDS
1. Optical coherence tomography (OCT)
2. Clinical trials
3. Visual function
4. Neurorepair
5. Multiple sclerosis

INTRODUCTION

Just over a decade ago, clinical trials for multiple sclerosis (MS) did not include visual outcomes. Experts recognized the need for more sensitive measures of visual function, and low-contrast letter acuity emerged as a leading candidate to measure visual impairment. While low-contrast acuity was quickly shown to correlate well with MRI lesion burden, visual-evoked potentials (VEPs), quality of life (QOL) in MS, it was the introduction of optical coherence tomography (OCT) to the field of MS that allowed for the direct assessment of structure-function correlations in the anterior visual pathway. This unique capacity to link axonal and neuronal loss with specific impairment (vision) in MS makes the anterior visual pathway and acute optic neuritis (ON) ideal models for testing novel agents for neuroprotection and repair. The latest OCT investigations involve high-resolution spectral-domain (SD) OCT with segmentation (measurement) of specific retinal layers using computerized algorithms. These methods allow quantitation of both retinal nerve fiber layer (RNFL, axonal) and ganglion cell layer (GCL, neuronal) loss in vivo. New therapies that reduce axonal and neuronal loss by neuroprotective or myelin repair mechanisms can now be assessed non-invasively by OCT and coupled with visual function data. Most MS clinical trials now include both OCT and visual function testing, and new clinical trials that use acute ON as a model will examine the capacity
for OCT measures in particular to demonstrate structural evidence for neuroprotection in patients with MS and other neurologic disorders. In this syllabus, we examine the data from observational studies and ongoing trials, presenting representative group data for visual function, OCT measures, and QOL scales in patients with MS, ON, and disease-free controls. These data, as well as those from meta-analyses within the past five years, may be used to provide reference values for the development of clinical trial protocols.

BACKGROUND
In 1974, Frisén and Hoyt first described thinning of the retinal nerve fiber layer (RNFL) in patients with MS (1). Post-mortem studies later confirmed the suspicion that atrophy was occurring in the RNFL in nearly 71% of the patients studied (2). The invention of optical coherence tomography (OCT) has allowed for objective measurement of the layers of the retina in vivo (3-5). While acute demyelination as a result of ON is an important contributor to visual loss, axonal and neuronal degeneration in the anterior visual pathway likely to be important contributors to visual dysfunction in MS, even in patients without an acute ON history (3, 6-10)

Because thinning of the RNFL and GCL+IPL by OCT are associated with reductions in visual function and QOL, OCT measures of axonal and neuronal loss have a unique ability to capture structure-function correlations in MS. Table 1 shows a mean difference in RNFL thickness of 11.8 m between disease-free control and all MS eyes (with and without a history of ON). The ability of OCT to detect these differences supports its potential role as a structural marker in MS clinical trials. OCT provides a non-invasive, objective measure of visual pathway integrity, and therefore could be used to determine effectiveness of neuroprotective and other MS therapies. Further, OCT can be used in conjunction with visual function testing to follow disease progression of patients with MS.

FEATURES AND ADVANTAGES OF OCT IMAGING
Within the retina, retinal ganglion cell axons are unmyelinated until they pass through the lamia cribosa. Therefore, RNFL imaging has the unique advantage of measuring the thickness of axonal and other retinal structures that can ultimately be used in assessing neurodegeneration and potentially neurorepair. OCT is similar to B-mode ultrasound B-mode imaging, but uses light instead of sound to form images. An optical beam is scanned along the retina and the machine measures echo-time delays in order to synthesize a picture of the retinal structure (11-14). Advances in OCT, including the development of spectral- (Fourier) domain technology, provide increased sensitivity and capacity for careful analysis of pathologic changes in the retina in vivo. Representative group data for OCT in patients with MS and disease-free controls are presented in Table 1. Time-domain (TD) OCT (first generation widely studied in MS)

shows substantial difference in RNFL thickness between eyes of patients with MS and disease-free controls (95.5 ±14.5 m vs. 104.5 ±10.7 m) MS eyes with a history of ON have even greater degrees of thinning on average (85.7 ±19.0 m). For spectral-domain (SD) OCT techniques, there are differences in scaling from TD OCT, leading to smaller absolute differences in RNFL thickness (92.9±10.0 m for controls vs. 87.6 ±11.1 m in MS eyes without a history of ON). Larger studies will further refine the precision of these representative average values. Statistically combined data for studies of TD OCT as of 2009 are presented in a meta-analysis by Petzold et al. that highlights >96 articles, with analyzable data from 36 studies of OCT in MS.

An advantage of OCT is that it demonstrates high degrees of both inter-rater and test-retest reliability for TD and SD techniques (15). In fact, recent studies of SD OCT show that this newer technology produces measurements that are more reproducible than TD OCT (16). A study of 58 patients and 38 controls found that intraclass correlation coefficients (ICCs) ranged from 0.92-0.97 for inter-visit, 0.83-0.99 for intra-rater, and 0.94-0.99 for inter-rater reproducibility. Given its high degrees of reliability, sensitivity and ease of use (pupillary dilation not usually needed), OCT is an ideal method for assessing pathologic changes in the visual pathway of patients with MS. As such, these techniques have been included in most recent MS clinical trials, and are now considered essential for evaluating new therapies for acute ON.

OCT INVESTIGATIONS IN MS AND OPTIC NEURITIS (ON)
During the course of their disease, between 30-70% of MS patients will have acute ON (17,18). Since patients with acute demyelinating ON typically have overt, subacute symptoms of pain on eye movement, visual acuity loss, color desaturation, and visual field abnormalities, followed by substantial RNFL axonal loss by OCT (20-40 µm on average), ON is an ideal model for studying neuroprotective and neurorepair agents in MS.

In 1999, OCT was first utilized in a study by Parisi et al. (19) to investigate a group of patients who had a history of ON with complete recovery of visual acuity. When compared with control eyes, RNFL thickness was found to be 46% worse in the eyes affected by acute ON. The affected eyes were also found to have RNFL thickness 28% worse when compared to the unaffected eyes of the same patient (P<0.01) (19). A subsequent investigation by Trip et al. (20) substantiated these findings among eyes of patients with a history of ON and incomplete recovery. This cohort of 25 patients with a history of unilateral ON found that ON eyes had a 33% reduction in RNFL thickness of patient eyes compared to disease-free control eyes (P<0.001) (20). These authors also reported reductions in total macular volume in ON eyes compared with controls (P< 0.001), and also showed differences and between affected and unaffected eyes of patients in the study (P<0.001).
### Table 1. Mean reference values from recent investigations of vision, QOL, and OCT in MS

<table>
<thead>
<tr>
<th></th>
<th>Disease-Free Controls</th>
<th>All MS</th>
<th>MS, No History of ON</th>
<th>MS, History of ON</th>
<th>References for Data*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-contrast visual acuity (VA), ETDRS, number of letters correct</strong></td>
<td></td>
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<tr>
<td></td>
<td>64 ± 5 (n=61 eyes)</td>
<td>59 ± 8 (n=239 eyes)</td>
<td>60 ± 6 (n=150 eyes)</td>
<td>58 ± 9 (n=87 eyes)</td>
<td>39* (22,24,25,32,44)</td>
</tr>
<tr>
<td><strong>Binocular testing</strong></td>
<td>66 ± 5 (n=324 pts)</td>
<td>62 ± 8 (n=1,007 pts)</td>
<td>63 ± 7 (n=544 pts)</td>
<td>61 ± 10 (n=463 pts)</td>
<td>44* (42,43)</td>
</tr>
<tr>
<td><strong>Low-contrast letter acuity (2.5%), number of letter correct</strong></td>
<td>34 ± 8 (n=61 eyes)</td>
<td>26 ± 11 (n=239 eyes)</td>
<td>28 ± 9 (n=150 eyes)</td>
<td>22 ± 12 (n=87 eyes)</td>
<td>39* (24,25,44)</td>
</tr>
<tr>
<td><strong>Binocular testing</strong></td>
<td>43 ± 6 (n=324 pts)</td>
<td>36 ± 10 (n=1,007 pts)</td>
<td>38 ± 9 (n=544 pts)</td>
<td>35 ± 11 (n=463 pts)</td>
<td>44* (42,43)</td>
</tr>
<tr>
<td><strong>Low-contrast letter acuity (1.25%), number of letter correct</strong></td>
<td>25 ± 7 (n=61 eyes)</td>
<td>16 ± 10 (n=239 eyes)</td>
<td>18 ± 10 (n=150 eyes)</td>
<td>11 ± 11 (n=87 eyes)</td>
<td>39* (22,25,44)</td>
</tr>
<tr>
<td><strong>Binocular testing</strong></td>
<td>34 ± 8 (n=324 pts)</td>
<td>24 ± 11 (n=1,007 pts)</td>
<td>26 ± 11 (n=544 pts)</td>
<td>22 ± 12 (n=463 pts)</td>
<td>44* (42,43)</td>
</tr>
<tr>
<td><strong>NEI-VFQ-25 composite score, best score=100</strong></td>
<td>96 ± 4 (n=31 pts)</td>
<td>88 ± 13 (n=122 pts)</td>
<td>90 ± 12 (n=544 pts)</td>
<td>85 ± 14 (n=463 pts)</td>
<td>39* (44)</td>
</tr>
<tr>
<td><strong>10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25, best score=100</strong></td>
<td>97 ± 3 (n=31 pts)</td>
<td>87 ± 13 (n=122 pts)</td>
<td>88 ± 12 (n=544 pts)</td>
<td>83 ± 14 (n=463 pts)</td>
<td>39* (44)</td>
</tr>
<tr>
<td><strong>Time-domain (TD) OCT</strong></td>
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<tr>
<td><strong>Peripapillary RNFL thickness, µm</strong></td>
<td>104.5 ± 10.7 (n=219 eyes)</td>
<td>92.5 ± 16.7 (n=1,058 eyes)</td>
<td>95.6 ± 14.5 (n=730 eyes)</td>
<td>85.7 ± 19.0 (n=328 eyes)</td>
<td>32* (22,24,25)</td>
</tr>
<tr>
<td><strong>Total macular volume, mm³</strong></td>
<td>6.84 ± 0.36 (n=219 eyes)</td>
<td>6.54 ± 0.51 (n=1,058 eyes)</td>
<td>6.63 ± 0.48 (n=730 eyes)</td>
<td>6.36 ± 0.53 (n=328 eyes)</td>
<td>32* (22,24)</td>
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<tr>
<td><strong>Spectral-domain (SD) OCT</strong></td>
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<td></td>
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<tr>
<td><strong>Peripapillary RNFL thickness, µm</strong></td>
<td>92.9 ± 10.0 (n=61 eyes)</td>
<td>84.3 ± 12.8 (n=239 eyes)</td>
<td>87.6 ± 11.1 (n=150 eyes)</td>
<td>78.4 ± 13.6 (n=87 eyes)</td>
<td>39* (38,45)</td>
</tr>
<tr>
<td><strong>Ganglion cell + inner plexiform layer (GCL+IPL), µm</strong></td>
<td>88.9 ± 6.9 (n=61 eyes)</td>
<td>84.1 ± 8.4 (n=239 eyes)</td>
<td>87.0 ± 6.6 (n=150 eyes)</td>
<td>79.7 ± 9.2 (n=87 eyes)</td>
<td>39* (38,45)</td>
</tr>
<tr>
<td><strong>Macular RNFL, µm</strong></td>
<td>29.6 ± 6.0 (n=61 eyes)</td>
<td>23.5 ± 8.2 (n=239 eyes)</td>
<td>25.5 ± 7.1 (n=150 eyes)</td>
<td>20.0 ± 9.0 (n=87 eyes)</td>
<td>39* (38,45)</td>
</tr>
</tbody>
</table>

Abbreviations: MS = multiple sclerosis; ETDRS = Early Treatment Diabetic Retinopathy Study; QOL = quality of life; NEI-VFQ-25 = 25-Item National Eye Institute Visual Functioning Questionnaire; TD = time-domain (OCT-3 platform); SD = spectral-domain (Cirrus platform); OCT = optical coherence tomography; RNFL = retinal nerve fiber layer.

* Reference with asterisk is source of data presented in table; references that contain similar data are in parentheses.
A more recent study by Costello et al. (21) showed that close to 75% MS patients with ON will have RNFL losses between 10-40 μm in their affected eyes within 3-6 months following the acute event. Considering that the average RNFL thickness by TD OCT in disease-free controls is ~105 m (92 m in MS eyes), and that healthy control eyes lose only 0.017% of total RNFL thickness annually, the RNFL thinning associated with acute ON is substantial and provides a target for reduction of axonal loss in future clinical trials of ON (16). Costello et al. (21) also established a threshold value of 75 μm by TD OCT, below which there was a corresponding decline in visual function by computerized static perimetry visual field mean deviation (21). Among eyes in a collaborative heterogeneous cohort of patients with MS, eyes with a history of ON appear to have a threshold of approximately 80 μm by TD OCT, below which they show sustained abnormalities by low-contrast letter acuity.

Trials of neuroprotective or repair agents for ON will also likely establish a “therapeutic window,” or time frame within which the agent should ideally be given in order to maximize the effect of preventing axonal/neuronal loss. A recent study used several tests, including high-contrast VA and low contrast visual acuity, Farnsworth-Munsell 100 Hue color testing, automated visual fields, pattern VEP and RNFL thickness by TD-OCT in order to investigate when changes occurred in the course of ON (22). This study determined that after a mean of 4.75 months follow-up, 99% of the total amount of RNFL axonal loss that was measured from baseline had occurred. After 1.65 months (95% CI, 0.96–2.32; P < 0.05), RNFL thinning could be observed when compared to the unaffected fellow eye. Worse recovery was associated with more significant RNFL decline over three months of observation (P = 0.002). Significant macular volume loss between initial assessment and follow-up was also established (22, 23).

ON is thus a predictable cause of axonal and neuronal degeneration in the eyes of patients with MS. Interestingly, recent reports have shown that regardless of a history of ON, RNFL thinning can be seen in heterogeneous MS cohorts. Low-contrast letter acuity loss is also associated with RNFL thinning in MS eyes without a history of ON (24). In a cross-sectional study of 90 patients and 36 disease-free controls, RNFL thickness was reduced in the eyes of patients without a history of ON (105 m; P = 0.03). This study also showed that both MS eyes with a history of ON and MS eyes without a history of ON had significant damage as compared with disease-free controls (24). There was a loss of 4 m of RNFL thickness for every one line of low-contrast letter acuity loss among eyes of MS patients. RNFL thickness was associated with overall degrees of neurologic impairment, worse EDSS scores and longer disease duration.

Studies have shown that RNFL thickness becomes reduced over time in MS regardless of the history of ON (25). MS patients and controls at three academic centers underwent OCT imaging and visual testing. In patients without a history of ON, an average RNFL thickness of MS eyes were reduced by 2.9 m after 2-3 years and by 6.1 m after 3-4.5 years (P<0.001). This data would indicate a significant need for monitoring the structural changes even in eyes without a history of ON.

RESEARCH ON OCT IN MS
Using GDx-VCC, a type of scanning laser polarimetry, our group has demonstrated that RNFL thinning is related to visual loss. While OCT RNFL thickness is reflective of structural changes in the ganglion cell axons, measurement of the RNFL by scanning laser polarimetry (GDx) can demonstrate underlying microtubule integrity based on the property of birefringence. (26). This technique is particularly valuable in the setting of MS because it is able to quantify integrity of the RNFL in the setting of optic disc edema.

OCT and GDx measurements of RNFL have similar associations with visual loss, particularly in eyes with a history of acute ON (26). Uniquely, GDx is able to detect changes in small specific areas within the retina. GDx may ultimately be used to evaluate patients in clinical practice who are experiencing acute ON, particularly since OCT may be less valuable in the setting of acute optic disc edema.

OCT has shown advancements in recent years which will improve reproducibility and allow for better image quality. Newer high-resolution SD OCT has features which make scan-to-scan variability and image quality better. Automated disc-centering and longitudinal co-registration reduces scan-to-scan variability. Correction for eye movement allows greater ease and improved image quality in patients with difficulty focusing their eyes. The new OCT scanners are faster, have greater resolution and can image more of the retina.

With the development of SD-OCT, segmentation of the layers of the retina has been made possible. This is an important advance since neuronal loss is regarded as a correlate of MS disability (27-31). Studies using TD-OCT had shown decreased total macular volume in MS patients and this measure could estimate ganglion cell neuronal loss (32). Now, SD-OCT has provided the first opportunity to more directly estimate thinning of the GCL+IPL through manual segmentation (33). In a pilot study, Davies et al, showed the eyes of patients with MS (n=16) had significantly lower GCL volume as compared with controls (P<0.001). There was not a significant association between GCL and high-contrast visual acuity loss, and low-contrast acuity correlated with GCL volume scores (P=0.003).

Given the amount of time required to segment retinal layers manually (approximately 2 hours), there is a need for computerized algorithms that allow for measurement of the retinal layers on a large scale. Studies of glaucoma had successfully used computerized segmentation algorithms to quantify the layers of the retina and these methods have now been applied to SD OCT images of eyes of MS patients (34, 35).
OCT measurements of RNFL thickness and other parameters can also differ among MS subtypes. Patients with secondary progressive MS (SPMS) have greater reductions in RNFL thickness (83.4 µm by TD OCT) compared to patients with clinically isolated syndrome (CIS) (101.2 µm, P=0.0009) and relapsing remitting MS (RRMS) (103.7 µm, P=0.001) (Costello et al., 2010). In eyes with a history of ON, patients with SPMS had greater thinning (39.5 µm at follow-up) than in CIS (58.1 µm, P=0.03) or RRMS (48.2 µm). From these data Costello et al. (36) concluded that RNFL thickness is likely to represent structural changes that are related to disease subtype.

Benign MS is another area in which definitions and diagnostic criteria may unintentionally minimize the apparent role of visual pathway disease. Patients with benign MS most typically have an EDSS ≤3 and ≥15 years disease duration, and are therefore thought to follow a milder course when compared to those with typical RRMS (37). Our group recently conducted a longitudinal analysis of EDSS scores, visual function, OCT measurements, and QOL assessments in a subset of patients with benign MS. RNFL thickness was measured using TD OCT, QOL scales included the NEI-VFQ-25 and SF-36. Using the most common benign MS definition of EDSS ≤3 and ≥15-year disease duration, 13 patients (26 eyes) met criteria. Despite the relatively lower EDSS score, patients with benign MS had similar if not greater degrees of RNFL thinning from baseline during an average follow-up of 1.6 years (benign MS eyes-3.6 µm, P=0.0008 vs. baseline, paired t-test; typical MS eyes -3.3 µm, P<0.0001). Vision-specific QOL scores were likewise worse among patients with benign MS compared to those with typical RRMS (NEI-VFQ-25 composite scores 75±21 vs. 88±11, P=0.005, accounting for age) and history of ON distinguished between the two (need to clarify what this means) (P=0.002). These data provide further evidence that the EDSS does not adequately capture visual pathway axonal loss and visual impairment, both of which are likely contributors to disability in patients with benign MS.

Patients with the macular thinning predominant (MTP) phenotype of MS are of interest to our understanding of gray matter/neuronal loss as manifested in the retina. Saidha et al. (38) examined a cohort of patients with normal peripapillary RNFL thickness but thinning of the macular region to the 5th percentile or less using SD OCT. While this group had thinning of the outer retinal layers (P=0.001 for inner and outer nuclear layers), they showed little thinning of the GCL layer, suggesting a unique pattern of retinal neuronal cell loss in patients with this phenotype.

Pathologic studies of postmortem eyes of patients with MS (n=82) have shown GCL loss in 79% (10). Using algorithms originally designed for investigation of GCL+IPL thinning in glaucoma and developed at the University of Pittsburgh, our collaborative research group has investigated in vivo measurement of the GCL+IPL and other retinal layers in MS (39). In a study of 122 patients (239 eyes) and 31 controls (61 eyes), macular RNFL (P<0.001) and GCL+IPL (P=0.001) was significantly thinner in MS eyes, accounting for age and within-patient, inter-eye correlations. Macular RNFL thickness and GCL+IPL were also found to be significantly thinner in MS eyes with a history of ON (P=0.001). GCL+IPL and macular RNFL (P<0.001 and P=0.006) were the retinal layers that were most strongly associated with reduced vision-specific QOL scores (NEI-VFQ-25 and 10-Item supplement composite) (Figure 1). Ganglion cell layer neuronal loss in MS is likely to be an important indicator of visual pathway disease in MS (39).

![Figure 1](image-url)
OCT IN CLINICAL TRIALS: ROLE FOR READING CENTERS

The incorporation of OCT and visual outcome measures into MS clinical trials has benefited from the presence of OCT reading centers. The University of California (UC) Davis Reading Center recently published the results of Stratus (time-domain) OCT quality control in two multicenter MS clinical trials (40). The authors evaluated 19,961 OCT scans from 981 patients with the goal of determining the influence of OCT quality control procedures on error rate. In Trial 1 (design and therapeutic agent not specified in publication), there was no ophthalmic technician certification and data were obtained by the Reading Center retrospectively. However, in Trial 2, technicians were certified and submitted data prospectively according to the study protocol. OCT scans in Trial 2 had higher signal strengths, fewer errors, and more usable data compared to Trial 1 scans. This study showed that certified technicians and prompt transmission of data for ongoing quality control monitoring provide higher data quality; these factors and the use of Reading Centers should be considered in the design of clinical trials for MS and other neuro-ophthalmologic disorders.

CONCLUSIONS

Visual dysfunction is not only an important contributor to impairment and disability in MS, but represents a unique opportunity for studying disease mechanisms and for testing new therapies that involve neuroprotection and repair. OCT has allowed investigators to examine in vivo the morphological changes that accompany visual loss. Sensitive visual function tests, including low-contrast letter acuity, have been shown to correlate with OCT measures of axonal and neuronal loss as well as with patient-reported assessments of QOL. These observations have been instrumental in the establishment of a structure-function paradigm for using the anterior visual pathway as a model in MS and other neurologic disorders that affect the anterior visual pathway. Emerging data from ongoing clinical trials will yield important findings for therapeutics in MS, ON, and other neuro-ophthalmologic causes of visual loss (41-43).

CME ANSWERS

1. b ganglion cell layer (GCL) + inner plexiform layer (IPL) thickness
2. d all of the above are correct
2. b low-contrast letter acuity

REFERENCES


THE DEVELOPMENTAL PIPELINE—MULTI-COLOR LASER IMAGING

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LEARNING OBJECTIVES

1. To understand the optical principles behind multicolor laser imaging and how infrared, green, and blue laser light produces composite images of the retina
2. To develop a systematic approach for recognition of artifacts with multicolor imaging and for interpretation of the findings
3. To compare and contrast findings with multicolor imaging versus traditional fundus imaging
4. To show case examples about how multicolor imaging adds an additional dimension to spectral domain optical coherence tomography and fundus autofluorescence in the evaluation of patients with complex and vision-threatening neuro-ophthalmic problems

CME QUESTIONS

1. Multicolor retinal imaging produces anatomically accurate images of all the following structures except:
   a. Inner retina
   b. Mid-retina including blood vessels
   c. Outer retina including retinal pigment epithelium and choroid
   d. Optic disc
2. The infrared images with multicolor provide details of which layers of the retina [more than 1 correct answer is possible]:
   a. Internal limiting membrane, retinal nerve fiber layer and macular pigment
   b. Blood vessels and inner nuclear layer
   c. Retinal pigment epithelium
   d. Outer nuclear layer
   e. Choroid
   f. Optic disc
3. Multicolor imaging has the following advantage over traditional fundus photography for macular lesions involving the outer retina such as macular degeneration
   a. Provides assessment of degree of lipofuscin deposition
   b. Provides better imaging of choroidal neovascular membranes
   c. Provides quantitative information about the extent of subretinal fluid and blood
   d. Provides the full extent of subretinal and retinal pigment epithelial alterations compared to fundus photography
4. Multicolor has which of the following properties:
   a. Enhances the appearance of the nerve fiber layer along the vascular arcades
   b. Enhances the imaging of the full extent of epiretinal membranes compared to spectral domain OCT
   c. Provides visualization of the capillary bed around the fovea with increased detail for better detection of microaneurysms with diabetic retinopathy.
   d. The artifacts occur practically only in the image center. Since the lens surfaces are curved, light reflected during the scan of the periphery is scattered out of the beam path and does not reach the multicolor image
   e. All of the above

KEYWORDS

1. Multicolor retinal imaging
2. Fundus photography
3. Retinal nerve fiber layer
4. Macular pigment
5. Retinal blood vessels
6. Retinal pigment epithelium
7. Choroid
INTRODUCTION
After its description in 1991 [1], optical coherence tomography (OCT) has fostered a more complete understanding of the pathological mechanisms of vitreo-retinal diseases and has also resulted in similar insights in neuro-ophthalmology, especially in neuro-degenerative syndromes.

The most recent advance in retinal imaging involves multicolor laser imaging with OCT cameras. With this technology, the retina and optic nerve are scanned simultaneously with three colored lasers: infrared [815 nanometers, nm], green [518 nm], and blue [486 nm].

Each laser color focuses upon a different depth within the retina. Because of this different depths of penetration, unique, precisely localizing histological information is obtained from three discrete retinal loci. [Figure 1].

The infrared laser penetrates into the deepest retinal layers resulting in detailed images of the choroid, retinal pigment epithelium (RPE), and photoreceptors. The green laser focuses upon the mid-retinal layers and is strongly absorbed by hemoglobin; thereby imaging blood vessels, hemorrhage, and exudates. Finally, the blue laser penetrates to the shallowest depth and therefore provides detailed images of the retinal nerve fiber layer, ganglion cells, macular pigment and any structures on the surface of the retina such as epiretinal membranes.

Confocal scanning lasers, in vivo eye tracking and noise reduction techniques produce images that are automatically color balanced to the appearance of fundus photography. Except for the appearance of the optic disc, the multi-color image is equivalent to the natural color of the retina.

Like OCT scanning, multi-color is painless, non-contact, and non-invasive and many patients may be examined without pupillary dilation although in some patients dilation will improve image quality. The lasers scan the fundus in a continuous manner so that camera alignment can be adjusted throughout the study while confocal optics suppress high contrast images by eliminating scattered light.

METHOD OF ANALYSIS
We recommend the following four step-approach to the interpretation of multi-color images [Figure 2].

1. Examine the color-balanced, composite multi-color image to develop an overall “sense” of the potential areas and types of pathology.
2. Examine the images from each colored laser, correlating these findings with the color balanced image.
3. Correlate the findings of the color-balanced image and the individual laser images with spectral domain OCT images in the pathological regions.
4. Compare the findings from each eye, correlating with the neuro-ophthalmological history and examination.

Figure 2

Multicolor composite laser imaging of geographic macular atrophy. Notice how the blue and blue laser images shows the outline of the pathological changes. In contrast, the infrared clearly localizes the abnormality to the outer retinal layers and retinal pigment epithelium. (Image is courtesy of Heidelberg Engineering and Professor Sebastian Wolf, Bern, Switzerland)

Figure 1: Traditional fundus photography [above] uses visible light to capture a fundus image. In comparison, multi-color takes advantage of the differences in penetration of different laser wavelengths from blue, green, and infrared sources to more precisely image and localize pathologic processes in different areas of the retina. (Image is courtesy of Heidelberg Engineering and Professor Sebastian Wolf, Bern, Switzerland)
In a scanning laser ophthalmoscope, the retina is imaged by light entering the pupil of the eye:

**ARTIFACTS**

In a scanning laser ophthalmoscope, the retina is imaged by light entering the pupil of the eye:

1. Telescope
2. XY-scan
3. Beam splitter
4. Filter
5. Detector
6. Laser

Reflections originating on the surfaces of the lenses between XYScan unit and the eye can cause artifacts in the acquired reflectance images.

![Figure 3: Schematic representation of the optics (image is courtesy of Heidelberg Engineering)](image)

The artifacts occur practically only in the image center. Since the lens surfaces are curved, light reflected during the scan of the periphery is scattered out of the beam path and does not reach the scan unit.

The appearance and brightness of the artifact depends on the ratio of the light intensity reflected from the retina and the intensity of the light reflected on the lens surfaces. No artifact is visible if the pupil is dilated and/or if the media of the patient are clear.

However, if a patient has a significant cataract and/or if the camera is improperly aligned an artifact appears. In these cases, the sensitivity of the detector will be increased in order to obtain a clearly illuminated retinal image and the light reflected on the lens surface becomes visible.

Patients with optically significant cataracts, poor pupillary dilation, and high myopia are prone to demonstrate artifacts with multi-color imaging.

A series of images will be presented illustrating the following:

1. Imaging artifacts
2. Retinal pathology
3. Neuro-Ophthalmology pathology

**CONCLUSIONS**

Multicolor laser imaging represents the next generation of retinal imaging that will further define and localizing pathological processes within the retina that are involved in neuro-ophthalmic diseases.

Multicolor imaging shares the patient friendly nature of OCT scanning with its non-invasive, non-contact, painless techniques. Proper interpretation of the imaging results depends upon correlation with “source images” from the infrared, green, and blue lasers as well as correlation with spectral domain OCT and the patients’ clinical findings.

Multicolor imaging may also prove valuable in clinical trials in providing reliable, reproducible measurements of the area of pathological process affecting the retina.
CME ANSWERS

1. d. Optic disc. Simultaneous scanning with blue reflectance [inner retina], 486 nm; green reflectance [mid-retina], 518 nm, and infrared reflectance [outer, deep retina, 815 nm] produces anatomically accurate images of the retina but not the optic nerve due to the different histological properties of the retina and optic nerve.

2. c., d., e. Blue reflectance images the internal limiting membrane, retinal nerve fiber layer and macular pigment. Green reflectance images blood vessels and the mid-retinal layers including the inner nuclear layer.

3. d. Lipofuscin produces the autoflorescent signal for fundus autoflorescence and with the current technology is not believed to be involved with multicolor imaging. Neovascular membranes are not always well visualized with multicolor, in fact, spectral domain OCT and intravenous fluorescein angiography are probably better. Ultimately the combination of multicolor, OCT and IVFA may provide the most accurate assessment of the extent of macular disease. No quantitative algorithms for subretinal fluid and blood now exist for multicolor.

4. e.

REFERENCES

INTRODUCTION

Treatment of idiopathic intracranial hypertension (IIH) is based on anecdotal uncontrolled data as there are no properly designed and executed clinical trials to guide therapy. With this in mind, investigators of the Neuro-Ophthalmology Research Disease Consortium (NORDIC) study group developed the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), a multicenter, double-blind, randomized, placebo-controlled study of 165 subjects with mild visual loss. All subjects received a lifestyle modification program of weight-reduction with a low sodium diet. Additionally, subjects were randomized to receive either acetazolamide or matching placebo. The baseline clinical and laboratory features of enrolled IIHTT subjects are detailed here.

METHODS

Table 1 has the modification of the Dandy criteria used for the trial. Table 2 has the major inclusion and exclusion criteria.

RESULTS

Demographics Of the 318 people (309 women, 9 men) interested, 152 (147 women, 5 men) failed screening and 165 (161 women, 4 men) were enrolled. The average age of enrollees was 29.2 (± standard deviation) ± 7.5 years with a range of 18 – 53. Five percent of the enrolled subjects identified family members with IIH. Sixty-five percent were white, 25% were black, 2% were Native American, and 8% reported another race or did not report a race.

Obesity Evaluation Mean BMI was 39.9 ± 8.3 with a range of 24.9 - 71.2.

Symptoms Reported at Study Entry Headache was the most common baseline symptom overall (84%). Transient visual obscurations occurred in 68%; the median number was one per day with a range of one per month to 25 per day. Pulse synchronous tinnitus occurred in 52% of subjects; it was bilateral in 2/3 of cases and unilateral in 1/3. It occurred on average 16.7 ± 12.3 days per month ranging from once monthly to daily. Tinnitus that was non-pulsatile was present in 23%; in 1/3 of these subjects the tinnitus occurred daily. Back pain, including pain in a radicular pattern, occurred in 53%.

HEADACHE

On a scale of 0-10, the average headache severity was 6.3 ± 1.9 with 9 subjects (5.4%) reporting a severity of 10. Of those reporting headache, in 2/3 the headache was constant and daily and was intermittent in the rest. For those with intermittent headache, the median number of days per month with headache was 12 with a range of 1 – 30. The average HIT Score was 59.7 ± 9.0 with a range 36 - 78. Forty-one percent reported a pre-morbid history of migraine (7.2% had migraine with aura).

Signs The average perimetric mean deviation (PMD) in the study (worst) eye was -3.5 ± 1.1 dB; results for the fellow eye were -2.3 ± 1.1 with a range of -5.2 to 0.8 dB. The average PMD difference between eyes was 1.3 ± 1.0 dB with a range of 0 to 5.2 dB.

The VFRC readers classified defects by superior and inferior hemifields since glaucoma-like nerve fiber bundle type damage occurs in IIH. They found that 80.6% of the superior hemifields in the study eye and 86.1% of the inferior hemifields had nerve fiber bundle type visual field loss; 59.4% of the superior hemifields and 64.8% of the inferior hemifields of the fellow eye had this type of loss. The most prominent baseline hemifield abnormality classification was a partial arcuate defect with an enlarged blind spot (about ¾ of the hemifields in the study eye and about half of the hemifields in the fellow eye; Figure 1 and Table 3).

Visual acuity was measured by the ETDRS method with a score of 55 equivalent to 20/20 vision. Visual acuity was 55 letters or better in 66.3% of the study eyes and 62.0% of the...
fellow eyes (Figure 2). There was no significant relationship between ETDRS score and PMD in the study eye.

Papilledema grading using the Frisén scale was done separately by the PRC using the study photographs and the site investigator using clinical ophthalmoscopy. Study entry required a grade of at least 1 by the PRC. Grade 2 was the most common finding. There was no discernible relationship between PMD and papilledema grade in the study eye (Spearman correlation = 0.01, p = 0.88). Twelve subjects (7%) had asymmetric papilledema defined as a two grade or more difference.

A relative afferent pupillary defect was found in 5.4% of eyes. While diplopia was reported in 19%, only 3% had an esotropia on examination suggesting presence of VI nerve palsy.

The average cerebrospinal fluid (CSF) opening pressure, obtained using a standardized lumbar puncture protocol was 345.6 ± 83.5 mm water, with a range of 210 - 670. There was no significant relationship between BMI and CSF pressure (Pearson correlation = 0.25, p = 0.09). There was also no statistically significant relationship between CSF pressure and PMD (CSF pressure = -5.73*PMD + 325.2; r² = 0.006, p = 0.35).

Sixty-four percent of subjects had a risk score of 2 or 3 on the Berlin questionnaire, putting them at high risk for sleep apnea.(2)

At baseline, the mean total score on the NEI VFQ-25 was 82.4 ± 15.1 with a range of 20.2 – 100, with higher scores representing better vision-related quality of life. Our cohort’s 10 item supplement scores had an average of 75.4 ± 14.5 with a median of 77 and a range of 26 – 100. The average the SF-36 physical health summary score was 45.8 ± 9.0 with a range of 16.8 – 62.0; the mean score for women in the United States, with age 25-34, of 53 with higher scores representing better quality of life. The average mental health summary score was 44.6 ± 12.6 with a range of 7.0 – 63.9, with the mean for US women, with age 25 – 34, of 48.(3)

**DISCUSSION**

Our cohort was composed almost exclusively of women (98%). This high percentage raises the possibility that IIH may be a disease of women and most men may have other disorders, such as sleep apnea related intracranial hypertension.

**Symptoms** in our subjects were similar in frequency and type to those found in other prospective studies.(4, 5, 10)

**Headache** was the most common initial symptom in our subjects (84%) as in other studies.(4, 11, 12) Of IIHTT subjects reporting headache, in 2/3 the headache was constant and daily. This supports considering IIH as a cause of new daily persistent headache in the appropriate demographic. A prior prospective study(4) revealed the headache to be usually daily pulsatile pain that gradually increased in intensity with nausea. The reduced HIT-6 mean score we found is consistent with substantial headache-related disability over the preceding month.(13, 14)

The mechanism of headache in IIH is unclear. Experimentally induced increased intracranial pressure in humans produced headache responses that were inconsistent.(15) Johnston and Paterson(16) observed no clear relationship between changes in intracranial pressure and headache. The mechanism of headache in IIH is clouded further by the common co-occurrence of medication overuse (“rebound”) headache.(17)

**Transient visual obscurations (TVO)** are transient episodes of visual loss that usually last less than 30 seconds, occur in one or both eyes, and are followed by full visual recovery. TVO occurred in 68% of our IIHTT subjects – similar to the 72% found by others.(4, 5) TVO are not specific for IIH(18) and are not associated with the extent of disc edema. (4, 19) Sadun et al. noted the occurrence of TVO in other conditions and proposed transient ischemia of the optic nerve head due to increased local tissue pressure as the likely etiology. Having TVOs was not related to the amount of vision loss at presentation and does not appear to be related to a poor visual outcome.(4)

**Pulse synchronous tinnitus**, also called pulsatile tinnitus, was reported by 52% of IIHTT subjects. It was usually bilateral and was noticed about once every two days. Pulsatile tinnitus was found in 60% of IIH patients in a consecutive prospective series of 50 subjects.(4) Sismanis(20) found pulsatile tinnitus in each of 20 patients with IIH. Low frequency hearing loss occurred in 18 of his 20 patients and improved with therapy. Temporary improvement of the intracranial sound occurred with digital pressure over the ipsilateral jugular vein. Pulsatile tinnitus...
may be due to the turbulent flow through the functional venous stenoses of the transverse sinus that are common in IIH. \(^\text{21}\)

**Signs** of IIH are primarily related to loss of afferent visual function. While the majority of the damage in the visual field is peripheral, subtle or mild degrees of central loss is found. \(^\text{22}\) Given the IIHT entry criteria required mild visual field loss in the worse (study) eye, our perimetric results are not representative of visual loss in IIH in general.

Visual acuity is assumed to remain normal in patients with IIH except in cases with severe visual loss, or when there is a neurosensory detachment in the papillomacular region. In our subjects, the ETDRS visual acuity score (number of letters correct) was 55 letters (20/20 equivalent) or better in only 66% of study eyes at baseline and 62% of the fellow eyes (Figure 1). This is an unexpected given the mild degree of visual field loss and indicates more acuity loss than what has been reported in other studies, \(^\text{4, 23, 24}\) especially since the population norm for this age group is 20/15 vision. To our knowledge, this is the first IIH study that has used a standardized refraction protocol and the ETDRS score for visual acuity outcome.

**Ophthalmoscopic examination and fundus photography** failed to reveal a relationship between PMD and papilledema grade in the worst eye. However, the small 5 dB, PMD range may have masked this relationship that has been reported. \(^\text{25}\) Highly asymmetric papilledema (2 Frisén grade or more difference) was found in 7%. This is similar to the previously reported 10%. \(^\text{22}\)

**Perimetry** demonstrated a PMD in the worst eye at baseline of -3.5 ± 1.1 dB. The average PMD for the other eye was about 1 dB less. The VFRC classification revealed that most of the hemifields had abnormalities in the study eye consisting of nerve fiber bundle type visual loss. This took the form of enlarged blind spots and arcuate defects. Blind spot enlargement is ubiquitous but since refraction with additional plus lenses can eliminate this defect, \(^\text{26}\) we do not consider this significant visual loss unless it encroaches on fixation. Retinal mechanisms of visual loss are neurosensory detachments and choroidal folds. \(^\text{27}\)

The latter cause cecocentral defects that can be reduced with the addition of plus lens at the perimeter. However, most visual loss in IIH is due to damage at the optic nerve head. It is thought that high cerebrospinal fluid pressure is reflected along the arachnoidal trabeculations of the optic nerve sheath causing a high pressure gradient across the optic nerve head. There is resultant axoplasmic flow stasis, intra-axonal swelling and compression of axons, capillaries and small arterioles resulting in ischemic damage to the optic disc. \(^\text{28}\)

The IIHTT represents the largest prospectively analyzed cohort of untreated IIH patients. Our data show that IIH is almost exclusively a disease of women in the childbearing years. IIH patients with mild visual loss have typical symptoms, may have mild acuity loss and have visual field defects with predominantly arcuate loss and enlarged blind spots that require formal perimetry for detection.

**ACKNOWLEDGEMENTS**

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**REFERENCE**


### TABLES

#### Table 1. Modified Dandy Criteria (modified from Smith)

| 1. | Presence of signs and symptoms of increased intracranial pressure |
| 2. | Absence of localizing findings on neurologic examination except those known to occur from increased intracranial pressure |
| 3. | Absence of deformity, displacement, or obstruction of the ventricular system and otherwise normal neurodiagnostic studies, except for evidence of increased cerebrospinal fluid pressure (>200 mm water). Abnormal neuroimaging except for empty sella turcica, optic nerve sheath with filled out CSF spaces, and smooth-walled non flow-related venous sinus stenosis or collapse should lead to another diagnosis |
| 4. | Awake and alert patient |
| 5. | No other cause of increased intracranial pressure present |

#### Inclusion Criteria

1. Diagnosis of IIH by modified Dandy criteria (Table 1)
2. Reproducible visual loss present on automated perimetry
3. Average perimetric MD -2 dB up to -7 dB in the eye with greatest loss
4. Opening CSF pressure > 250 mm water or pressure of 200 to 250 mm water and at least one of the following:
   - Pulse synchronous tinnitus
   - VI palsy
   - Grade II papilledema
   - Negative echography for drusen and no other optic disc anomalies mimicking the presence of disc edema
   - Magnetic resonance venogram with lateral sinus collapse/stenosis
   - Partially empty sella on coronal or sagittal views and optic nerve sheaths with filled out CSF spaces next to the globe on T2 weighted axial scans
5. Presence of bilateral papilledema

#### Exclusion Criteria

1. Total treatment of IIH of more than two weeks (except for acetazolamide which is limited to 1 week). For every day on treatment there must be a one-day washout period.
2. Previous surgery for IIH including optic nerve sheath fenestration, CSF shunting procedures, subtemporal decompression and venous stenting
3. Previous gastric bypass surgery
4. Abnormal CSF contents
5. Other disorders causing visual loss
6. Optic disc drusen on exam or in previous history
7. Presence of diagnosed untreated obstructive sleep apnea
8. Exposure to a drug, substance or disorder that has been associated with elevation of intracranial pressure within 2 months of diagnosis such as lithium, vitamin A, and various cyclines
9. Other condition requiring diuretics, steroids or other pressure lowering agents including topiramate
10. Pregnancy or unwillingness for subject of childbearing potential to use contraception during the first year of the study
Table 3. Visual field defects in study and fellow eyes of IIHTT subjects at study entry by superior and inferior hemifield.

<table>
<thead>
<tr>
<th>Hemifield defect</th>
<th>STUDY EYE</th>
<th>FELLOW EYE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2nd Test</td>
<td>2nd Test</td>
</tr>
<tr>
<td></td>
<td>Superior</td>
<td>Inferior</td>
</tr>
<tr>
<td>Nerve Fiber Bundle Defects with and without Enlarged Blind Spot</td>
<td>115 69.7%</td>
<td>129 78.2%</td>
</tr>
<tr>
<td>Enlarged Blind Spot</td>
<td>19 11.5%</td>
<td>20 12.1%</td>
</tr>
<tr>
<td>Normal hemifield</td>
<td>13 7.9%</td>
<td>3 1.8%</td>
</tr>
<tr>
<td>Paracentral scotomas with and without an Enlarged Blind Spot</td>
<td>9 5.5%</td>
<td>7 4.27%</td>
</tr>
<tr>
<td>Other</td>
<td>9 5.5%</td>
<td>6 3.6%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>165 100.0%</strong></td>
<td><strong>165 100.0%</strong></td>
</tr>
</tbody>
</table>
QUALITY OF LIFE IN IDIOPATHIC INTRACRANIAL HYPERTENSION AT DIAGNOSIS: A PROSPECTIVE STUDY

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Presented on behalf of the NORDIC Idiopathic Intracranial Hypertension Study Group

LEARNING OBJECTIVES
1. Review quality of life literature in IIH
2. List 3 areas of quality of life that are affected in IIH
3. Factors that are associated with worsened quality of life

CME QUESTIONS
1. True/False: The IIHTT is the first study to look at Quality of Life in IIH
2. What are three domains affected by IIH?
3. True/false: Headache is associated with worsened quality of life

KEYWORDS
1. Idiopathic intracranial hypertension
2. Quality of Life
3. SF-36
4. NEI-VF25

ABSTRACT
Quality of life (QOL) is an important factor in assessing patients with neuro-ophthalmologic conditions.

Objective: We sought to measure the baseline vision-specific and overall health-related QOL at baseline in a clinical trial of patients with newly-diagnosed IIH and mild visual loss.

Methods: We assessed QOL using the SF-36 Health Survey, the 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ25), and the 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25). There were 161 women and 4 men. We compared these results with previously reported QOL studies. We also assessed the QOL in relation to sleep, headache values, and obesity.

Results: Among 165 patients with baseline assessments in the trial (161 women and 4 men), vision-specific QOL (NEI-VFQ-25 composite score 82 ±15, 10-Item Supplement score 75 ±14) was reduced compared to published values for disease-free controls, and were comparable to those for patients with multiple sclerosis (MS) and history of optic neuritis (ON). Both vision-specific and overall QOL (SF-36) were reduced (worse scores) among IIH patients with increased HIT scores for headache (Pearson linear correlations: $r = -0.45, p<0.0001$ for HIT vs. NEI-VFQ-25 composite; $r = -0.41, p<0.0001$ for HIT vs. 10-Item Supplement; $r = -0.58, p<0.0001$ for HIT vs. SF-36 Physical Components Summary; $r = -0.33, p<0.0001$ for HIT vs. SF-36 Mental Components Summary). In terms of the relation of vision-specific QOL to visual function at baseline, best PMD scores were lower (worse) among patients with worse scores for the NEI-VFQ-25 ($r = 0.16, p=0.04$).

Conclusions: IIH affects quality of life even early-on in the period following diagnosis, and even in patients mild visual loss. Compared with previous studies where individuals had the diagnosis longer, the quality of life is better at the onset. However, vision-specific QOL in patients with newly diagnosed IIH may be as bad as for patients with MS, ON, and other neuro-ophthalmic disorders. Treatment in patients with IIH should target both visual loss and headache, since QOL is linked to these important IIH symptoms.

Idiopathic intracranial hypertension (IIH) is a condition of increased intracranial pressure with normal imaging except for signs of ICP, normal cerebrospinal indices but with raised intracranial pressure. The cause of the condition is unknown, but it affects predominantly women (Durcan), and it is not rare occurring in 10-20/100,000 obese women (Durcan). Quality of life (QOL) may be affected by the commonly associated symptoms in IIH of headache, pulse synchronous tinnitus, back and neck pain, photophobia and visual loss.(Wall, George) While previously termed “benign intracranial hypertension” it is recognized to cause visual loss (Corbett) and affect the QOL of individuals who have it; previous studies (Kleinschmidt; Daniels) have demonstrated reduced QOL in women with IIH. The Kleinschmidt study was cross-sectional and retrospective in nature, while the Daniels investigation was a prospective case-control study of risk factors and disease characteristics for IIH. The Idiopathic Intracranial Treatment Trial (IIHTT) is the first study to prospectively assess the QOL of patients with only mild visual loss and within one month of their IIH diagnosis.

METHODS
The study was approved by each site’s Institutional Review Board and individual written informed consent was
obtained. The tenets of the Declaration of Helsinki were followed. We enrolled 165 newly diagnosed IIH patients who met the modified Dandy criteria for IIH (Smith JL). All subjects were enrolled within 4 weeks of the diagnosis. To qualify for enrollment, subjects had baseline visual field mean deviation between -2 and -7 dB on a 24-2 SITA standard test. See the entry criteria listed in the baseline presentation. The primary outcome for the study was the change in mean deviation of the eye with the worse mean deviation at baseline. All patients also gave historical data.

Each subject underwent MRI scan of the brain, lumbar puncture with measurement of opening pressure and constituents, fundus photography, and complete ophthalmologic and neurologic examinations. Details of the methods of this trial are reported elsewhere (reference) All patients had baseline BMI data reported, with measurement of height and weight.

Vision-specific and overall health-related QOL were assessed by the 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25); this self-administered scale includes 25 questions graded using a Likert scale. The more recently designed (Raphael 2006) 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 was also administered. General (overall) QOL was measured by the SF-36 Health Survey, and each patient underwent the HIT-6 questionnaire to evaluate headache disability. All questionnaires were administered at baseline prior to treatment and at 6 months’ follow-up.

The possibility of underlying sleep apnea was assessed using the Berlin Sleep apnea questionnaire at baseline. The present report includes only the baseline data for the IIHTT.

Statistical analyses were performed using Stata 13.0 (StataCorp, College Station, TX). Pearson linear correlation coefficients were calculated to examine the magnitudes of associations between baseline QOL scores and measures of visual function or headache severity.

RESULTS

There were 309 women and 9 men screened for the trial; 161 women and 4 men met all inclusion and exclusion criteria and were enrolled. Patient characteristics are presented in Table 1. The mean age of patients in the study was 29.2 ± 7.5 years with an average educational level of 14 years. The majority (65%) of subjects self-identified as white/Caucasian while 25% were African American, 2% were Native American, and 8% were other or did not report race.

Symptoms at study entry were headache in 84%, and visual symptoms (transient visual obscurations) in 68%. Patients also reported tinnitus—both pulsatile (52%) and non-pulsatile (23%), radicular back pain (52%), dizziness (51%), photophobia (48%), and neck pain (42%).

Headache severity on entry was 6.3 (on a 0-10 Visual Analogue Scale) and only 5.4% reported headache severity of 10/10. The headache was described as daily in the majority (2/3) of patients. The HIT score averaged 60 ± 9 and ranged 36-78. A substantial proportion (41%) of patients reported a previous history of migraine. Visual fields were mildly abnormal with the mean deviation of the worst study eye being -3.5 +/-1.1 dB. A BMI greater than 30 kg/meter² was present in 73% of patients.

Table 1: Comparison of the Current Study with previous quality of life studies in IIH

<table>
<thead>
<tr>
<th></th>
<th>Current Study 2014</th>
<th>Daniels 2007</th>
<th>Kleinschmidt 2000</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Prospective—not case-controlled</td>
<td>Prospective case controlled</td>
<td>Retrospective, case controlled</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>NONE</td>
<td>Neuro-ophthalmology patients</td>
<td>Age and Weight and normal-weight controlled</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>165</td>
<td>34</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>29.2 ± 7.5</td>
<td>32 ±10</td>
<td>33 ± 7</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Women 161, Men 4</td>
<td>Women 34</td>
<td>Women 28</td>
<td></td>
</tr>
<tr>
<td>length of diagnosis (months)</td>
<td>1 month</td>
<td>5.1 (0.5-57 mo)</td>
<td>55 mo (0-204 mo)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>39.9 ± 8.3 (24.9-71.2)</td>
<td>31.8 (20-70)</td>
<td>37.42 ± 7</td>
<td></td>
</tr>
<tr>
<td>Weight gain in the previous year</td>
<td>45% gained within 6 months</td>
<td>7.4% (0-43)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>14 (1-24)</td>
<td>NA</td>
<td>13.8 ±2.4</td>
<td></td>
</tr>
<tr>
<td>VA study eye EDTRS</td>
<td>57.4 ±6 (30-70)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>VF defect Db</td>
<td>-3.5 ±1.1(-3.2—6.4)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>ICP mm CSF</td>
<td>345.6+/-1 83.5 (210-670)</td>
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<td>NA</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>% Present</td>
<td>NA</td>
<td>% Women</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>----------</td>
<td>---------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Headache</td>
<td>84%</td>
<td>NA</td>
<td>78%</td>
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</tr>
<tr>
<td>HIT-6</td>
<td>59.7 ± 9 (36-78)</td>
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</tr>
<tr>
<td>Migraine</td>
<td>41%</td>
<td>NA</td>
<td>NA</td>
<td>20% women</td>
</tr>
<tr>
<td>Fatigue</td>
<td>NA</td>
<td>NA</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>NA</td>
<td>33% by report</td>
<td>68% (by BDI)</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>NA</td>
<td>NA</td>
<td>30% (by Spielberger State-Trait Anxiety Inventory (STAI))</td>
<td></td>
</tr>
<tr>
<td>Sleep difficulty</td>
<td>64% at risk for sleep apnea</td>
<td>NA</td>
<td>82% sleep difficulties by report</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Baseline Scores for overall and Vision-Specific QOL scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Score</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36</td>
<td>45.8 ±9.0</td>
<td>42.2 ±11.6</td>
<td>45.4</td>
<td>National norms women ages 25-34 (mean) (Ware et al)</td>
</tr>
<tr>
<td>Physical functioning subscale</td>
<td>48.2±9.4</td>
<td></td>
<td>58</td>
<td>52.96</td>
</tr>
<tr>
<td>Role physical</td>
<td>45.7±11.8</td>
<td>35</td>
<td>51.73</td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>43.9±11.4</td>
<td>42</td>
<td>51.44</td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>43.7±10.4</td>
<td>40</td>
<td>50.86</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>42.9±11.3</td>
<td>30</td>
<td>48.08</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>44.9±13.1</td>
<td>52</td>
<td>49.43</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>45.3±12.0</td>
<td>58</td>
<td>49.43</td>
<td></td>
</tr>
<tr>
<td>Role emotional</td>
<td>46.1±13.1</td>
<td>48</td>
<td>47.78</td>
<td></td>
</tr>
<tr>
<td>Physical component score</td>
<td>45.8 ±9 (17-62)</td>
<td></td>
<td></td>
<td>49.71</td>
</tr>
<tr>
<td>Mental composite score</td>
<td>44.6 ±12.6 (7-64)</td>
<td></td>
<td></td>
<td>47.14</td>
</tr>
<tr>
<td>NEI-VFQ 25 total</td>
<td>82.4 ±15 (20-100)</td>
<td>75 ±9</td>
<td>NA</td>
<td>Control (Mangione)</td>
</tr>
<tr>
<td>General health</td>
<td>49.7±24.4</td>
<td></td>
<td></td>
<td>69 ±24</td>
</tr>
<tr>
<td>General vision</td>
<td>73.8±16.8</td>
<td></td>
<td></td>
<td>83 ±83</td>
</tr>
<tr>
<td>Near vision</td>
<td>86.0±17.8</td>
<td></td>
<td></td>
<td>92±13</td>
</tr>
<tr>
<td>Distance vision</td>
<td>83.4±17.7</td>
<td></td>
<td></td>
<td>93±11</td>
</tr>
<tr>
<td>Driving</td>
<td>76.5±23.5</td>
<td></td>
<td></td>
<td>87±18</td>
</tr>
<tr>
<td>Peripheral vision</td>
<td>80.0±29.9</td>
<td></td>
<td></td>
<td>97±10</td>
</tr>
<tr>
<td>Color vision</td>
<td>98.1±8.2</td>
<td></td>
<td></td>
<td>98±8</td>
</tr>
<tr>
<td>Ocular pain</td>
<td>73.8±23.5</td>
<td></td>
<td></td>
<td>90±15</td>
</tr>
<tr>
<td>Vision specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role difficulties</td>
<td>82.5±24.7</td>
<td></td>
<td></td>
<td>93±13</td>
</tr>
<tr>
<td>Dependency</td>
<td>89.4±21.6</td>
<td></td>
<td></td>
<td>99±6</td>
</tr>
<tr>
<td>Social functioning</td>
<td>95.2±12.9</td>
<td></td>
<td></td>
<td>99±3</td>
</tr>
<tr>
<td>Mental health</td>
<td>74.1±23.2</td>
<td></td>
<td></td>
<td>92±12</td>
</tr>
</tbody>
</table>
Vision-specific QOL (NEI-VFQ-25 composite score 82 ±15, 10-Item Supplement score 75 ±14) was reduced compared to published values for disease-free controls, and were comparable to those for patients with multiple sclerosis (MS) and history of optic neuritis (ON). Both vision-specific and overall QOL (SF-36) were reduced (worse scores) among IIH patients with increased HIT scores for headache (Pearson linear correlations: \(r = -0.45, p<0.0001\) for HIT vs. NEI-VFQ-25 composite; \(r = -0.41, p<0.0001\) for HIT vs. 10-Item Supplement; \(r = -0.58, p<0.0001\) for HIT vs. SF-36 Physical Components Summary; \(r = -0.33, p<0.0001\) for HIT vs. SF-36 Mental Components Summary). Figure 1 demonstrates the moderate and significant correlation between reduced vision-specific QOL and worse HIT scores at baseline in this patient cohort. In terms of the relation of vision-specific QOL to visual function at baseline, best PMD scores were lower (worse) among patients with worse scores for the NEI-VFQ-25 (\(r = 0.16, p=0.04\)).

**Figure 1:** Scatter plot of the NEI-VFQ-25 composite scores (y-axis) vs. HIT-6 scores at baseline in patients with newly diagnosed IIH in the IIHTT. The line represents the fitted values from univariate linear regression of the two questionnaire scores.

**DISCUSSION**

Quality of life is important in the diagnosis of IIH. The first study to assess the QOL in IIH was done by Kleinschmidt. This retrospective, weight-control matched study done with 28 women who had IIH for 0-204 months (mean 55 months) showed that patients with IIH had a worse quality of life than their weight-matched and normal weight controls as assessed by the SF-36. Daniels et al showed that compared to neuro-ophthalmology patients, IIH patients who had the diagnosis of IIH (0.5-57 months) mean of 5 months also had a worse quality of life, and reduced visual quality of life (VFQ25) as well as the neuro-ophthalmology additional questions than the controls who also had visual problems diagnosed.

This study is the first to examine the quality of life of individuals with IIH at the time of their diagnosis and with individuals with very mild visual loss. In this way it complements previous studies of IIH and QOL (Daniels; Kleinschmidt) since these studies capture individuals who are diagnosed within the first year following diagnosis (Daniels) and those who have had it chronically (Kleinschmidt). It is also the first that shows the baseline of QOL of IIH when individuals do not have medication use for IIH, acetazolamide which is known for its side effects.

Vision in IIH and QOL (VF and acuity): our patients have mild visual loss in this study. Despite the mild visual field loss, the neuro-ophthalmology supplement was reduced in the areas of the two eyes seeing differently, blurred vision, and eyes feeling fatigued. In the VFQ25 ocular pain and distance driving were affected.

Obesity and QOL: This study shows that individuals with IIH are obese. Obesity by itself has been associated with lower QOL scores (Forhan; Taylor; Burkert). IIH patients however compared to obese controls (Kleinschmidt) show lower scores on the SF36. The obese controls in that study showed a higher incidence of depression and anxiety than normal weight individuals.

Headache in IIH and QOL: Headache severity does appear to correlate with the quality of life. One might expect that headache alone would worsen quality of life. However, Santanello et al. reported that individuals with migraine had quality of life scores similar to the general population. This may be because most migraineur headaches are intermittent and headache in IIH is usually chronic. Kleinschmidt et al found that patients with IIH had lower scores than weight controlled individuals and suggested that headache alone does not account for lower quality of life scores. The scales that have been most affected in QoL scales were role physical and bodily pain. (Solomon)

IIH appears to affect the QOL even at the time of diagnosis. The studies by Daniels and Kleinschmidt suggest that the longer you have the illness the worse the quality of life measures.

Sleep deprivation could account for a decreased quality of life.

Fatigue is a common complaint in iih (Kleinschmidt). In this study, while fatigue was not directly assessed, the vitality score was reduced compared to national normative data.
Depression appeared to affect the quality of life in IIH in the Kleinschmidt study. In this study while there was no specific screening for depression, there was a slight decline in mental composite compared with national norms. (Elliott)

Limitations of this study are several. First, there were no weight-matched or other controls to the study. This study did not assess daily coping skills as suggested by Daniels et al.

In conclusion, quality of life is affected in IIH. It appears that both vision and headache affect the quality of life measures and that the longer the diagnosis, the worse the quality of life scores. Vision related quality of life is similar to other chronic neurological disorders such as multiple sclerosis. Aggressively addressing the root cause of decreased quality of life—for example visual loss and headache—may improve quality of life over time.

CME ANSWERS:
1. False
2. Vitality, general health, bodily pain
3. False

REFERENCES:


44. Solomon GD. Evolution of the measurement of quality of life in migraine.


52. Ware J, Kosinski M. SF-36 Physical and mental health summary scales a manual for users of version 1, 2nd ed. 2001. Lincoln RI, Quality Metric Incorporated.


SUPPORTED BY
NIH 1U10EY017281-01A1 and 1U10EY017387-01A1
ARRA for NORDIC 3U10EY017281-01A1S1 and DCBC XXXXX
Supplements for NORDIC 3U10EY017281-01A1S2
Using the Swedish Interactive Threshold Algorithm (SITA) standard 24-2 test pattern on the Humphrey Field Analyzer (HFA) II perimeter (Model 750), 165 eligible IIHTT participants underwent at least two screening visual field examinations at least 30 minutes apart. Since lowering CSF pressure may transiently improve visual field function, at least one set of screening visual fields was required to be performed after the lumbar puncture (Figure 1). The 660 baseline visual fields were evaluated for quality control and visual field abnormality classification.

Three trained readers developed a classification system to characterize the types and severity of IIHTT visual field defects. A total of 12 mutually exclusive categories representing four general types of IIH visual loss (localized nerve fiber bundle-like, neurologic-like, diffuse, and other) were developed to include patterns of visual field loss characteristic of ocular and neurologic-like diseases, as well as patterns that were associated with testing artifact (Table 1).

Figure 1 Timing of Lumbar Puncture and Visual Field Testing
### Table 1: Classification of Visual Field Abnormalities in the iiHTT

1. A visual field is definitely **normal** if all locations are within normal limits on the Total Deviation Plot.

2. A visual field or hemifield is definitely **abnormal** if any of the conditions below are met:
   - The GHT visual field index is abnormal (Outside Normal Limits or General Reduction of Sensitivity), and/or
   - The PSD visual field index is abnormal ($p < 5\%$), and/or
   - A single point is worse than the 0.5% probability level on the Total and/or Pattern Deviation Plot, and/or
   - Two clustered points are beyond normal limits ($p < 5\%$) in a clinically suspicious area, and at least one point is worse than the 1% level on the Total and/or Pattern Deviation Plot (a cluster is defined as two or more horizontally or vertically – not diagonally -- contiguous abnormal points with $p < 5\%$), and/or
   - Two or more points are beyond normal limits ($p < 5\%$) in and/or around the peripapillary zone, and/or
   - Three or more clustered points are worse than the 5% level on the Total and/or Pattern Deviation Plot

3. A hemifield may have more than one classification with Enlarged Blind Spot (EBS) listed last.

4. In general, the pattern of abnormal points on the deviation plot (Total or Pattern) showing the greater number of abnormal points should be used to determine the appropriate classification for an abnormality. However, the other deviation plot as well as the grayscale should be evaluated to confirm the appropriateness of the classification. Abnormal points that are extraneous to the salient pattern should be ignored.

5. The superior and inferior hemifields of an abnormal field are evaluated separately, with the first designation being the superior hemifield and the second designation being the inferior hemifield.

6. A **normal** visual field is designated as **NL**.

7. An **abnormal** visual field is given a designation from the list below:

<table>
<thead>
<tr>
<th>NORMAL</th>
<th><strong>All locations are within normal limits on the Total Deviation Plot.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>NEUROLOGIC-LIKE</td>
<td><strong>Chiasmal, retrochiasmal, optic nerve chiasm (listed from least severe to most severe).</strong></td>
</tr>
<tr>
<td>Vertical Step (VS)</td>
<td>Limited visual field loss that respects the vertical meridian and that includes at least two abnormal points at or outside 15 degrees along the vertical meridian. One or more points must persist on both the Total and Pattern deviation plots.</td>
</tr>
<tr>
<td>Quadrant (Q)</td>
<td>Significant visual field loss throughout an entire quadrant that respects the vertical midline. Essentially all points must have a $p &lt; 5%$ value on the Total Deviation Plot and one or more points must persist on both the Total and Pattern deviation plots.</td>
</tr>
<tr>
<td>OPTIC NERVE</td>
<td><strong>Chiasmal, retrochiasmal, optic nerve chiasm (listed from least severe to most severe).</strong></td>
</tr>
<tr>
<td>Nerve Fiber Bundle</td>
<td>Listed from least severe to most severe</td>
</tr>
<tr>
<td>Enlarged Blind Spot (EBS)</td>
<td>A visual field abnormality in the nerve fiber bundle region that involves at least one point at the 0.5% or 1% level or two or more points at the $p &lt; 5%$ level, and is contiguous with the blind spot. In addition, the grayscale abnormality will be weighted heavily for this determination.</td>
</tr>
<tr>
<td>Nasal Step (NS)</td>
<td>If limited field loss adjacent to the nasal horizontal meridian with at least one abnormal point at or outside 15 degrees on the meridian. One or more points must persist on both the Total and Pattern deviation plots.</td>
</tr>
<tr>
<td>Pericentral (Pe)</td>
<td>A relatively small visual field abnormality (2 or more adjacent locations that are outside normal limits) that is outside the papillomacular bundle region and beyond the 9 degrees of fixation, where one or more points are within this region and appear on both the Total and Pattern Deviation Probability plots.</td>
</tr>
<tr>
<td>Partial Arcuate (Par)</td>
<td>Visual field loss in the nerve fiber bundle region that extends incompletely from the blind spot to the nasal meridian. The defect is generally contiguous with either the blind spot or the nasal meridian and must include at least one abnormal location in the temporal visual field. One or more points must persist on both the Total and Pattern deviation plots.</td>
</tr>
<tr>
<td>Arcuate (Arc)</td>
<td>Significant visual field loss in the nerve fiber bundle region, extending across contiguous abnormal points from the blind spot to at least one point outside 15 degrees adjacent to the nasal meridian. The majority of the points must persist on both the Total and Pattern deviation plots.</td>
</tr>
<tr>
<td>Diffuse (Dif)</td>
<td>Listed from least severe to most severe</td>
</tr>
<tr>
<td>Widespread (Wsp)</td>
<td>Diffuse visual field loss that includes all four quadrants. The GHT may show a General Reduction of Sensitivity or the MD must show $p &lt; 5%$. The PSD must not show a $p &lt; 5%$ value. The majority of abnormal points on the Total Deviation Plot are not abnormal on the Pattern Deviation Plot.</td>
</tr>
<tr>
<td>OTHER</td>
<td><strong>Listed from least severe to most severe.</strong></td>
</tr>
<tr>
<td>Paracentral (PC)</td>
<td>A relatively small visual field abnormality that is within 9 degrees of fixation, where one or more points are within this region and appear on both the Total and Pattern Deviation Probability plots and is generally not contiguous with the blind spot or the nasal meridian. In particular, it does not involve points outside 15 degrees that are adjacent to the nasal meridian.</td>
</tr>
<tr>
<td>Superior Depression (SD)</td>
<td>Two or more abnormal points in the very superior region. One or more points must persist on both the Total and Pattern deviation plots.</td>
</tr>
<tr>
<td>Inferior Depression (ID)</td>
<td>Two or more abnormal points in the very inferior region. One or more points must persist on both the Total and Pattern deviation plots.</td>
</tr>
<tr>
<td>Partial Peripheral Rim (PPR)</td>
<td>Generally continuous field loss outside 15 degrees, but not in all quadrants and must have some curvature. One or more points must persist on both the Total and Pattern deviation plots.</td>
</tr>
</tbody>
</table>
The three readers independently evaluated the baseline visual fields (1,320 superior and inferior hemifields) using this classification system (Tables 2, 3 & 4).

### Table 2: IIHTT Hemifield Abnormality Classification Frequency (study and non-study eyes)

<table>
<thead>
<tr>
<th>Classification (n = 1,320)</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localized:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parc/ebs</td>
<td>416</td>
<td>31.5%</td>
</tr>
<tr>
<td>EBS</td>
<td>201</td>
<td>15.2%</td>
</tr>
<tr>
<td>parc</td>
<td>93</td>
<td>7.0%</td>
</tr>
<tr>
<td>arc/ebs</td>
<td>62</td>
<td>4.7%</td>
</tr>
<tr>
<td>ns/ebs</td>
<td>59</td>
<td>4.5%</td>
</tr>
<tr>
<td>ns</td>
<td>49</td>
<td>3.7%</td>
</tr>
<tr>
<td>pericentral/ebs</td>
<td>44</td>
<td>3.3%</td>
</tr>
<tr>
<td>Pericentral</td>
<td>38</td>
<td>2.9%</td>
</tr>
<tr>
<td>arc</td>
<td>14</td>
<td>1.1%</td>
</tr>
<tr>
<td>ns/id/ebs</td>
<td>3</td>
<td>0.2%</td>
</tr>
<tr>
<td>ns/pericentral</td>
<td>3</td>
<td>0.2%</td>
</tr>
<tr>
<td>ns/pericentral/ebs</td>
<td>2</td>
<td>0.2%</td>
</tr>
<tr>
<td>parc/id/ebs</td>
<td>2</td>
<td>0.2%</td>
</tr>
<tr>
<td>ns/id</td>
<td>1</td>
<td>0.1%</td>
</tr>
<tr>
<td>ns/paracentral</td>
<td>1</td>
<td>0.1%</td>
</tr>
<tr>
<td>ns/sd</td>
<td>1</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td>989</td>
<td>74.9%</td>
</tr>
<tr>
<td><strong>Diffuse:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wsp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wsp/ebs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td>83</td>
<td>6.3%</td>
</tr>
<tr>
<td><strong>Neurologic-Like:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs/ebs</td>
<td>8</td>
<td>0.6%</td>
</tr>
<tr>
<td>vs</td>
<td>6</td>
<td>0.5%</td>
</tr>
<tr>
<td>q/ebs</td>
<td>1</td>
<td>0.1%</td>
</tr>
<tr>
<td>Q/pc/ebs</td>
<td>1</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td>16</td>
<td>1.2%</td>
</tr>
<tr>
<td>Normal</td>
<td>156</td>
<td>11.8%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>1,320</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

### Table 3: IIHTT Hemifield Abnormality Classification Frequency (Study Eye)

<table>
<thead>
<tr>
<th>Classification (n = 660)</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localized:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parc/ebs</td>
<td>257</td>
<td>38.9%</td>
</tr>
<tr>
<td>EBS</td>
<td>78</td>
<td>11.8%</td>
</tr>
<tr>
<td>parc</td>
<td>52</td>
<td>7.9%</td>
</tr>
<tr>
<td>arc/ebs</td>
<td>51</td>
<td>7.7%</td>
</tr>
<tr>
<td>ns/ebs</td>
<td>37</td>
<td>5.6%</td>
</tr>
<tr>
<td>ns</td>
<td>26</td>
<td>3.9%</td>
</tr>
<tr>
<td>pericentral/ebs</td>
<td>18</td>
<td>2.7%</td>
</tr>
<tr>
<td>pericentral</td>
<td>13</td>
<td>2.0%</td>
</tr>
<tr>
<td>arc</td>
<td>11</td>
<td>1.7%</td>
</tr>
<tr>
<td>ns/pericentral</td>
<td>2</td>
<td>0.3%</td>
</tr>
<tr>
<td>ns/id/ebs</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>ns/pericentral/ebs</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>ns/sd</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>parc/id/ebs</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td>549</td>
<td>83.2%</td>
</tr>
<tr>
<td><strong>Diffuse:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wsp</td>
<td>34</td>
<td>5.2%</td>
</tr>
<tr>
<td>wsp/ebs</td>
<td>2</td>
<td>0.3%</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td>36</td>
<td>5.5%</td>
</tr>
<tr>
<td><strong>Neurologic-Like:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs/ebs</td>
<td>7</td>
<td>1.1%</td>
</tr>
<tr>
<td>Q/ebs</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>Q/pc/ebs</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td>9</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>Other:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parc/central/ebs</td>
<td>16</td>
<td>2.4%</td>
</tr>
<tr>
<td>paracentral</td>
<td>9</td>
<td>1.4%</td>
</tr>
<tr>
<td>id</td>
<td>3</td>
<td>0.5%</td>
</tr>
<tr>
<td>sd/ebs</td>
<td>3</td>
<td>0.5%</td>
</tr>
<tr>
<td>ppr</td>
<td>2</td>
<td>0.3%</td>
</tr>
<tr>
<td>id/ebs</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>id/ns</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>id/ns/ebs</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>sd/pericentral</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td>9</td>
<td>1.4%</td>
</tr>
<tr>
<td>Normal</td>
<td>29</td>
<td>4.4%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>660</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

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Table 4: IIHTT Hemifield Abnormality Classification Frequency (Non-Study Eye)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localized:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parc/ebs</td>
<td>159</td>
<td>24.1%</td>
</tr>
<tr>
<td>ebs</td>
<td>123</td>
<td>18.6%</td>
</tr>
<tr>
<td>parc</td>
<td>41</td>
<td>6.2%</td>
</tr>
<tr>
<td>pericentral</td>
<td>26</td>
<td>3.9%</td>
</tr>
<tr>
<td>pericentral/ebs</td>
<td>26</td>
<td>3.9%</td>
</tr>
<tr>
<td>ns</td>
<td>23</td>
<td>3.5%</td>
</tr>
<tr>
<td>ns/ebs</td>
<td>22</td>
<td>3.3%</td>
</tr>
<tr>
<td>arc/ebs</td>
<td>11</td>
<td>1.7%</td>
</tr>
<tr>
<td>arc</td>
<td>3</td>
<td>0.5%</td>
</tr>
<tr>
<td>ns/id/ebs</td>
<td>2</td>
<td>0.3%</td>
</tr>
<tr>
<td>ns/id</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>ns/paracentral</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>ns/pericentral</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>ns/pericentral/ebs</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>parc/id/ebs</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td>441</td>
<td>66.8%</td>
</tr>
<tr>
<td><strong>Other:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>paracentral/ebs</td>
<td>19</td>
<td>2.9%</td>
</tr>
<tr>
<td>paracentral</td>
<td>15</td>
<td>2.3%</td>
</tr>
<tr>
<td>id</td>
<td>3</td>
<td>0.5%</td>
</tr>
<tr>
<td>sd</td>
<td>3</td>
<td>0.5%</td>
</tr>
<tr>
<td>id/ebs</td>
<td>2</td>
<td>0.3%</td>
</tr>
<tr>
<td>id/ebs</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>id/ns</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>id/ns/ebs</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>sd/pericentral</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td>461</td>
<td>7.0%</td>
</tr>
<tr>
<td><strong>Diffuse:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wsp</td>
<td>40</td>
<td>6.1%</td>
</tr>
<tr>
<td><strong>Neurologic-Like:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs</td>
<td>6</td>
<td>0.9%</td>
</tr>
<tr>
<td>Normal</td>
<td>127</td>
<td>19.2%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>660</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
The most common type of IIHTT baseline visual hemifield abnormality was a localized nerve fiber bundle-like defect (74.9%) with the majority (31.5%) of the baseline hemifields consisting of partial arcuate defects combined with an enlarged blind spot (Figure 2).

Figure 2: Partial Arcuate with Enlarged Blind Spot
Inferior localized hemifield loss was greater than superior loss for both study and non-study eyes. Additional nerve fiber bundle-like abnormalities are shown in Figure 3.

Figure 3:

Enlarged Blind Spot (EBS)

Superior Pericentral

Superior Arcuate with EBS
Figure 3 (cont)

Inferior Nasal Step

Superior and Inferior Nasal Step with EBS
Diffuse, Neurologic-like and Other defects are shown in Figures 4, 5 & 6:

**Figure 4**

- Widespread

**Figure 5**

- Quadrant

**Figure 6**

- Vertical Step
Figure 6

Paracentral

Total Deviation

Pattern Deviation

Superior Depression

Total Deviation

Pattern Deviation

Inferior Depression

Total Deviation

Pattern Deviation

Partial Peripheral Rim

Total Deviation

Pattern Deviation
Within and between reader agreements were > 90% for both inferior and superior hemifields for 2 out of 3 readers (Table 5). Test-retest reliability agreement for individual readers was 95% for both hemifields (Table 6). Quality control was also excellent for the IIHTT with very few QC errors (average of only 5.48 error points out of 100 points per visual field) (Figure 7).

**Table 5: Abnormality Classification Inter-Reader Agreement**

<table>
<thead>
<tr>
<th>Superior Hemifields</th>
<th>Inferior Hemifields</th>
<th>Total Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more in agreement</td>
<td>2 or more in agreement</td>
<td>2 or more in agreement</td>
</tr>
<tr>
<td>n = 660</td>
<td>n = 660</td>
<td>n = 1,320</td>
</tr>
<tr>
<td>628 (95%)</td>
<td>597 (91%)</td>
<td>1,225 (93%)</td>
</tr>
</tbody>
</table>

**Table 6: Abnormality Classification 20% Retest Reader Agreement**

<table>
<thead>
<tr>
<th>Superior Hemifields</th>
<th>Inferior Hemifields</th>
<th>Total Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more in agreement</td>
<td>2 or more in agreement</td>
<td>2 or more in agreement</td>
</tr>
<tr>
<td>n = 132</td>
<td>n = 132</td>
<td>n = 264</td>
</tr>
<tr>
<td>125 (95%)</td>
<td>126 (95%)</td>
<td>251 (95%)</td>
</tr>
</tbody>
</table>

**Figure 7: IIHTT Baseline Visual Field Quality Control Errors**

![IIHTT Baseline Visual Field Quality Control Errors](image)
Since the IIHTT enrolled IIH patients with mild visual loss, we cannot generalize what loss might be seen in IIH patients with more acute optic nerve damage. Wall and George\(^1\) reported 96% of patients had visual loss in at least one eye using Goldmann perimetry and 92% using automated perimetry. Loss of inferonasal portions of the visual field and visual field constriction with both arcuate defects, nasal step defects and combinations of both were the most common. Similar to the findings of IIHTT visual loss from papilledema, altitudinal defects were less common, temporal sector defects were rare, and 14% had central or paracentral defects with automated perimetry. Based on the patterns of glaucomatous visual loss, there is considerable evidence that the optic nerve head is the main site of damage for papilledema.\(^2\) The primary insult in papilledema is a slowing of axonal transport due to elevated CSF pressure transmitted down the optic nerve sheath.\(^3,5\) This elevated CSF pressure results in increased optic nerve tissue pressure, interfering with axoplasmic flow and producing flow stasis. Reduction of both slow and fast axoplasmic transport resulting in intra-axonal edema has been reported by Tso and Hayreh,\(^6\) and Hayreh showed delays in prelaminar arterial filling on fluorescein angiography. Thus, ischemia could also be a possible contributing factor. Neurosensory retinal detachments, macular exudates or hemorrhage, hyperopic shifts (related to an enlarged blind spot), and choroidal folds are other mechanisms resulting in visual loss.\(^7,8\) We believe that axoplasmic flow stasis resulting in elevated optic nerve head pressure with intraneuronal optic nerve ischemia may likely be the main mechanism of visual loss in patients with papilledema.

**SUMMARY**

Our present findings reveal that 75% of the baseline IIHTT visual fields consisted of localized nerve fiber bundle-like defects with inferior hemifield loss more common than superior hemifield loss. Approximately one-third (31.5%) of the hemifield classifications consisted of a partial arcuate abnormality combined with an EBS, thus making it the most common type of hemifield classification for both the study eye and non-study eye. A > 90% within and between reader agreement was outstanding for the IIHTT. Due to an outstanding adherence to the protocol and testing procedures, IIHTT visual field quality control was also excellent with an average of only 5.48 error points per 100-point visual field.

**REFERENCES**

OCT IMAGING IN PATIENTS WITH IDIOPATHIC INTRACRANIAL HYPERTENSION: EXPLORATIONS, ISSUES, TECHNICAL DIFFICULTIES AND NORDIC IIHTT BASELINE RESULTS

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Roosevelt Hospital/NYEEI
New York, NY

Presented on behalf of the NORDIC Idiopathic Intracranial Hypertension Study Group

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Quantitative assessments of optic disc changes of papilledema and RNFL alterations (Wang 2012) and to improve segmentation reproducibility and quantification advances with new algorithms based on 3D volume appears over a wider area reducing sampling errors. Coupling these methods, such as a cube volume scans for data collection, treatment effects. High definition spectral OCT (SD-OCT) method, measures papilledema changes on a continuous continuous ordinal staging. OCT, an additional objective Papilledema due to intracranial hypertension is typically measured using fundus photography with Frisén scale non-continuous ordinal staging. OCT, an additional objective method, measures papilledema changes on a continuous interval scale by quantifying the volume of optic nerve, the degree of RNFL and retina swelling, and to monitor treatment effects. High definition spectral OCT (SD-OCT) methods, such as a cube volume scans for data collection, give flexibility to find the exact measures of interest and increase resolution and scanning speed to acquire data over a wider area reducing sampling errors. Coupling these advances with new algorithms based on 3D volume appears to improve segmentation reproducibility and quantification of papilledema and RNFL alterations (Wang 2012) and improve quantitative assessments of optic disc changes in papilledema, including volumetric analysis by OCT and digital morphometric analysis of stereo photo images (Scott 2010; Echegaray 2011; Tang 2012)10-12. OCT imaging of papilledema was performed as a substudy of the IIHTT that included exploration of new approaches of analyzing the structural effects of papilledema and the peripapillary retina. These methods should overcome the limitations associated with swelling of the optic nerve head and the peripapillary retina (Mandel G, et al. IOVS 2010;51:ARVO-EAbstract 555). This study compared Frisén scale, OCT volumetric determinations, and disc morphometry from photographs for subjects enrolled in the IIHTT at baseline and over time and relate the findings to clinical parameters such as visual acuity, HVF mean deviation, and spinal fluid opening pressure.

Recent advances in analysis of OCT imaging of the macula region demonstrate the thinning or loss of the retinal ganglion cell layer (GCL) combined with the inner plexiform layer (IPL) in eyes with glaucoma or chronic MS.5,6,7 The 3D segmentation is one method that appears to be reliable at measuring the GCL+IPL. Thinning of this layer may be a structural indicator of irreversible loss of neurons in the setting of thickened RNFL due to edema that precludes demonstrating axonal thinning or loss. Further study of these eyes at subsequent time points will show whether this early loss of RGC correlates with failure to improve visual field dysfunction and if it predicts permanent vision loss. We will investigate how soon RGC loss begins in the setting of continued ONH swelling and RNFL thickening and whether treatment assignment is a relevant factor. In the setting of ONH and peripapillary retina swelling or edema, segmental analysis shows the RGC layer loss better than commercially available methodology (Kupersmith. IOVS 2013 ARVO E-abstract 3233). This suggests that segmental analysis might also reveal early RGC loss with ONH swelling due to optic neuritis and non-arteritic anterior ischemic optic neuropathy.

Eyes with papilledema have the plane created by the RPE/BM bordering the neural canal of the ONH deviated inward towards the vitreous instead of the normal outward deviation. The amount of deviation is significant and, in some patients, we found that measures that alleviate the intracranial pressure (lumbar puncture or ventricular shunt) normalize this disturbed angulation (Kupersmith IOVS 2011)24. This may be a novel non-invasive way to monitor the raised intracranial pressure. We have also applied a sophisticated mathematical paradigm, called geometric morphometric, to more precisely enhance this shape analysis (Sibony IOVS 2011).25 We will use 3D image analysis techniques to perform segmentation analysis and automate the process to more accurately assess the dynamics of this biomechanical distortion.

**Preliminary ONH Shape Analysis Results**

We compared HD-OCT optic nerve and peripapillary RNFL findings in papilledema eyes due to IIH (not in the IIHTT) with findings in eyes with ONH swelling due to...
optic neuritis and non-arteritic anterior ischemic optic neuropathy (NAION), conditions without intracranial hypertension. We measured average RNFL thickness and the angle of the RPE/BM at the temporal and nasal borders of the neural canal opening. The angle was measured as positive with inward (towards the vitreous) angulation and as negative with outward angulation. Of 30 eyes with papilledema, 20 eyes (67%) had inward RPE/BM rim angles. Seven of 8 optic neuritis (88%) eyes and 11/12 NAION (92%) eyes had outward angulation. On follow up, 22 papilledema eyes had less RNFL swelling and 17 of these eyes had reduced abnormal RPE/BM angulation. This indicated that the direction and magnitude of deformation of BM bordering the neural canal correlated with the status of intracranial pressure.

Figure 1. Right eye sequential SD-OCT from a patient with papilledema followed for a 12 week period. A) At presentation, marked optic disc elevation, thickening of the RNFL and inward angulation of the nasal > temporal RPE/BM at the margin are shown. Note the sclera/choroid are also deflected inward (worse at nasal border – N); B) At 8 weeks after a 15 lb weight loss, there is significant decrease in disc elevation, RNFL thickening and straightening of the RPE/BM layer; C) At 12 weeks, after 24 lb weight loss, there is resolution of papilledema with a negative RPE/BM. At each time point, the left eye (not shown) had similar findings.

Figure 2
Figure 2. (top) Procrustes superimposition of 20 semilandmarks from 75 optic discs. The semilandmark scatter from each group is color coded: Blue, papilledema; red, normals; black, AION. (2nd line) Consensus shape from each group of patients. Line tracing of semilandmarks are shown in (3rd line). (Bottom) 3-fold vertical expansion to emphasize difference and exhibit the mean shape differences as they would be appear on commercial displays with a 3:2 aspect ratio. The last figure compares papilledema to normals (excludes AION). All these plots demonstrate the RPE/BM layer in patients with papilledema have an asymmetric inverted U shape that is inwardly bowed toward the vitreous and slightly skewed nasally. Those with AION and normals have a relatively symmetrical V-shaped RPE/BM.

OCT Substudy Baseline Results with IIHTT Subjects
We enrolled 126 subjects, 122 women and 4 men, at 24 sites in the OCT substudy out of 165 subjects enrolled in the IIHTT. OCT imaging was performed by 68 certified technicians.

Baseline OCT data
Table I summarizes the descriptive statistics for the demographics and clinical data of the patient population which we used to correlate with the HD-OCT parameters. Given the IIHTT study subject entry criteria and protocol, the age, PMD, and days between distributions were
relatively narrow (Table 1). Study entry criteria required the opening pressure be at least 25 cm H\textsubscript{2}O so the elevation of CSF opening pressure in all subjects was expected, but the range of pressures was wide. The distribution for low contrast visual acuity was much larger than for high contrast visual acuity. Most eyes had mild to moderate papilledema, Frisén grade 2-4, with grading scored from photos slightly worse (higher grades) than those scored at the sites by ophthalmoscopy (Table 2a and 2b).

Table 1 Description (quartiles, limits) of the screening/baseline demographics for subjects in the OCT substudy

<table>
<thead>
<tr>
<th>LABEL</th>
<th>N</th>
<th>LOWER QUARTILE</th>
<th>MEDIAN</th>
<th>UPPER QUARTILE</th>
<th>MEAN</th>
<th>STD DEV</th>
<th>MINIMUM</th>
<th>MAXIMUM</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>126</td>
<td>24.0</td>
<td>27.0</td>
<td>33.0</td>
<td>28.9</td>
<td>7.5</td>
<td>18.0</td>
<td>52.0</td>
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<tr>
<td>Calculated BMI</td>
<td>125</td>
<td>33.8</td>
<td>38.9</td>
<td>45.4</td>
<td>40.1</td>
<td>8.3</td>
<td>26.3</td>
<td>71.2</td>
</tr>
<tr>
<td>CSF pressure (mmH\textsubscript{2}O)</td>
<td>125</td>
<td>274.0</td>
<td>330.0</td>
<td>370.0</td>
<td>340.5</td>
<td>82.9</td>
<td>220.0</td>
<td>560.0</td>
</tr>
<tr>
<td>days from LP to OCT</td>
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<td>0.0</td>
<td>2.0</td>
<td>7.0</td>
<td>4.6</td>
<td>9.3</td>
<td>-13.0</td>
<td>55.0</td>
</tr>
<tr>
<td>Amount of weight gain (lbs)</td>
<td>73</td>
<td>10.0</td>
<td>20.0</td>
<td>30.0</td>
<td>22.3</td>
<td>16.3</td>
<td>4.0</td>
<td>100.0</td>
</tr>
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<td>visual acuity total number correct for worst eye</td>
<td>126</td>
<td>53.0</td>
<td>57.0</td>
<td>59.0</td>
<td>56.0</td>
<td>5.6</td>
<td>36.0</td>
<td>70.0</td>
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<td>34.0</td>
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<td>11.1</td>
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<td>66.0</td>
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<tr>
<td>PMD in the study eye (dB)</td>
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<td>-3.2</td>
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<td>-3.5</td>
<td>1.0</td>
<td>-6.4</td>
<td>-1.9</td>
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</tbody>
</table>

Table 2a

<table>
<thead>
<tr>
<th>Grade</th>
<th>#</th>
<th>%</th>
<th>Cumulative Frequency</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>1.59</td>
<td>2</td>
<td>1.59</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>15.08</td>
<td>21</td>
<td>16.67</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>30.16</td>
<td>59</td>
<td>46.83</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>27.78</td>
<td>94</td>
<td>74.60</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>21.43</td>
<td>121</td>
<td>96.03</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>3.97</td>
<td>126</td>
<td>100.00</td>
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Table 2b

<table>
<thead>
<tr>
<th>Grade</th>
<th>#</th>
<th>%</th>
<th>Cumulative Frequency</th>
<th>Cumulative Percent</th>
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<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>11.90</td>
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<td>11.90</td>
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<tr>
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<td>42</td>
<td>33.33</td>
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<td>45.24</td>
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<td>27</td>
<td>21.43</td>
<td>84</td>
<td>66.67</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>29.37</td>
<td>121</td>
<td>96.03</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>3.97</td>
<td>126</td>
<td>100.00</td>
</tr>
</tbody>
</table>
The OCT measurements for each parameter reflecting swelling of the optic nerve and retina, RNFL, TRT, ONH volume calculated with either algorithm were elevated (for ZM algorithm RNFL almost all eyes were beyond the 95th percentile for controls) and showed a wide range of values among study subjects (Table 3). 3D-segmentation calculated GCL+IPL thickness values had a narrower range of values and standard deviation compared with ZM algorithm GCL+IPL measurements.

The variability for OCT parameters tested twice at baseline was minor (data not shown). Interocular comparisons showed strong correlation between eyes in each subject for all OCT parameters (Table 3), which were comparable for ZM and 3D-segmentation algorithms. Interocular scatter graphs for the 3D-segmentation derived RNFL, average TRT, ONH volume, and GCL+IPL values show the strong symmetry between eyes (To Be Shown). Correlations for the ONH height by raster line 3 (r = 0.72, p = 0.01) and on average (r = 0.75, p =0.01) were also strong.

The 3D-segmentation algorithm and from the Zeiss-Meditec algorithms calculated average RNFL thickness (r = 0.91, p = 0.01) and average TRT thickness (r = 0.82, p = 0.01) showed strong correlation (To Be Shown). The GCL+IPL thickness for both methods were not correlated (r = 0.08).

The Zeiss-Meditec algorithms appeared to fail in 12 eyes for the RNFL thickness and in 20 eyes for the TRT measurements when the swelling or thickness measurements were at the higher levels (Figures 7-8). The ZM calculated GCL+IPL thickness measurements were less than the control fifth percentile in 34 study eyes (50 of all 252 eyes) and by 3D-segmentation nine eyes had measurements that were thinned (To Be Shown). All nine eyes thinned by 3D-segmentation were also thinned by the ZM algorithm. For these 34 study eyes thinned by the proprietary ZM method, we considered 25 to have thinning results due to algorithm “failure.” Early in the study the quality control evaluations showed this disparity between the two methods. We then determined that if the GCL+IPL thickness was < 5th percentile by only one method, the finding would be considered an algorithm failure; see discussion for rationale). Additionally, the amount of thinning by the proprietary ZM method was extreme, beyond what has been seen in other disorders of the optic nerve with similar levels of vision dysfunction (Table 2, minimum and standard deviation results). These 34 eyes had mean 3D-segmentation values for RNFL (385±185 µm), average RNFL thickness (375.2 ± 18.7 µm), average GCL (74.8 ± 7.1 µm), and average TRT (371.0 ± 16.2 µm). Table 3 Description (quartiles, limits) of the measures studied based on the first measure of the study eye (worst eye)

<table>
<thead>
<tr>
<th>LABEL</th>
<th>N</th>
<th>LOWER QUARTILE</th>
<th>MEDIAN</th>
<th>UPPER QUARTILE</th>
<th>MEAN</th>
<th>STD DEV</th>
<th>MINIMUM</th>
<th>MAXIMUM</th>
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<tr>
<td>Line 3 of raster lines (µm)</td>
<td>120</td>
<td>855.5</td>
<td>998.5</td>
<td>1141.0</td>
<td>999.7</td>
<td>224.9</td>
<td>516.0</td>
<td>1528.0</td>
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<tr>
<td>Total Volume ONH (µm³)</td>
<td>122</td>
<td>13.6</td>
<td>15.6</td>
<td>19.1</td>
<td>16.5</td>
<td>3.8</td>
<td>10.5</td>
<td>25.9</td>
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<tr>
<td>Average RNFL (µm)</td>
<td>122</td>
<td>134.2</td>
<td>213.7</td>
<td>388.6</td>
<td>274.0</td>
<td>166.7</td>
<td>71.1</td>
<td>703.6</td>
</tr>
<tr>
<td>Average TRT (µm)</td>
<td>122</td>
<td>372.2</td>
<td>477.5</td>
<td>675.7</td>
<td>540.4</td>
<td>207.4</td>
<td>272.2</td>
<td>1061.1</td>
</tr>
<tr>
<td>Average GCL(µm)</td>
<td>124</td>
<td>80.7</td>
<td>85.8</td>
<td>89.8</td>
<td>85.2</td>
<td>7.1</td>
<td>65.8</td>
<td>103.1</td>
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<td>Average GCL as Percentile of ZM controls</td>
<td>124</td>
<td>24.9</td>
<td>58.2</td>
<td>82.5</td>
<td>53.7</td>
<td>31.4</td>
<td>0.1</td>
<td>99.9</td>
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<td>ZM algorithm calculated Measures</td>
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<tr>
<td>Center fovea Macula Thickness (µm)</td>
<td>125</td>
<td>237.0</td>
<td>250.0</td>
<td>265.0</td>
<td>251.3</td>
<td>22.0</td>
<td>197.0</td>
<td>310.0</td>
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<tr>
<td>Inner nasal Macula Thickness (µm)</td>
<td>125</td>
<td>306.0</td>
<td>321.0</td>
<td>332.0</td>
<td>319.6</td>
<td>18.5</td>
<td>281.0</td>
<td>373.0</td>
</tr>
<tr>
<td>Outer nasal Macula Thickness (µm)</td>
<td>125</td>
<td>260.0</td>
<td>274.0</td>
<td>285.0</td>
<td>273.7</td>
<td>19.5</td>
<td>232.0</td>
<td>329.0</td>
</tr>
<tr>
<td>Average RNFL (µm)</td>
<td>122</td>
<td>135.2</td>
<td>220.9</td>
<td>356.8</td>
<td>256.8</td>
<td>137.4</td>
<td>76.3</td>
<td>621.2</td>
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<tr>
<td>Average GCL (µm)</td>
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<td>73.0</td>
<td>83.0</td>
<td>88.0</td>
<td>76.4</td>
<td>18.7</td>
<td>28.0</td>
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<tr>
<td>Average TRT (µm)</td>
<td>126</td>
<td>369.8</td>
<td>420.7</td>
<td>497.7</td>
<td>436.0</td>
<td>88.4</td>
<td>278.0</td>
<td>657.8</td>
</tr>
</tbody>
</table>

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μm), TRT (683±227 μm), and ONH volume (19.2±3.9 μm) significantly increased compared with RNFL (227±131 μm, p=0.001), TRT (482±165 μm, p=0.001), and ONH volume (15.4±3.1 μm, p=0.001) for the remaining 88 eyes, in which the algorithm appeared not to fail. We hypothesized those eyes with GCL+IPL thickness < 5th percentile could arise from edema or disorganization of retinal layers due to retina swelling. However, eyes with GCL+IPL thickness < 5th percentile of controls for the ZM (data not shown) or 3D-sementation (Table 4) did not have thicker total retinal thickness in the nasal sectors (papillomacular region) than for eyes without reduced GCL+IPL. For all 252 eyes, the GCL+IPL thickness measurements for both methods did not correlate (r = 0.08).

Frisén grades, as determined by evaluation on ophthalmoccopy and by photos, correlated with the OCT measures of swelling in the ONH and peripapillary retina (To Be Shown), but not GCL+IPL values.

Eyes with GCL+IPL thickness less than the Zeiss control fifth percentile (defined as thinned) had worse vision testing that was significant for high contrast visual acuity (p = 0.01). These eyes also had a trend for reduced low contrast visual acuity or PMD compared with eyes with GCL+IPL thickness equal to or greater than the control fifth percentile (defined as normal). Frisén grades were not changed by whether the GCL+IPL was thinned or not.

Thirteen study eyes had GCL+IPL thickness greater than the 95th percentile for Zeiss controls. All 13 eyes had RNFL, TRT, and ONH volume thicker (401±154, 715±187, 19.9±3.2, respectively) than for eyes with GCL+IPL less than the 95th percentile of controls (253±158, 514±198, p = 0.002; 16.0±3.6, p = 0.001, respectively).

There was no significant correlation for any OCT parameter when compared with the high or low contrast visual acuity or PMD for study eyes (To Be Shown). None of the clinical features of IIH correlated with the OCT parameters except for the CSF opening pressure. The correlations between CSF opening pressure and ONHV, TRT, and RNFL thickness were minor but significant.

### DISCUSSION

The OCT IIHTT substudy shows that reliable, consistent, quality data OCT can be collected for IIH patients with papilledema from multiple sites with commercially available HD-OCT machines. To optimize data quality, multi-site studies must use of a specific protocol with the same optical imaging device across sites and have an OCTRC involved from the earliest planning stages of the trial.\(^\text{27}\)

The success of this study, which used 24 sites naïve to OCT data collection, further supports the need for such reading centers in multi-site clinical trials not only to provide quality data assessment, standardize procedures, and certify technicians, but to also implement the procedures necessary to improve the quality and reduce the number of poor (unusable) study data by providing feedback to test sites. Examples of quality control evaluations for OCT data have been shown for a number of other clinical disorders, such as multiple sclerosis, glaucoma and retinal vein occlusion.\(^\text{15-20,27}\)

The OCT images provide continuous variable measures that show most IIH patients in the early stage of disease have symmetrical amounts of papilledema effects on the peripapillary retina and ONH. In contrast, prior studies using the Frisén grade suggested that marked asymmetry in papilledema occurred in approximately 10% of all IIH patients.\(^\text{29}\) Further our findings support the supposition that truly unilateral papilledema is rare.

In clinical practice, OCT data are typically presented and analyzed using the algorithms provided by the manufacturer of the specific OCT machine but these have been designed to evaluate RNFL loss due to common disorders such as glaucoma and recently GCL loss in the macula. These algorithms may not accurately measure or might even fail when there is significant optic nerve head swelling as occurs in papilledema. For example, prior work that showed the OCT intrinsic machine algorithm for RNFL thickness measurement can fail when papilledema induced average RNFL is > 200 μm.\(^\text{23}\) Analyzing OCT data using a 3D-segmentation methodology, is another approach for analyzing the effects of papilledema. 3D-segmentation seems to be more reliable or less disrupted in evaluating

<table>
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<th>High Contrast Visual Acuity number correct</th>
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<tr>
<td>N LOWER QUARTILE</td>
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<tr>
<td>------------------</td>
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<tr>
<td>&lt;5%</td>
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<tr>
<td>&gt;5%</td>
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the ONH, peripapillary retina and layers of retina in the papillomacular region that have structural changes due to ONH swelling.9,26

The results suggest commercial or proprietary algorithms that evaluate effects of swelling on the data from the volume scan centered on the optic disc, for the RNFL and TRT, can be inaccurate with papilledema. This method appears to be more susceptible to failure with any process, such as edema due to swelling of the peripapillary RNFL and adjacent retina, which disrupts the regular retinal layer position or shape or boundaries. Less often, the 3D-segmentation method for evaluating the ONH falters as well if the RPE layer in the peripapillary retina cannot be identified, likely to due to poor penetration through edematous inner retinal layers.

Given that IIHTT study eyes had visual field loss at baseline, albeit mild, we anticipated that some IIH eyes would have GCL less than fifth percentile of normal eyes suggesting the presence of structural neuronal loss not apparent from RNFL and TRT measurements due to swelling. By 3D-segmentation, compared with age matched controls from ZM, only 7.3% of eyes of substudy subjects had macula region GCL+IPL thinning (< 5th percentile) at presentation. Compared with the 3D-segmentation methodology, the proprietary technique for measuring the RGC layer failed (20% of all eyes) particularly when there was significant RNFL, TRT, or ONH volume marked swelling.

It is likely that most commercially available applications for determining GCL thickness frequently fail when the peripapillary retina or RNFL is considerably thickened, presumably due to edema or factors that distort normal retinal layer architecture. This algorithm failure caused the presentation average GCL+IPL thickness to be significantly less using commercial method than the values using 3-D segmentation methods. This was previously documented in two other disorders that cause optic nerve head swelling, non-arteritic anterior ischemic optic neuropathy and optic neuritis.26 Our results suggest that in patients with recent onset IIH and mild vision loss, detectable thinning or loss of retinal ganglion cells is infrequent.

We included the 5 line HD raster line program, originally designed to study retinal layers in the macula, to the protocol in order to explore alterations in shape of the ONH due to papilledema. The ONH shape results have not been analyzed and are pending completion of a 3D-segmentation method to perform the analysis. Severe amounts of papilledema caused some problems with these images. Technicians had difficulty getting the temporal and nasal retinal pigment epithelial borders horizontally oriented without truncating the top of the ONH. Significant edema in the overlying retina layers made accurate demonstration of the retinal pigment epithelial borders difficult. We used these images to successfully measure the ONH height manually. These results correlated with the 3D-segmentation method measurement of peripapillary retinal thickening or ONH volume. Until commercial algorithms to calculate ONH volume become available, measuring ONH height manually provides another measure for following ONH swelling due to papilledema.

It remains to be determined whether eyes with reduced GCL+IPL at baseline will have poorer vision or worse RNFL thinning or loss outcomes. For example, GCL thinning might reflect optic nerve injury while the ONH swelling persists and precludes demonstrating the typical RNFL loss usually associated with optic nerve injury. We have not analyzed the macula images to determine the nature and frequency of alterations in the retinal layers macula. These could reflect an aspect of retina rather than optic nerve dysfunction as a mechanism of vision dysfunction. As in ONH alterations, the retinal changes would more likely to be reversible as treatment lowers the intracranial hypertension. The retinal abnormalities should normalize as ONH swelling lessens over time in response to therapy. However, it is possible that some permanent structure changes might occur in some retinal layers.

In a prior report using time domain OCT, IIH patients in the pediatric age group, appeared to have selective thickening of the nasal macula in the papillomacular region.26 Given the proximity of this region to the swollen ONH, we also anticipated we would find this. In contrast, in IIHTT subjects no eyes showed either inner or outer nasal total retina paramacular regions thicker than the corresponding temporal area and the temporal areas. In fact, the temporal regions were frequently thicker. There was no significant difference between outer temporal (299 ± 34 µm) and nasal (271 ± 18 µm) regions and inner temporal (326 ± 17 µm) and nasal (317 ± 14 µm) macula thickness values.

OCT imaging provides continuous measures of structural changes due to optic nerve head swelling associated with papilledema. Prior to treatment and early in the course, the average peripapillary RFNL thickness, peripapillary total retinal thickness, and optic nerve head volume calculated using 3-D segmentation all show a major significant correlation with the Frisén grade reported by the site investigators and by fundus photo analysis. The modified Frisén staging system used in the IIHTT is an ordinal scale based on the degree and the location of axonal distension and opacification. In contrast the HD-OCT provides continuous structural measures of the degree of optic disc edema. The IIHTT OCT sub-study showed that Frisén grade as reported both by the site investigators and by fundus photo analysis significantly correlated with the average peripapillary RFNL thickness (r = 0.77), the peripapillary total retinal thickness (r = 0.76), and the optic nerve head volume (r = 0.80). This is in concert with a study using time domain by Scott et al, who showed a significant correlation, for RNFL (r = 0.85) and for TRT (r = 0.87), with Frisén grades of photographs in 36 eyes of 36 IIH patients. Their reported correlations were higher than our significant but slightly smaller correlation coefficients for average RNFL, TRT, and ONH volume compared with
either investigator exam or photograph Frisén grades. The TRT measurement was more reliable than the proprietary algorithm for RNFL calculation for these time domain results. Using 3D-segmentation, we had only a three percent failure for determining the average RNFL or TRT or ONH volume. Additionally, we did not find a broader range of RNFL thickness, TRT or ONH volume values in eyes with worse Frisén grades as in the Scottt et al study.\(^{10}\) In another study that used HD-OCT, the RNFL and TRT thickness correlated with papilledema severity, but the study only evaluated 22 eyes with intracranial hypertension, 16 of which were due to IIH. In addition, the TRT correlated better than RNFL thickness in the 18 eyes with a mild papilledema grade.\(^{30}\)

There was a small but statistically significant correlation between cerebrospinal fluid opening pressure with the Frisén grade and all four OCT parameters swollen by papilledema (ONH volume and height, TRT, RNFL thickness). The amount of ONH volume and height had a modest correlation with CSF opening pressure. This result differs from the findings of Heckman, who used optic disc height and found a much stronger correlation (\(r\) was approximately 0.60) with CSF opening pressure.\(^{31}\) However the LP in his 17 cases was performed just prior to optical scanning and laser scanning tomography. The timing of the OCT relative to the LP may be important. It is known that the ICP can transiently normalize after a lumbar puncture and pilot data performed on non-study IIH patients alters the ONH shape and reduces RNFL thickening slightly after an LP before (see P Sibony NANOS 2014). Thus difference between the results in the current study and Heckman study may be explained by the timing of the OCT since the IIHTT subjects had OCTs performed on average 4.6 days after the lumbar puncture. It is possible that lumbar puncture could decompess the intracranial hypertension, even if temporary, similar to a ventricular shunt which can rapidly alter the OCT findings of ONH swelling.\(^{24}\) Any OCT changes might not appear obvious unless there was major improvement, given the wide range of increased retinal thickness and ONH volume measurements. However, there was no correlation between the number of days from the lumbar puncture and the OCT performance for any OCT parameters measuring the swelling effects of papilledema or the Frisén grade. Additionally, subjects with OCTs performed before lumbar puncture did not have worse OCT findings or Frisén grades.

All four OCT parameters of optic nerve head swelling, ONH volume and height, and peripapillary retina, RNFL thickness and TRT, were strongly correlated. The manual measurement of ONH height, using the raster scans, appears equally effective in showing the effects of intracranial hypertension. We utilized this sole measure or average ONH height utilizing the heights from all 5 HD raster lines and combining all of the raster measurements could be used to calculate a manually determined volume measurement of the swelling of the optic nerve in the neural canal.

Given the limits on IIHT study eligibility, no subjects had major visual acuity or visual field deficits; thus it is likely that few if any subjects had significant axonal loss. However, it is possible that the amount of RNFL edema and axonal swelling limited our ability to show early RNFL axonal thinning or loss. At presentation, no measure of vision performance, high or low contrast acuity or PMD, correlated with any OCT measure of peripapillary retinal or optic nerve head swelling. This differs from prior reports suggesting the extent of papilledema or TRT or RNFL swelling correlated with the amount of visual performance deficits. For example, in 20 newly diagnosed patients with IIH (and other cases that had symptoms for longer than five years), vision function was said to correlate with time domain calculated RNFL and TRT thickness.\(^{32}\) Rebolleda described a -0.45 correlation coefficient (\(p = 0.002\)) with PMD for the initial evaluations in 44 eyes of 22 IIH patients, including eyes with moderate visual field loss.\(^{35}\) None of the prior reports included a cohort using similar criteria as in IIHTT, which included only patients with IIH symptoms of six weeks or less and with vision loss that was mild. Thus, it is possible that the difference in results may be explained by the differences in in disease severity or duration. Since all IIHTT study eyes had abnormal (albeit mild, PMD = -2 db to -7 db) mean deviation in the study eye, we were not surprised that the low contrast visual acuity (median 28 letters) was frequently reduced in these eyes. This level of reduced low contrast vision is similar to reported results in patients with multiple sclerosis without a history of optic neuritis (mean 26+11) and clearly worse than controls (34+8), with mean age of 33 + 15 years, which was similar to the age of IIHTT subjects.\(^{34}\)

OCT calculated GCL+IPL thickness was in the normal range in 93% of IIHTT study eyes, suggesting that permanent injury of macula area GCL at presentation is infrequent. Peripheral field loss might have been associated with RNFL thinning with retina ganglion cells outside the macula area, but the concomitant RNFL swelling prevented assessing any loss or thinning. GCL thinning (defined as < fifth percentile of age-matched controls) via 3D-segmentation was found at study entry in only nine eyes (7%). These nine eyes had mild but significant reduced high contrast visual acuity and a trend of worse low contrast visual acuity and mean deviation than eyes without GCL thinning. However, when all study eyes were considered, no vision test result correlated with the measured average thickness of the GCL+IPL. This is not surprising given the wide range of normal GCL+IPL thickness and the small number of cases with measured thinning. We will determine whether GCL thinning at baseline is risk factor for not improving or having a worse outcome.

GCL layer thickness appears to be mildly correlated with the swelling of the ONH, retina and RNFL. GCL+IPL thickening greater than the 95th percentile of Zeiss controls occurred in 10% of eyes and this was associated with thicker ONH volume, RNFL and TRT. Both results suggest
that that the axonal stasis associated with papilledema can affect the axons immediately connected to the retina ganglion cells. If this is occurs, early loss or thinning of the GCL associated with IIH may not be apparent. This is similar to, but considerably less than, what occurs when peripapillary RNFL swelling prevents early detection of axonal loss associated with non-arteritic anterior ischemic optic neuropathy or optic neuritis. Thickening of GCL is not typically seen at presentation of optic neuritis or NAION (Kupersmith et al. Inv Ophthalmol Vis Sci 2013;54:ARVO E-abstract 3233), suggesting the acute onset of these two causes of optic neuropathy is different from the chronic, possibly gradual onset of IIH. Since acute vision loss is not typically seen and we do not know when IIH actually starts, in clinical practice and in the IIHTT, we only know when the patient presents with symptoms.

The OCT measures reflecting swelling due to papilledema, RNFL thickness, TRT, ONH volume and height are all correlated with each other and the Frisén grade at presentation in eyes with mild vision loss due to IIH. The ONH volume correlated best with the grading of photos which is not surprising since ONH volume measured the swelling of the optic disc head. We do not know whether the findings of this study can be extrapolated to patients with chronic disease or to eyes with moderate or severe vision loss. We do not know if all of the OCT measures of swelling in one or more retinal layers or in the neural tissue not in the peripapillary retina will change in parallel and remain correlated with the Frisén grade as the disease state improves or worsens. The Frisén grade is a complex ordinal measurement based a number of visual observed features, which includes, but is not limited to, swelling of the optic disc and peripapillary retina. We anticipate that IIH progresses and swelling normalizes, mechanisms of papilledema associated optic nerve and axonal injury occur, some of the OCT parameters and the Frisén grade will likely diverge. Even a study with lower resolution OCT imaging showed RNFL thickness can be used to monitor changes over time and in response to therapy in a case series of 20 patients with IIH,13,14 It remains to be determined which OCT measurement at baseline or OCT measurement that changes over time will best correlate with vision outcome, such as high and low contrast visual acuity and visual field defects or mean deviation or whether interventions will alter these measurements.

REFERENCES

Thursday, March 6, 2014

6:30 a.m. – 12:30 p.m.  Registration  Rio Mar Foyer
6:30 a.m. – 7:30 a.m.  Breakfast  Rio Mar 6-10/Caribbean
7:30 a.m. – 9:30 a.m.  Eye Pain in the “Quiet Eye” [2 CME]  Rio Mar 1-5

Moderators: Benjamin Frishberg, MD & Julie Falardeau, MD

Eye pain in the absence of clear neurologic or ophthalmologic findings is a common clinical presentation encountered by neuroophthalmologists on a daily basis. In this session, we will present the usual and unusual etiologies and diagnoses with special attention to clinical relevance. This is case based learning with use of the ARS system and will include walking through several interesting cases and 30 minutes for questions and discussion. Each lecture will include clinical cases with an additional 15 minutes of case presentation and questions using ARS to see how people would work up and treat some of the various conditions.

At the conclusion of this program, participants should be able to: 1) Provide a practical evaluation of the patient with eye pain secondary to ocular and orbital/cavernous sinus disorders; 2) Provide a practical evaluation of the patient with eye pain secondary to various headache disorders; and 3) Review the clinical characteristics and disorders associated with photophobia and provide an approach to diagnosis and treatment.

This course is designed to procure the following desirable physician attributes: medical knowledge; practice-based learning and improvement.

7:30 – 7:50 a.m.  Eye Pain: A Neurologic Perspective - Primary Headache Disorders 495
Benjamin Frishberg, MD

7:50 – 8:10 a.m.  Eye Pain: A Neurologic Perspective - Secondary Headache Disorders 505
Kathleen Digre, MD

8:10 – 8:30 a.m.  Eye Pain: An Ophthalmic Perspective 511
Howard Krauss, MD

8:30 – 8:45 a.m.  Photophobia – What’s New? 517
Bradley Katz, MD, PhD

8:45 – 9:00 a.m.  Case Presentation 519
Julie Falardeau, MD

9:00 – 9:30 a.m.  Discussion/Closing Remarks

9:30 a.m. – 10:00 a.m.  Coffee Break  Rio Mar Foyer

Schedule continued on next page
This symposium will provide an overview of the spectrum of non-organic neuro-ophthalmic presentations and review the testing techniques used to determine their non-physiologic basis. The history of somatoform disorders will be reviewed with an update on current concepts and definitions. The neurobiology of these disorders, as demonstrated by electrophysiologic and neuroimaging techniques, will be reviewed. Treatment options, natural history and prognosis will be also be discussed.

At the conclusion of this symposium, the attendee should be able to: 1) Recognize the common neuro-ophthalmic presentations of non-organic disease; 2) Be adept at demonstrating the non-physiologic nature of these disorders using “bedside” testing techniques; 3) Understand current psychiatric concepts regarding somatoform disorders; 4) Establish a management plan for these patients, including knowing the indications for psychiatric referral; and 5) Understand ancillary testing that taps into the neurobiologic basis for these conditions.

**This course is designed to procure the following desirable physician attributes: patient care; medical knowledge**
LEARNING OBJECTIVES

1. The learner will be able to differentiate primary from secondary headache disorders
2. The learner will accurately diagnose migraine as opposed to other painful disorders that cause eye pain
3. The learner will learn to differentiate the trigeminal autonomic cephalalgias
4. The learner will gain a more intimate knowledge of the International Classification of Headache Disorders system

KEYWORDS

1. Migraine
2. Tension type headache
3. Cluster headache
4. Trigeminal autonomic cephalalgias
5. Headache history

INTRODUCTION

Headache is one of the most common disorders presenting to the physicians office. Epidemiologic studies show that in a given year, the majority of people within the United States will have headache, and approximately 5% will seek medical attention. It is estimated that 25% of all new visits in a neurologists office is for headache. Over 90% of headaches are primary headache disorders that are they have no underlying secondary cause. As physicians, our main concern is finding the underlying disease or disorder that is causing headache. The primary headache disorders by definition have no significant abnormalities on their examination, nor relevant findings on neuroimaging. The key to making a diagnosis in the primary headache disorders taking a thorough history.

Before 1988, the classification of headache and the diagnostic criteria for headaches was not uniform. Even the definition of migraine differed between the US and Europe. As a result of the need for clear headache definitions, and specifically migraine definitions, the International Headache Society formed a working group.

In 1988, the International Headache Society released its first edition of a classification system for headache disorders. This classification system that has become the standard for headache diagnosis and has enhanced our ability to do multi-center headache research studies throughout the world. It has also facilitated medical practice, epidemiologic studies, and multinational clinical trials. The classification system is based on clinical consensus backed by data, experience, judgment, and compromise. The classification system has become the standard for headache diagnosis and clinical research and has become known as the International Classification for Headache Disorders (ICHD). The third edition of this classification is just been released in 2013 and is available

EYE PAIN: A NEUROLOGIC PERSPECTIVE—PRIMARY HEADACHE DISORDERS

Benjamin Frishberg, MD
The Neurology Center
Oceanside, CA

CME QUESTIONS

1. Which of the following must be present to make a diagnosis of migraine without aura?
   a. Unilateral location
   b. Throbbing
   c. Moderate or severe in intensity
   d. Nausea or light and sound sensitivity

2. Which of the following are allowed in the definition of tension type headache?
   a. Nausea
   b. Aura
   c. Photophobia
   d. Chemosis

3. Which of the following is not included in the category of “Trigeminal Autonomic Cephalalgia”?
   a. SUNCT
   b. Chronic paroxysmal hemicrania
   c. Hemicrania continua
   d. Idiopathic stabbing headache

4. Unilateral eye pain associated with tearing and redness of the eye lasting 20 seconds and dissipating only to reoccur dozens of times a day is consistent with which of the following primary headache disorders?
   a. SUNCT
   b. Paroxysmal hemicrania
   c. Idiopathic stabbing headache
   d. Cluster headache
This classification will be utilized in the new ICD-10 coding system (note that the US still uses ICD-9, but will be going to ICD-10 in 2014 as mandated by CMS). The classification system separates out the primary and secondary headache disorders, as well as many other disorders that are at least somewhat linked to migraine.

The primary headache categories and coding is broken into the four sections:

1. Migraine
2. Tension-type headache (TTH)
3. Trigeminal autonomic cephalalgias
4. Other primary headaches

THE HISTORY
Since most headache patients have normal examinations, and since primary headache disorders by definition are normal interictally, the history becomes the most important tool for making a correct diagnosis. Patients often have more than one type of headache and it is important to have the time to sort out the nuances of the headache history. Family history is especially important in migraine, as 70% of migraine sufferers have first degree relatives with migraine.

A. AGE AT ONSET
Primary headache disorders often start in childhood and early adulthood. A childhood history of car sickness is very frequently seen in migraineurs. Also, a history of recurrent bouts of abdominal pain or vomiting in childhood may be the first manifestation of a migraine disorder. Later onset headaches have a more ominous differential diagnosis, and patients with onset of a new headache disorder after age 50 will need a more extensive evaluation, often including neuroimaging. It is important to start at the beginning of the headache disorder when headaches first started. Headache patterns often change over time, and new types of headache may appear. While open-ended questions are useful, one must drill down on specifics and ask specific questions. How has the headache changed? Are there new and different types of headache? Are the associated symptoms changing?

B. LOCATION
Unilateral headaches are often associated with migraine, while cluster headaches are not only unilateral, but are always side locked; that is, always on the same side within each cluster period and in each subsequent cluster. Tension type headache on the other hand is typically bilateral.

Secondary headaches may also have very specific areas of pain. Supratentorial lesions often produce bi-frontal pain, while infratentorial lesions often cause occipital pain. Pain in and around the eye, which is of special importance to this group, may be related to diseases not only involving the orbit and the eye itself, but also may be referred pain from the cervical spine, the sinuses, the carotid artery, and the temporomandibular joint. However, in my practice, the most common cause of recurrent headache with pain in and around the eye is migraine.

C. FREQUENCY AND TIMING
Some headache disorders have fairly standard frequency; cluster headache is such an example. Most patients have one to three cluster headaches on a daily basis during the cluster episode, followed by a year or two of headache freedom. Cluster headache frequently occurs at the same time of day and night entraining to a circadian rhythm as well as a circannual rhythm. Migraine has common triggers that can be identified that lead to specific timing, for example, menstrual migraine. When dealing with the trigeminal autonomic cephalalgias (TAC), the symptoms may be very similar, but it is the duration of pain and frequency of attacks that differentiates them. Frequency is important not only to make a diagnosis, but also to determine degree of disability and thereby help select the most appropriate therapy. Headache specialists often use headache diaries to keep track of headache frequency, trigger factors, and use of medication. It is important to sort out clearly identifiable timing factors that will help in making a specific diagnosis and avoiding an unnecessary work-up. The one related red flag to always consider is a headache that is increasing in frequency and or severity. This may be a harbinger of a secondary headache disorder.

D. ONSET, DURATION, CHARACTER, AND SEVERITY
Headache duration is one of the more important factors in sorting out the primary headache disorders. Pain intensity is also very important not only for diagnosis, but to determine best therapy. Patients with frequent but very mild headaches will often not require the same intensity of treatment than the much less frequent but very severe headache sufferer may require. It is helpful to have the patient use a pain scale. The most commonly used scale is a 1 to 10 scale. It’s always interesting however, when a patient is asked this question and responds that all of the headaches are a 12, while sitting in front of you with their “12” headache, smiling, engaging, and looking well. Headaches with sudden onset and peaking over seconds are termed thunderclap headaches. While this may represent primary thunderclap headache, one must assume a potentially serious etiology such as aneurysmal rupture or venous sinus thrombosis, and evaluate on an emergent basis leaving primary thunderclap headache as a diagnosis of exclusion. While severity is certainly a factor when considering the etiology of a headache, it’s important to remember that the quality of migraine is often severe, and pain severity does not necessarily equate to a more ominous diagnosis. More serious causes of headache such as brain tumor or AVM are often associated with mild nonspecific headaches types of headache. The overall intensity of the headache is not directly correlated with the seriousness of the underlying cause.

Headache duration is very helpful in determining the type of headache disorder a patient has, especially when dealing...
with the primary headache disorders. Headaches lasting less than 4 hours are termed the short-lasting headaches, and are in a different bucket that the longer lasting primary headaches, i.e. Migraine, and Tension Type Headache. Migraine by definition lasts 4 to 72 hours. Cluster headaches typically last 30-120 minutes, while SUNCT, one of the TACs has episodes of pain that last 5-120 seconds.

**E. ASSOCIATED SYMPTOMS**
The type of associated symptoms that occur with each headache disorder can be very important in limiting the differential diagnosis. Some rules to live by:

a. Nausea may be seen with any severe headache, be it primary or secondary, but usually points to migraine. Tension type headache by definition is not associated with nausea
b. Vertigo is a common symptom seen with migraine
c. While visual aura is typical of migraine, there are patients with cluster headache who may have aura
d. Headaches starting in the neck or shoulder may still be migraine
e. Nasal congestion may be seen with migraine and does not indicate “sinus headache”
f. Migraine visual aura may rarely be secondary to an irritative lesion such as an occipital lobe tumor or AVM in which case the visual disturbance is always on the same side and a visual field defect is usually present
g. Polyuria may be associated with migraine, but not other headache disorders
h. Mood disorders and cognitive dysfunction are commonly seen both as a prodrome to migraine and with migraine
i. Lying down may exacerbate migraine pain and some patients are more comfortable sitting quietly in a chair
j. Headaches worsened by standing and much improved by laying down suggests intracranial hypotenosis
k. Side locked headaches are common in migraine, and while they are red flags in some textbooks, there is no evidence of increased incidence of secondary headache

**THE EXAMINATION**
Patients referred to neuro-ophthalmologist will receive a thorough examination of the eyes as well as a neurologic examination. The emphasis may change according to the specialty training of the examiner, but there are several important features to review with regards to headache disorders.

a. Palpate (gently) and listen to the carotid artery
b. Palpate the temporal arteries at the ear and forehead looking for thrombosis, nodules, absent pulse, and tenderness
c. Palpate the sinuses, globes, trochlear apparatus, temporal regions, and temporomandibular joint
d. Palpate the sub-occipital region, especially when the patient has chronic unexplained retro-orbital pain looking for a trigger point
e. Listen for a cranial bruit
f. Take the blood pressure
g. Examine all three distributions of the trigeminal nerve including muscles of mastication

**THE PRIMARY HEADACHE DISORDERS**

**A. MIGRAINE**
Migraine is a common disorder with a similar epidemiology throughout the world. In the US, the prevalence of migraine is 8% in men and 18% in women. In a survey of neurologists attending a headache course, the 1-year and lifetime prevalence of migraine in the 220 respondents were as follows: male neurologists, 34.7%, 46.6%; male headache specialists, 59.3%, 71.9%; female neurologists, 58.1%, 62.8%; and female headache specialists, 74.1%, 81.5%. 4% of the population has chronic daily headache, and 1% have chronic migraine (15 or more headache days a month). 20% of migraine sufferers have migraine with aura, and 80% have migraine without aura. Migraine is a diagnosis of inclusion. The IHS criteria for the diagnosis of migraine are relatively simple and straightforward. The diagnosis of migraine is made on the basis of history alone, as there are no objective findings on examination or any laboratory tests that confirm the diagnosis. Studies have shown that the majority of patients who visit a physician with the chief complaint of headache have migraine. In a study done in England, Europe, and the United States, patients seen in a primary care setting for a chief complaint of headache were evaluated and asked to keep a diary of their subsequent headaches. Headache specialists reviewed these diaries and the headaches were classified. In this study, 76% of patients met the International Headache Society criteria of migraine, 18% satisfied the criteria for probable migraine, 3% had tension-type headache, and 3% had other types of headache In another interesting observational study of patients seen in an emergency department with a primary diagnosis of headache, only 32% received a diagnosis of migraine while 59% received a diagnosis of “headache not specified.” When the charts were reviewed and the patients interviewed, 95% of the patients seen for primary complaint of headache in the emergency department met the IHS criteria for migraine.

Other features that strongly suggest migraine include predictable timing around menses, stereotyped premonitory symptoms, characteristic triggers, and improvement with sleep especially in children, positive family history, and smell sensitivity. Many patients have premonitory symptoms including yawning, food cravings, and behavioral changes, which may precede their headache by hours to a day or more. A positive family history is seen in up to 70% of migraine patients if the patient is correctly questioned. Sometimes it is difficult to tease out the history, and leading questions may provide more information. Rather than just asking if there is a positive family history of migraine, one might ask if anybody
in the family has sick headaches, headaches that put them in bed or headaches that are disabling. Many patients also have characteristic triggers for their migraine. Certain foods such as nuts, citrus fruits, aged cheeses, and cured meats may be triggers for some patients. Alcohol, especially red wine, is a potent migraine trigger. Other triggers include sleeping longer than usual in the morning, sudden increase or reduction of stress, and missing meals. So-called “let down” migraine is especially troubling to patients. These occur in migraine patients who have a reduction in stress due to vacation, weekends, or after major life events.

Although some patients with migraine never receive a diagnosis of migraine, a significant number are misdiagnosed. Of the 52% of patients with migraine who’ve not been diagnosed as having migraine in Lipton’s American Migraine study, 32% of those patients had been diagnosed as having tension-type headache, and 42% of those patients had been diagnosed as having sinus headache 4. They typically receive the diagnosis of tension headache because the pain starts in the neck, the headache is bilateral, or the headache is associated with stress. While a diagnosis of tension-type headache is often given in a patient who actually has migraine, the most common diagnosis mistakenly given to a migraine patient is “sinus headache.” Acute sinusitis may be associated with headache and facial pain, but chronic allergic sinus disease, as well as sinus and nasal congestion, are not associated with severe and disabling headaches. Patients are often given a diagnosis of sinus headache because their headaches come on with weather change, and the location of the headache is typically behind the eyes and in the forehead, which patients interpret as coming from the sinuses. In an interview study of 177 patients with definite migraine headaches, 46% of patients had at least one autonomic symptom during their migraine attack; 46% had both nasal and ocular symptoms; 14% had nasal symptoms alone; and 41% had ocular symptoms alone 5. The ocular symptoms included tearing, redness, and eyelid edema. In an interesting study done by Cady, 24 patients were recruited through a newspaper advertisement seeking patients who believed they had sinus headache, or sinus and nasal headache that put them in bed or headaches that were disabling. Many patients also have a reduction in stress due to vacation, weekends, or after major life events. In addition, they responded to sumatriptan in the same manner as a typical migraine patient 6. Despite the frequency with which a diagnosis of sinus headache is given, the data and clinical experience suggests that the vast majority of patients who are given a diagnosis of sinus headache, or believe they have sinus headache, actually have migraine.

Migraine without aura: ICHD 1.1

Description:
Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic Criteria
A. At least five attacks, fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia

Migraine with Aura: ICHD 1.2

Description:
Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   1. visual
   2. sensory
   3. speech and/or language
   4. motor
   5. brainstem
   6. retinal
C. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually within 60 minutes, by headache
   2. each individual aura symptom lasts 5–60 minutes
   3. at least one aura symptom is unilateral
   4. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been ruled out

B. TENSION TYPE HEADACHE

Tension type headache (TTHA) is the most common type of headache, and it is estimated that lifetime prevalence is 90%. TTHA is everything that is “not migraine”. It is typically mild to moderate in intensity, bilateral, non-throbbing, not increased with exertion, and not associated with nausea. Due to the relatively mild nature of these headaches, patients with episodic TTHA typically do not seek medical care and tend to self-treat with over the counter medications. In the past it was believed that most chronic daily headache was TTHA, but we now understand that most of these patients more likely have chronic migraine.
A study by Schwartz and coworkers\(^8\) estimated the overall prevalence of episodic tension-type headache at the following:

- 38.3% of the population
- Females age 30–39 years, approximately 47%
- African-American descent overall, 22.8%
- Increased with increasing levels of education
- Graduate school level education, approximately 50%

### Tension Type Headache ICHD 2.X

**Description:**
Episodes of headache, typically bilateral, pressing or tightening in quality and of mild to moderate intensity, lasting minutes to days. The pain does not worsen with routine physical activity and is not associated with nausea, but photophobia or phonophobia may be present.

**Diagnostic criteria:**

A. At least 10 episodes of headache fulfilling criteria B
   - Infrequent (<1/d/month)
   - Frequent (1-14/d/month)
   - Chronic (>14/d/mo)
B. Lasting from 30 minutes to 7 days
C. At least two of the following four characteristics:
   1. bilateral location
   2. pressing or tightening (non-pulsating) quality
   3. mild or moderate intensity
   4. not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. no nausea or vomiting
   2. no more than one of photophobia or phonophobia

### C. THE TRIGEMINAL AUTONOMIC CEPHALALGIAS

#### 1. Cluster Headache:
Cluster headache is a relatively rare primary headache disorder, but the symptoms are so stereotyped that it is usually not difficult to diagnose to the informed care provider. It may be the most painful of all of the primary headache disorders. Known in the past by a variety of monikers (migrainous neuralgia, histamine cephalgia, petrosal neuralgia, sphenopalatine neuralgia, vidian neuralgia, and Sluder’s neuralgia), it was classified as a variety of migraine until the 1988 IHS classification, when it was included in the trigeminal autonomic cephalalgias. The best early description was made by Horton at the Mayo in 1939, at which time they treated with histamine desensitization and the syndrome became known as Horton’s histamine cephalgia \(^9\). In 1952, E.C. Kunkle named the syndrome “cluster headache” and this is the name that has been adopted by the Ad Hoc Committee in 1962 and the World Federation of Neurology in 1969 \(^10\). The cluster headache itself often referred to as an attack, typically lasts 60-90 minutes, while the cluster period, which is the time in which the patient has recurrent headaches typically, lasts 4-8 weeks. Most patients have episodic cluster with cluster periods occurring once a year or every other year, often at the same time of year (circannual). Patients with chronic cluster, have headaches on a nearly daily basis with no prolonged headache free interval. There are some patients with typical cluster headache who also have typical lancinating facial pain consistent with trigeminal neuralgia and this has been referred to as “cluster-tic”. The term “cluster migraine” was coined by Medina and Diamond \(^11\) in 1977 to describe patients who have both cluster headache and migraine headache. However it is a term that is misused to describe patients with migraine who have “clusters” of migraine followed by periods with no migraine. The term cluster migraine should be avoided. The usual attack consists of the rapid onset of unilateral periorbital headache that builds to a peak in about 10 to 15 minutes and lasts for approximately 30 to 180 minutes. During a cluster attack, patients are agitated and prefer to pace in contradistinction to migraine where they want to be still. Attacks are characterized by excruciating pain that is regarded by sufferers as the worst pain that they have ever experienced. The pain is associated with ipsilateral cranial parasympathetic over activity with may cause one or more of the following: lacrimation, conjunctival injection and nasal stuffiness or rhinorrhea, lid edema, and an ipsilateral partial (third order neuron) Horner syndrome with ptosis and miosis. The headache is unilateral. In order of decreasing frequency, common sites of pain are: orbital, retro-orbital, temporal, supraorbital, and infraorbital. The number of attacks per day varies, usually from 1 to 3, but the International Headache Society classification allows from 1 every second day to 8 per day within the definition of cluster headache. Migrainous features, such as nausea, photophobia, and phonophobia, can be present in as many as half of cluster headache cases \(^12\). Moreover, between 6% \(^13\) and 14% \(^12\) of patients report typical migraine aura with their cluster headache.

Cluster headache involves dysfunction of central nervous system elements concerned with pain control and with links to circadian and circannual mechanisms. Research suggests the hypothalamus is intricately involved in the pathophysiology of cluster headache.

#### Cluster Headache ICHD 3.1

**Description:**
Attacks of severe, strictly unilateral pain, which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15–180 minutes and occurring from once every other day to eight times a day. The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid edema, and/or with restlessness or agitation.
Diagnostic criteria:
A. At least five attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)
C. Either or both of the following:
   1. at least one of the following symptoms or signs, ipsilateral to the headache:
      a) conjunctival injection and/or lacrimation
      b) nasal congestion and/or rhinorrhea
      c) eyelid edema
      d) forehead and facial sweating
      e) forehead and facial flushing
      f) sensation of fullness in the ear
      g) miosis and/or ptosis
   2. a sense of restlessness or agitation
D. Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active

2. Paroxysmal Hemicrania: This is a rare headache disorder, seen much less commonly than cluster headache. It can be episodic or chronic, but the chronic form is more typical. Some patients start with the episodic form and over time transform into the more typical chronic form. Chronic paroxysmal hemicrania (CPH), was first described in 1974 by Sjaastad 15 on the basis of the first 2 patients, who had daily solitary, limited attacks (i.e., paroxysmal) of unilateral headache that did not shift sides (i.e., hemicrania). The clinical diagnosis is based on attacks of severe, unilateral orbital, supraorbital, and/or temporal pain, always on the same side, lasting 2–45 minutes. Pain is associated with at least 1 of the following signs/symptoms on the symptomatic side:
   • conjunctival injection
   • lacrimation
   • nasal congestion
   • rhinorrhea
   • ptosis
   • eyelid edema

Most patients who have CPH exhibit lacrimation (62%), followed by nasal congestion (42%), conjunctival injection and rhinorrhea (36%), and ptosis (33%) 16. There may be mild meiosis, but not a typical sympathetic defect as one sees in cluster headache. In some patients CPH attacks can be triggered by a variety of triggers such as rotating the neck or flexing the head to the side of the headaches or by applying external pressure to the transverse processes of C4 to C5 or the C2 nerve root on the symptomatic side. The attack frequency typically ranges from 10–20 attacks daily, but may be more. Attacks usually last 2–25 minutes, but they may last as long as 60 minutes. By definition, this is one of the Indomethacin responsive headache disorders, and in order to make the diagnosis, the patient must respond to Indomethacin. There are case reports of paroxysmal hemicrania like headaches that are secondary to parasellar disease, orbital pathology, and vascular disorders. These patients should be imaged with contrast enhanced MRI. The etiology of this headache disorder is unknown, and there is no genetic component. Functional imaging studies have demonstrated involvement of the hypothalamus. 17 Average age of onset is 34, and this entity may be seen in children. There is a 3:1 female predominance.

Paroxysmal Hemicrania ICHD 3.2

Description:
Attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal or in any combination of these sites, lasting 2–30 minutes and occurring several or many times a day. The attacks are associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid edema. They respond absolutely to Indomethacin.

Diagnostic criteria:
A. At least 20 attacks fulfilling criteria B–E
B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2–30 minutes
C. At least one of the following symptoms or signs, ipsilateral to the pain:
   1. conjunctival injection and/or lacrimation
   2. nasal congestion and/or rhinorrhea
   3. eyelid edema
   4. forehead and facial sweating
   5. forehead and facial flushing
   6. sensation of fullness in the ear
   7. miosis and/or ptosis
D. Attacks have a frequency above five per day for more than half of the time
E. Attacks are prevented absolutely by therapeutic doses of Indomethacin
F. Not better accounted for by another ICHD-3 diagnosis

3. SUNA (Short-lasting Unilateral Neuralgiform headache with cranial autonomic features) and SUNCT: (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing syndrome)

The SUNCT syndrome was first described by Sjaastad and colleagues in 1978 18. The description of the complete syndrome came in 1989 again by Sjaastad 19. In the ICHD-3 classification, SUNCT and SUNA are both a subclass of “short-lasting unilateral neuralgiform headache attacks”. By definition, SUNCT patients always have both conjunctival injection and tearing, and the symptoms are a prominent part of the syndrome. Patients with SUNA have at least one autonomic feature, and the autonomic symptoms tend to be much less intense than in SUNCT. These symptoms include:
   • conjunctival injection and/or lacrimation
   • nasal congestion and/or rhinorrhea
   • eyelid edema
   • forehead and facial sweating
   • forehead and facial flushing
   • sensation of fullness in the ear
   • miosis and/or ptosis
SUNCT is much more common in men than women with a M:F ratio of 17:2. The typical age of onset is between 40 and 70 years and the mean age of onset is 51 years. Pain severity is normally moderate to severe, unlike cluster headache, which is always severe. Pain duration is extremely short, usually lasting between 5 and 240 seconds, with an average duration of 10 to 60 seconds. The brevity of SUNCT sets it apart from all of the other primary headache disorders except for cranial neuralgias such as trigeminal neuralgia and stabbing headache pains. Pain onset is typically abrupt, with maximum intensity being reached in a few seconds. The pain normally plateaus at a maximum intensity for several seconds and then quickly abates. Mean attack frequency is 28 attacks per day, but may range form 1-80 with a tendency to have frequent attacks followed by a period of remission. SUNCT syndrome is an episodic disorder that presents in a relapsing and remitting pattern. Each symptomatic period can last from several days to several months, and a person who has SUNCT syndrome typically has one to two symptomatic periods a year. By definition, patients with SUNCT have conjunctival injection and tearing, but many may have other autonomic features. Ipsilateral rhinorrhea or nasal congestion occurs in 2/3 of patients. Other less common associated symptoms include eyelid edema, narrowed palpebral fissure, facial erythema, and photophobia. Typically, conjunctival injection and eye tearing start within 1 to 2 seconds of pain onset and remain until the head pain ceases. While SUNCT can occur spontaneously, many suffers have triggers including chewing, nose blowing, coughing, forehead touching, eyelid squeezing, neck movements (rotation, extension, and flexion), and eating ice cream. SUNCT and SUNA are not Indomethacin responsive like most of the other trigeminal autonomic cephalalgias. There is some evidence that microvascular compression of the trigeminal nerve may be causative in some patients as microvascular decompression has been successful in providing complete remission is greater than 50% of patients. 

**Short-lasting unilateral neuralgiform headache attacks (SUNCT)**

**ICHD 3.3**

**Description:**
Attacks of moderate or severe, strictly unilateral head pain lasting seconds to minutes, occurring at least once a day and usually associated with prominent lacrimation and redness of the ipsilateral eye.

**Diagnostic criteria:**

- At least 20 attacks fulfilling criteria B–D

- Moderate or severe unilateral head pain, with orbital, supraorbital, temporal and/or other trigeminal distribution, lasting for 1–600 seconds and occurring as single stabs, series of stabs or in a sawtooth pattern

- At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:
  1. conjunctival injection and/or lacrimation
  2. nasal congestion and/or rhinorrhea
  3. eyelid edema

**Diagostic criteria:**

A. Attacks fulfilling criteria for 3.3 Short-lasting unilateral neuralgiform headache attacks

B. Both conjunctival injection and lacrimation (tearing).

**Short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)**

**Diagnostic criteria:**

A. Attacks fulfilling criteria for 3.3 Short-lasting unilateral neuralgiform headache attacks, and criterion B below

B. Only one or neither of conjunctival injection and lacrimation (tearing).

4. **Hemicrania Continua (HC):**

The term hemicrania continua was first introduced in 1984 by Sjaastad and Spierings. HC is a unilateral headache with varying intensity. It is continuous for months and years at a time and there are paroxysmal episodes of worsening pain lasting 20 minutes to 48 hours associated with autonomic features. These include:

- conjunctival injection
- lacrimation
- nasal congestion
- rhinorrhea
- eyelid edema
- forehead and facial sweating
- forehead and facial flushing
- sensation of fullness in the ear
- miosis and/or ptosis.

Patients often become agitated and irritable. During these exacerbations, there may be typical migraine symptoms as well, including nausea, vomiting, photophobia, and phonophobia. Some patients complain of a foreign body sensation in the eye, and others have typical ice-pick pains, especially with exacerbations.

In Cittadini and Goadsby’s study of 39 patients, the pain was reported in the following locations: temporal, 82 percent; orbital, 67 percent; frontal, 64 percent; retro-orbital, 59 percent; occipital and parietal, 54 percent; vertex and periorbital, 51 percent; neck, 33 percent; maxillary and ear, 30 percent; upper teeth, 20 percent; shoulder, 18 percent; nose, 15 percent; jaw, 15 percent; eyebrow and lower teeth, 10 percent; retro-auricular area, eight percent; and upper and lower gum, two percent. HC can be labeled chronic when daily and continuous without pain-free periods for a minimum of one year and episodic when there are pain-free intervals of at least a day without treatment.
HC is one of the Indomethacin responsive headache disorders, and like CPH, absolutely responds to Indomethacin at appropriate doses.

**Hemicrania continua ICHD 3.4**

**Description:**
Persistent, strictly unilateral headache, associated with conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid edema, and/or with restlessness or agitation. The headache is absolutely sensitive to Indomethacin.

**Diagnostic criteria:**
A. Unilateral headache fulfilling criteria B–D
B. Present for >3 months, with exacerbations of moderate or greater intensity
C. Either or both of the following:
   1. at least one of the following symptoms or signs, ipsilateral to the headache:
      a) conjunctival injection and/or lacrimation
      b) nasal congestion and/or rhinorrhea
      c) eyelid edema
      d) forehead and facial sweating
      e) forehead and facial flushing
      f) sensation of fullness in the ear
      g) miosis and/or ptosis
   2. a sense of restlessness or agitation, or aggravation of the pain by movement
D. Responds absolutely to therapeutic doses of Indomethacin

**D. PRIMARY STABBING HEADACHE (PSH)**
This entity is associated with brief sharp recurrent pains that occur in the head and face, mostly in the V1 distribution. This condition has been known in the past as ice-pick pains, jabs and jolts, needle-in-the-eye syndrome, and ophthalmodynia periodica. It seen more commonly in migraine patients, but is quite common in the general population with one study suggesting a prevalence rate as high as 35% with average age of onset of 28 and a female predominance 24. Raskin compared the incidence and the clinical characteristics of PSH in 100 migraineurs and 100 control subjects 25. PSH was found in 42 % of migraineurs versus only 3 % of healthy controls. These sharp stabbing or ice pick pains are often felt in the eye and periocular region prompting ophthalmologic or neuro-ophthalmologic evaluation. The examination is always normal Studies show 80% of stabs last 3 seconds or less. Attack frequency is generally low, with one or a few per day. In rare cases, stabs occur repetitively over days. It may move from one area to another on the head and face, in either the same or the opposite hemicranium: in only one-third of patients it has a fixed location. When stabs are strictly localized to one area, structural changes at this site and in the distribution of the affected cranial nerve must be excluded. A few patients have accompanying symptoms, but not including cranial autonomic symptoms. Presence of any autonomic symptoms help to differentiate PSH from Short-lasting unilateral neuralgiform headache attacks. There is some speculation that PSH may be associated with venous sinus stenosis 26. The headache disorder is usually responsive to Indomethacin, but treatment is rarely necessary.

**Primary stabbing headache ICHD 4.7**

**Description:**
Transient and localized stabs of pain in the head that occur spontaneously in the absence of organic disease of underlying structures or of the cranial nerves.

**Diagnostic criteria:**
A. Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B–D
B. Each stab lasts for up to a few seconds
C. Stabs recur with irregular frequency, from one to many per day
D. No cranial autonomic symptoms

**E. TRIGEMINAL NEURALGIA (TGN)**

TGN is not typically included as a primary headache disorder, but rather but rather it is classified as a neuralgia. Nicolas André coined the term tic douloureux in 1756 in a book, Observations pratiques sur les maladies de l’urethre et sur plusieurs faits convulsifs. There is a rich history of descriptions of the condition, which likely represents TGN which can be found in the writings of Galen, Aretaeus of Cappadocia (born circa AD 81), and in the 11th century by Avicenna (“tortura oris”) 27–28.

John Fothergill was the first to give a full and accurate description of this condition in a paper titled “On a Painful Affliction of the Face,” which he presented to the medical society of London in 1773 29. It was called Fothergill’s disease for the next 150 years.

Average age of onset is about 60 and it is more common in women than men in a ratio of 2.5:1. While vascular compression is the most common cause of TGN, posterior fossa tumors, and multiple sclerosis should be considered, especially in the younger patient. As many as 15% of trigeminal cases are due to secondary causes so neuroimaging is often recommended. Red flags in trigeminal neuralgia include sensory loss and bilateral involvement 30.

TGN typically presents with brief stabbing unilateral facial pain, more often on the right side of the face. Patients may only have one or two attacks a day, but some may have hundreds. Typical triggers include: chewing, talking, smiling, drinking cold or hot fluids, touching a specific pain trigger point, shaving, brushing teeth, blowing the nose or a draft. Patients can usually localize their pain precisely and the pain usually stays in the distribution of one division of the trigeminal nerve or occurs at the border zone of two nerves. The most common location is the corner of the mouth with radiation to the angle of the jaw. The ophthalmic distribution is involved in less than 5% of cases, so ophthalmologists are usually not involved in the
early diagnosis. The pain is typically severe, paroxysmal, and lancinating. It is described as like an electrical shock which lasts 1-2 seconds but may continue for 20-30 seconds leaving the patient with a deep aching. Many patients have a refractory period and become pain free between paroxysms of pain.

**Trigeminal Neuralgia ICHD 13.1**

**Description:**
Trigeminal neuralgia developing without apparent cause other than neurovascular compression.

**Diagnostic criteria:**
A. At least three attacks of unilateral facial pain fulfilling criteria B and C
B. Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution
C. Pain has at least three of the following four characteristics:
   1. recurring in paroxysmal attacks lasting from a fraction of a second to 2 minutes
   2. severe intensity
   3. electric shock-like, shooting, stabbing or sharp in quality
   4. precipitated by innocuous stimuli to the affected side of the face
D. No clinically evident neurological deficit

**CME ANSWERS**
1. d
2. c
3. d
4. a

**REFERENCES**
LEARNING OBJECTIVES
1. The learner will recognize 3 historical findings that would suggest a neurological cause to eye pain
2. The learner will be able to discuss why intracranial pathologies can present with eye pain
3. The learner will describe at least 5 different neurological causes of eye pain and know how to make the diagnosis by imaging findings

CME QUESTIONS
1. What headache type would lead you to look for reversible cerebral vasoconstriction syndrome?
   a. Orthostatic
   b. Stabbing
   c. Thunderclap
   d. Asthenopic
2. Which of the following is true regarding intracranial tumor and associated headache.eye pain?
   a. Tumors can cause headache approximately 25% of the time
   b. Early morning headache is highly indicative of an intracranial tumor
   c. Pituitary tumor usually presents with headaches commensurate with the size of the tumor
   d. The headache type associated with intracranial tumors often cannot be differentiated from tension type
3. Various intracranial processes can present with headache and eye pain. Which of the following statement is true?
   a. Head and neck pain is the most common symptom of a carotid dissection
   b. Orthostatic headache is highly suggestive of an intracranial tumor
   c. Bleeding from an intra cavernous carotid artery aneurysm typically presents with a thunderclap headache
   d. Over 80% of patients with chronic headache.eye pain have rhinosinusitis as a cause of their chronic headache disorder

KEYWORDS
1. Eye pain
2. Trigeminal
3. Aneurysm
4. Reversible cerebral vasoconstriction syndrome
5. Intracranial pressure

INTRODUCTION
That the eye would be a source of pain from a neurological cause should not be surprising since the trigeminal nerve, especially the first division, innervates the meninges, arteries and veins, and the nasal sinuses. Involvement of the first division of the trigeminal nerve causes referred pain, which is felt in and around the eye. Almost all intracranial disease processes be they vascular, tumor, pressure, infection or inflammation have the ability to cause eye pain and headache.

TRIGEMINAL ANATOMY REVIEW
The trigeminal system is composed of 3 divisions: the ophthalmic (V1), the maxillary (V2), and the mandibular (V3—the only one that has associated motor and sensory components). The ophthalmic branch V1 is purely sensory and serves sensation to the eyeball, upper eyelid, conjunctiva, cornea, scalp, and tip of the nose, frontal sinuses, and lacrimal sac. In addition, in the cavernous sinus, the ophthalmic nerve gives small fibers to the oculomotor, trochlear and abducens nerves so that the muscles receive sensory innervation from V1 as well.

The reason intracranial processes can elicit eye pain is that V1 also innervates the dura in the anterior fossa, tentorium, falx, and superior sagittal sinus. That means the recurrent Nerve of Arnold innervates much of the meninges, arteries (including the circle of Willis), and veins intracranially. The maxillary nerve has important connections supplying the dura in the middle cranial fossa.
All sensation from the V1 is sent to the trigeminal nucleus and this nucleus extends from the midbrain through the upper cervical cord. The spinal trigeminal nucleus receives fibers that transmit pain and temperature, while the main trigeminal nucleus receives fibers that transmit touch and position and the mesencephalic nucleus receives fibers for proprioception.

The spinal trigeminal nucleus has a different representation with the lowest levels in the upper cervical cord (to C2) representing more peripheral areas of the face; the medulla representing more central areas; and the pons representing the mouth and teeth. The nucleus of the spinal tract has three distinct nuclei: nucleus oralis, nucleus interopolaris and nucleus caudalis. The ophthalmic division is ventral vs the mandibular division which is more dorsal. The ophthalmic division also extends the furthest caudally, stretching to the C2 region and it is contiguous with the dorsal horn in the spinal cord. This nucleus also perceives PAIN and TEMPERATURE. Kerr found that C1-2 stimulation could refer pain to the eye, forehead, vertex and rarely the back of the head (Kerr 1961).

When this track is affected, the sensory loss is described as an “onion skin” distribution.

Pain afferents from the dura are known to project to the nucleus caudalis and some to the nucleus interpolaris. The spinal trigeminal nucleus connects with several thalamic nuclei (ventral posterior nucleus) and these nuclei connect with the sensory cortex. The eye sensation is usually in the precentral gyrus. See Walsh and Hoyt 6th edition by Grant Liu for a nice review of trigeminal anatomy and connections.

HEADACHE HISTORY – THIS IS CRITICAL
While most individuals will have primary headache disorder (migraine, tension-type headache, cluster headache) it is the secondary headache disorders presenting as eye pain that can be ominous.

Migraine disorders usually present with a positive family history, a life history of headaches, and attacks will be stereotypically associated with photophobia, phonophobia, nausea and/or vomiting and worsen with activity. They are usually episodic, but can be chronic. There are usually NO neurological symptoms except for possibly aura.

The red flags I look for in the history for a secondary headache disorder includes:
- A new headache in a non-headache sufferer
- An unusually severe headache with rapid onset: “sudden onset of the worst headache of my life”
- Unexplained worsening of eye pain
- Change in the character of a typical headache
- Eye pain with nocturnal awakening
- Eye pain and headache in older individuals
- Eye pain and headache in individuals with cancer, HIV, systemic conditions (fever, stiff neck)
- Any eye pain or headache with abnormal neurological findings

Certain headache types deserve mention and attention. “Thunderclap headache” or the sudden onset of the worst headache of one's life—needs an explanation. While it may end being a “benign” primary thunderclap headache, consider other causes such as subarachnoid hemorrhage (either sentinel bleed or unruptured aneurysm), dissection of the cervical or vertebral artery, venous sinus thrombosis, reversible cerebral vasoconstriction syndrome, intracranial hypotension, and posterior reversible encephalopathy syndrome (PRES) (Ju et al 2010). In one study, 40% of those with thunderclap headache had reversible vasoconstriction syndrome (Chen et al 2006).

THE EXAMINATION
A neuro-ophthalmologic and neurological examination should ensue, with careful attention to:
- Any signs of optic disc swelling (high pressure)
- Any signs of subtle esotropia or eye movement dysfunction
- Careful attention to cranial nerve, especially the trigeminal nerve function
- Subtle signs of motor weakness: hands outstretched there is no drift
- Subtle signs of ataxia: finger to nose; heel to shin; Romberg; tandem gait
- Asymmetry to the deep tendon reflexes.
- Changes in the sensory examination.
- I also look at the neck (is there straightening or abnormal curvature, is there good range of motion)
- Look for tenderness of the temporal arteries

EVALUATION OF SUSPECTED ABNORMALITIES
I usually start with a brain MR unless I am looking for an acute bleed from an aneurysm or arteriovenous malformation. MRV/CTV if I suspect venous sinus disease for example in pregnancy or post-partum period of time.

CBC, ESR and CRP in any elderly patient with new eye pain or headache to consider giant cell arteritis.

Lumbar puncture if I suspect intracranial hypertension or intracranial hypotension.

CAUSES OF EYE PAIN FROM NEUROLOGICAL CAUSES
(while there is a wealth of information about each of these conditions, I will concentrate on the eye pain/headache associated with each condition)

1. VASCULAR CAUSES of eye pain are important to recognize since the price of not recognizing can be serious mortality or morbidity.

a. UNRUPTURED ANEURYSMS
Aneurysms in general occur in 1-6% of the adult population and more frequently in women. There is a risk of subarachnoid hemorrhage approximately 0.5%-1% annually in those aneurysms that are 7-10 mm (Wardlaw 2000; Komotar 2008). Headache can be the presenting complaint in about 1/3 of patients who harbor an unruptured aneurysm (Komotar 2008; Schwedt 2011). The clinical feature of subarachnoid hemorrhage—the “thunderclap” headache or the “sudden onset of the worst headache of one’s life” occurs.
in about 43% of those with a subarachnoid hemorrhage as the sentinel headache. The sentinel headache from smaller hemorrhages portend aneurysmal rupture usually within the following month (Komotar 2008).

Evaluation of the acute headache should be with CT scan looking for blood. A lumbar puncture may be required to look for xanthochromia. Blood on the cortical surface could suggest reversible cerebral vasoconstriction syndrome, cortical vein thrombosis, or vasculitis.

Treatment of unruptured aneurysms can also cause headaches. These are usually short-lived and the risk factors for their development are no previous hypertension and aggressive coiling of the aneurysm (Markwalder, Meinberg 1983). These aneurysms can be diagnosed by MR and CT angiography.

**b. CAROTID ARTERY DISEASE: DISSECTION**

Internal carotid artery dissection is not a rare event occurring about 1-2/100,000 (Lee et al 2006). The most common symptom is head or neck pain (80%). Other neurological manifestations include transient ischemic attack (often transient monocular blindness) or infarct (56%) and Horner syndrome (25%) (Lee et al 2006). Head pain as an isolated symptom occurs rarely (Guillon et al). More frequently a painful Horner syndrome (45%) is a presenting symptom (Bioussse 1998). Risk factors for the development of carotid artery dissection include: trauma, cervical manipulation, hereditary connective tissue disorders (e.g. Marfan or Ehlers Danlos syndrome), homocysteinemia, fibromuscular dysplasia, and other genetic disorders. (Debette 2005) The best evaluation for a carotid artery dissection is MR or CT angiography. Key to the diagnosis: think of it; look for a subtle Horner syndrome, and imaging. The cause of the eye pain with dissection is the trigeminal innervation of the carotid artery.

**c. CAROTID ARTERY STENOSIS**

and ocular ischemia can cause eye pain. Frequently there will be signs of hypoperfusion on dilated funduscopic examination such as venous stasis retinopathy or proliferative retinopathy. The pain often gets better with lying flat (Bioussse 1997).

Ischemic strokes present with headaches about 19-27% of the time (Ju et al). However, there are usually other associated symptoms and signs (e.g hemiparesis, language deficit).

**d. REVERSIBLE CEREBRAL VASCULAR SYNDROME (RCVS)** is increasingly recognized as a cause of “thunderclap headache” associated with light sensitivity, nausea and vomiting. It is considered a cerebrovascular disorder associated with multifocal arterial constriction. It has had many names over the years: first called Call-Fleming syndrome, and later benign angiopathy or migraine angiitis. Precipitating events to RCVS include the post-partum period of time, hypertension, and ingestion of vasoactive drugs such as ephedrine, SSRIs, triptans, amphetamines, ergotamine, nasal decongestants, tacrolimus, cannabis. While the syndrome may be self-limited and benign, occasionally individuals will have ischemic stroke (7%), or non-aneurysmal subarachnoid hemorrhage (about 22%). Posterior reversible encephalopathy syndrome may also occur with RCVS (Yancy 2013). The age of onset is usually between 20-and 50 with women more frequently affected (3 to 1). The diagnosis is made with the onset of the “thunderclap headache” and possibly associated neurological symptoms. Imaging, especially CT (may show convexity small SAH) and MR and MRA may show the characteristic diffuse arterial narrowing. Angiogram may show arterial stenosis and dilation. CSF can be normal, but may show a pleocytosis.

Calcium channel blockers (IV nimodipine; IV verapamil) are the standard therapies (Sattar 2010).

2. GIANT CELL ARTERITIS, a vasculitis of the elderly occasionally causes eye pain, and certainly causes headache. The most common (almost 90% of all patients) presenting symptom is headache, which is described as severe, boring sometimes burning in the temporal, frontal, or occipital areas (Ward et al 2005).

Jaw claudication with associated pain during chewing food or speaking that resolves with resting the muscles of mastication is one of the most specific symptoms of GCA. (Smetana et al) Scalp tenderness may be so severe, that the individual no longer wears a hat; this symptom has been associated with scalp necrosis. Hayreh showed that jaw claudication, neck pain, anorexia/weight loss, fever, and scalp tenderness to be the most important symptoms and signs (Hayreh 2003).

The location of the headache can be anywhere: temporal > occipital > frontal > whole head > ear pain and usually non-pulsatile. (Imai 2011)

The evaluation should include CBC, ESR, CRP, and a temporal artery biopsy.

Systemic corticosteroids remain the mainstay of treatment for GCA and treatment should be started immediately even before the result of the temporal artery biopsy is known.
3. INTRACRANIAL TUMORS - Tumors that cause eye pain and headache are often ones that come from the sphenoid ridge, pituitary area, and cavernous sinus since the trigeminal system richly innervates areas of the dura and blood vessels at the base of the brain. Tumors cause headache about 60% of the time (Goffaux et al, 2010). Most surgeons believe that it is traction on neighboring structures especially veins and arteries that cause the head pain. Posner examined consecutive patients with primary brain neoplasms and found the headache type could not be differentiated from tension type, which was present in about 77% and migraine 9%. He found that while the early morning headaches were NOT indicative of brain tumors, headaches with abnormal neurological examination or a change in headache pattern seemed to correlate more with brain tumor associated headaches. Headaches associated with high intracranial pressure were distinctive for the associated nausea, vomiting, severity and their poor response to analgesics. Patients who had previous headaches (e.g. migraine) were more likely to have headache with their tumors than those who did not have a history of headache (Forsyth and Posner, 1993).

Pituitary tumors may present with headaches. Some have found the headaches to be out of proportion to the size of the tumor (Levy et al). Many of these also have autonomic features and often get misdiagnosed as cluster headache or paroxysmal hemicrania (Levy et al; Kirby et al; Purdy et al). Sudden hemorrhage into the tumor or pituitary apoplexy is of sudden onset and can be life or vision threatening. Over half will present with reduced acuity, visual field defects or cranial nerve palsies (Simon et al).

4. DISORDERS OF PRESSURE
   a. INTRACRANIAL HYPERTENSION
      —can be primary or secondary. Primary intracranial hypertension (idiopathic intracranial hypertension) can be associated with headache and eye pain. In fact, headache is the most common symptom in this disorder occurring in 94% of patients. The headache is usually daily, but it can vary in intensity. Features that seem to distinguish the headache of IIH include: retrobulbar pain with eye movements (thought to be characteristic of IIH headache according to Wall 1990), and pain in the neck and shoulders as well as radicular pain in almost 20% (Digre, Corbett 2001). The interesting thing about headache in IIH is that the degree of ICP elevation may not correlate with the headache (Johnston, Paterson 1974). Many of the headaches do have migraine characteristics (nausea, photophobia, pain) and tension type headache features (Friedman 2002).

      The diagnosis is made with imaging including venous imaging, usually MRI and MRV or CTV, lumbar puncture with pressures over 250 mm CSF, and typical finding of papilledema and occasionally 6th nerve palsy (Friedman, Liu, Digre 2013).

      Headache treatment with IIH includes acetazolamide, and topiramate (Finsterer et al). Rarely surgical procedures are used for headache treatment. In one study, 42 patients had 115 shunt procedures (LP, VP, VAT) for intractable headache associated with IIH. They found that 95% (40 patients) had immediate improvement of intractable headaches with the shunt. However, at 12 months 19% (8 patients) and 36 months 48% (20 patients) had very severe headaches with working shunts. They found that the factors that were associated with treatment failure were the lack of papilledema and long-standing symptoms (> 2 years) (McGirt et al 2004).

   b. INTRACRANIAL HYPOTENSION
      may be due to trauma, lumbar puncture, or be spontaneous. It is the spontaneous ones that create the most problems in diagnosis and treatment. Headache is almost invariably present. While the headache often has a proclivity to be orthostatic or postural (worse upright, and better lying down), they can be chronic and even can have a thunderclap onset.

      Rarely no headache is present. The diagnosis is often made on MR imaging with findings of diffuse pachymeningeal enhancement, sagging brain with cerebellar tonsils below the foramen magnum (mimicking a Chiari 1), distorting of the brainstem, and crowding of the posterior fossa, along with flattening of the pons. The optic chiasm may appear flattened and the pituitary is enlarged.

      The cause is often spontaneous leaks along the meningeal diverticula (Tarlov cysts). Finding the leaks can be made occasionally with high contrast MRI. CT myelogram is the best way to find the site of the CSF leak. The treatment is to close the leak usually with blood patch, bed rest, hydration, time, medications (theophylline, caffeine, corticosteroids), or abdominal binder. Surgical repair and other measures can be used (intrathecal fluid, epidural saline, IV saline). See the excellent review by Mokri 2013. Some of these patients have connective tissue disorders such as Ehlers-Danlos syndrome or Marfan syndrome.

      Treatment consists of 1) conservative treatment (caffeine, theophylline, abdominal binders, hydration) 2) large volume autologous blood patches sometimes will suffice for treatment 3) targeted blood patches at the leak site demonstrated by CT myelography can be helpful.

5. NASAL SINUS DISEASE
   has been touted as a VERY common cause of headache and eye pain. It is true that the nasal cavities have many trigeminal nerve endings and it is also true that sinus infections can cause headaches. It is very interesting that migraine is associated with numerous cranial autonomic features that resemble sinus disease. In adults with migraine, the presence of at least one autonomic symptom (nasal stuffiness or congestion, eyelid edema, rhinorrhea, conjunctival injection, lacrimation, and ptosis) is noted about 56%-73% of the time (Lai 2009; Gupta 2007). In pediatrics, 62% of 125 pediatric patients with migraine had one cranial autonomic symptom (Gelfand et al, 2013). Several studies have found that anyone who self-diagnoses “sinus headache” has migraine.
(Schreiber 2004; Foroughipour et al 2011; Eross et al 2007) or a primary headache disorder. The Sinus, Allergy and Migraine Study (SAMS) showed that of 100 subjects that self-diagnosed “sinus headache”: 52% had migraine with or without aura, 11% had chronic migraine (with medication overuse), 23% had probable migraine, 1% had cluster or hemicrania continua. Headsalgia related to rhinosinusitis occurred in only 3%. They reported pain to be present in the maxillary region in 76% and in the forehead in 62%.

The proposed mechanism of nasal symptoms in migraine include stimulation of parasympathetic and sympathetic pathways in migraine as well as the release of vasoactive peptides such as CGRP and VIP (Bellamy et al 2006). To diagnose a true sinus headache, one needs evidence of sinus disease and the headache resolves when the sinus disease is treated (see ICHD III beta criteria 2013).

Treatment of “self-described” sinus headache in a randomized double blind placebo controlled study showed that treatment with sumatriptan tablets was very effective in these individuals (Ishkanian et al).

6. SYSTEMIC CONDITIONS

a. ASEPTIC MENINGITIS

occurs in about 1-3% of adults presenting to the ER and 5% in children. Meningitis in general can be caused by infectious agents (bacterial, viral, fungal), as well as by vasculitis, sarcoidosis, and medications or chemicals. (Davis 2008) The headache accompanying meningitis can sound like migraine and/or tension type headache. There are a few characteristic headache features that should alert a neuro-ophthalmologist to consider meningitis. The three symptoms form a classic triad: headache, fever, and stiff neck. In studies that have analyzed the typical findings these are: abrupt onset of a severe headache (often the “worst of ones life”), a prodromal illness including fatigue, gastrointestinal symptoms. Other symptoms include nausea, vomiting, photophobia, stiff neck and back pain. Fever may occur as well as focal neurologic deficits. These symptoms should provoke the provider to get some type of imaging (e.g. CT scan) and lumbar puncture. Aseptic meningitis is more common than bacterial, fungal, tuberculous, or carcinomatous meningitis (Lamonte 1995). Recurrent aseptic meningitis can also occur. While most of these are due to Herpes Simplex type 2 cases (Tyler, 2004), Mollaret’s meningitis is usually thought to be due to recurrent, idiopathic aseptic meningitis; the chief symptom is headache (Pearce 2008).

b. DRUG-INDUCED MENINGITIS

presents with headaches as well as fever and many medications have induced increased white cell counts. These include: ibuprofen, diclofenac, allopurinol, intravenous immunoglobulin therapy, amoxicillin, rifampin, lamotrigine, trimethoprim sulfa and other antibiotics, famotidine, and others. Of course intrathecal drugs frequently cause an aseptic meningitis due to direct meningeal irritation.

The cause is thought to be a type of immunological hypersensitivity to the drug. Withdrawal of the drug usually brings remission (Jolles 2000; Moris et al 1999; Gordon 1999).

c. HYPERTENSION:

Hypertension can cause headache in a couple of settings. First, hypertension is associated with the development of posterior reversible encephalopathy syndrome or PRES. PRES is often present in women with eclampsia who present with seizures, visual loss, headache and hypertension (Digre 2012). It can also occur with uncontrolled hypertension due to systemic lupus, nephrotic syndrome, and medications among other causes. It usually presents with headache, seizure, and sometimes cerebral blindness. The imaging features are characteristic on MR with predominantly posterior flair signal especially in the occipital and parietal lobe (Staykov 2012).

Hypertension is also seen more frequently in individuals with chronic daily headache—especially with tension-type headache (Prudenzano et al 2005). Whether it is causative is not known (Gipponi et al 2010). Systolic hypertension can be predictive of ischemic stroke associated with hypertension (Hong et al 2003).

CONCLUSIONS

Headache and eye pain are very common accompaniments to neurological disorders. The neuro-ophthalmologist must be vigilant to consider these when symptoms, signs suggest the diagnosis. Once the diagnosis is made, then treatment can be directed at the underlying pathology.

CME ANSWERS

1. c
2. d
3. a

REFERENCES

LEARNING OBJECTIVES
1. The learner will recognize 3 historical findings that would suggest an ophthalmic cause to eye pain
2. The learner will be able to discuss why ophthalmic pathologies can present with eye pain
3. The learner will describe at least 5 different ophthalmic causes of eye pain and know how to make the diagnosis by clinical examination.

KEYWORDS
1. Scleritis
2. Trochleitis
3. Myositis
4. Perioptic neuritis
5. Optic neuritis

INTRODUCTION
“Doctor, my eye hurts ...”

Eye pain may have an ophthalmic or orbital source even in the absence of ocular redness or eyelid edema or erythema (Fiore, et al, 2010). Yet, on the other hand, ocular redness, and/or lid edema or proptosis may be secondary to non-ocular or non-orbital disease processes (Brazis PW, 2002 and Friedman DI, 2008).

PERTINENCE OF PAST MEDICAL HISTORY
A past medical history should be inclusive of family history (especially regarding ocular disorders or headache syndromes; Dr. Frishberg will cover migraine) and should cover injuries, illnesses, treatments and surgeries from prenatal to current time. Review all medications and supplements in use, and check for any temporal relationship between changes in medication regimen and onset of symptoms. Consider whether any medications in use may be contributing to ocular dryness. The patient should specifically be questioned regarding past circumstances of eye, face, head or neck pain and should be queried regarding any history of injury or surgery of the eyes, face, head or neck. The patient should be specifically questioned regarding periocular, facial and/or scalp or neck injections of botulinum toxin, steroids, fillers or other agents. The patient should be queried as to whiplash injury or any “therapeutic” manipulation of the neck. A specific inquiry regarding history of any type of cancer anywhere in the body should be made, and the patient should be queried regarding any “removal, burning off or freezing off” of any facial or scalp lesions. Anyone with a cancer history deserves a lower threshold for obtaining neuroimaging, in the event of persistent, recurrent, extended or metastatic
cancer as etiologic of their eye pain. A specific inquiry should be made regarding history of known auto-immune disease or of present or prior episodes of inflammation or pain in any region of the body.

REVIEW OF SYSTEMS
Any known abnormalities of smell or taste? Any visual symptoms? Any facial, head or neck pain, swelling or numbness? Have there been any recent periocular or facial rashes or vesicles? Any epiphora? Any nasal congestion, post-nasal drip, coughing or alterations in voice? Change in sensorium or general well-being? Recent unintended weight gain or loss? Loss of appetite? Malaïse? Fevers or night sweats? Any aches, pains, areas of tenderness or swelling in any part of the body? (Dr. Digre will cover GCA).

HISTORY OF THIS EYE PAIN
Location and distribution of the pain; does it follow a sensory dermatome? When the pain precedes the rash and eruption, an astute examiner may have an opportunity for early diagnosis and treatment of herpes zoster ophthalmicus, thereby significantly reducing the risk of years of painful neuralgia or keratouveitis (Sanjay S, et al, 2011 and Liesegang TJ, et al, 2008). Although pain typically precedes the rash, sometimes the presenting dermatomal symptom is itching or paresthesia, rather than pain (Goh CL, et al, 1997). Sometimes, a patient may present for consultation with a history of chronic pain, which if dermatomal, should prompt consideration of prior herpes zoster, sometimes with no history of rash or vesicles.

Onset, variability, factors which improve or worsen it? Pain secondary to recurrent corneal erosions is often of diagnostic frustration to patient and physician, as symptoms and findings may be absent when the patient is seen for evaluation, but a history of sharp intense ocular pain, sometimes accompanied by tearing, which may awaken the patient from sleep and/or be present upon arising in the morning is characteristic.

Is the pain altered by visual activity or experience; if so is the character or severity of the pain altered by use of spectacles or contact lenses?

Does the pain vary with blinking, lid closure, eye position or eye movement?

Is the pain altered by instillation of topical lubricants?

Is the eye painful right now?

CHARACTER OF PAIN

EXAMINATION

INSPECTION
Is there a head tilt, face turn or chin up or chin down position? Is there facial asymmetry? Is facial muscular strength normal and symmetric? Is there facial swelling or alteration in coloration? Are there any facial scars, lumps, bumps, scaly or crusted lesions, vesicles or scabs; if so, inquire about each.

COMPLETE OPHTHALMOLOGIC EXAMINATION
Sometimes, even a neuro-ophthalmologist should consider the utility of a manifest refraction. Phorias or tropias should be evaluated with and without lens correction. Accommodation may be assessed, and, at times, after pupil evaluation and slit lamp biomicroscopy, even a cycloplegic refraction may be indicated. Richards, et al (Richards AL, et al, 2010) found a high incidence of complaints of eye pain offered by pre-school children with refractive error, amblyopia, blepharospasm or nystagmus. They wondered if children in the 2-6 year old age range may have had “difficulty communicating vague visual symptoms to caregivers,” and therefore offered complaints of “eye pain.” Nonetheless, it is evident that those who may not see clearly, or who may have phorias or intermittent tropias, will exert more subconscious and conscious effort to maintain clarity of vision, with diminished blink rate, squinting and/or head positioning for optimization of visual clarity. These adaptive mechanisms may reduce blink rate, with resultant dry eye symptoms, and may lead to neck and shoulder muscle spasm, with potential consequent “tension headache,” and/or migraine. Additionally, squinting may result in orbicularis fasciculations and/or spasm, along with “pressure” discomfort around the eyes, and sometimes, an “uncomfortable tight band” sensation above the brow, which may extend into the temples. Appropriate correction of refractive errors and/or strabismic disorders not only improves vision, but very often ameliorates ocular discomfort, headaches and/or neck and shoulder discomfort.

Is there any discernible abnormality or tenderness of superficial temporal or scalp arteries?

Sensation of light touch in the distributions of V1, V2 and V3 should be assessed. Following pupil evaluation and slit lamp biomicroscopy, a test of corneal sensation may be indicated.

INSPECTION OF LIDS

INSPECTION OF ORBITS
Exophthalmometry. Is there any relative vertical or horizontal displacement of the globe? Is there trociliar
tenderness? Any asymmetry or abnormality in resistance to retropulsion?

**SENSORIMOTOR EVALUATION**, with assessment of phorias, tropias, ductions and versions, with more detailed evaluation for any abnormality.

**PUPIL EVALUATION**

**SLIT LAMP BIOMICROSCOPY**, followed by assessment with fluorescein and/or vital staining with assessment of tear film and tear flow. Is there any tarso-conjunctival abnormality or asymmetry? Conjunctival injection, chemosis or other abnormalities or asymmetries? episcleral abnormalities or asymmetries? Measurement of intraocular pressure in primary position and in additional positions in the presence of any ductional deficit to check for potential alterations in IOP in different gaze positions to assist in characterizing ductional deficits as restrictive or paretic. If pain was present at the time of the examination, did the anesthetic drop alter the pain? If the pain is clearly diminished by topical anesthetic, reassess the tear film, ocular surface, entire conjunctival sac and seek evidence of past or present keratitis. Check for superficial punctate corneal epithelial abnormalities, subepithelial scars or infiltrates and basement membrane dystrophies. Infectious keratitides of varied etiology (herpes simplex or varicella, Epstein Barr virus, fungal, bacterial or acanthamoeba) may sometimes present with severe pain and yet only mild abnormalities in biomicroscopy. Be sure to lift the lid and look for superior limbic keratoconjunctivitis.

Cycloplegic refraction if indicated and dilated ophthalmoscopy.

**CHAIRSIDE DYNAMIC ULTRASONOGRAPHY** for screening for posterior scleritis, myositis, lacrimal gland enlargement, orbital vascular abnormality, orbital mass or infiltrative process.

**DIFFERENTIAL DIAGNOSIS OF EYE PAIN, NOT RELIEVED BY TOPICAL ANESTHETIC**

Pain from a conjunctival or episcleral source may not be relieved by topical anesthetic.

Pain from deep stromal keratitis and/or endotheliitis may not be relieved by topical anesthetic.

**GLAUCOMA**

Persons with very high intraocular pressure (generally greater than 40 mm Hg) may present with headache or eye pain, vision changes, or nausea and vomiting. Although the eye is usually inflamed, inflammation may be absent. Headache pain may be far more severe than eye pain, and is characteristically ipsilateral forehead pain. The mechanisms of glaucoma are many, including angle closure, pupillary block, uveitic, rubeotic, post-traumatic, steroid-induced or even primary open angle.

Uveitis

Ciliary spasm: just as a drop of pilocarpine in a normal eye produces intense headache and eye discomfort with brow and forehead pain, so may ciliary spasm, such as that which may accompany low-grade uveitis in a “quiet eye.” In such a case, cycloplegia is both diagnostic in evaluation of pain, and therapeutic.

Meibomitis, chalazia.

Orbicularis, and/or corrugator or procerus spasm (primary or secondary).

Canaliculitis with or without dacryocystitis.

**ISCHEMIC PAIN**

1. Carotid artery stenosis is noted by Dr Digre; ophthalmic artery stenosis may similarly be responsible.
2. May be a consequence of vasculitis.
3. May be a consequence of embolization or thrombosis.
4. May be secondary to a CC fistula or dural cavernous sinus fistula
5. Anterior segment ischemia may present as achy pain following strabismus surgery or scleral buckling surgery.
6. May evolve and worsen in association with ischemic tissue damage.
7. Pain may be a prodrome of a microvascular mononeuropathy or cranial nerve III, IV or VI.

Pre-phthisis

**ORBITAL INFLAMMATORY DISEASE**

Severe, life-threatening fungal infections may first present with severe ocular or periorbital pain, with little evident external abnormality. In appropriate clinical settings, early endoscopic sinonasal evaluation with biopsy and early diagnosis and treatment may be eye, vision and life-saving interventions.

Thyroid Eye Disease (TED) in its early manifestations, or in mild cases, may present with ocular or orbital or peri-orbital discomfort in the absence of evident ocular redness or eyelid or periorbital edema or erythema. The discomfort may be a manifestation of mild or intermittent lid lag, incomplete blink, stare or night-time exposure, with or without associated reduction in basal tear secretion. The discomfort may be a pressure sensation or sense of “fullness” or ocular awareness, in association with mild-to-moderate myopathy, with or without limited ductions. The discomfort may be a pressure sensation in reaction to reflex orbicularis, corrugator and procerus spasm.

Orbital Wegener's granulomatosis may present with eye or periorbital pain prior to diagnosis, which is generally established following imaging studies and biopsy. Imaging, in most cases, will reveal paranasal sinus disease, with bony erosion and extension into the orbit (Provenzale JM, et al, 1996).
Dacryoadenitis, infectious or inflammatory (sarcoid, non-specific orbital inflammatory disease)

Scleritis, especially posterior scleritis, may present with severe pain, but in early stages without redness, chemosis, periorbital edema or proptosis. There may be an associated anterior periorbital neuritis with reduced vision, or there may be choroidal folds, choroid effusion, serous retinal detachment and/or macular edema. Even in the absence of externally visible signs of inflammation, there is generally tenderness and pain on eye movement. Chairside ultrasonography is very sensitive in detecting the associated posterior sub-tenon’s fluid accumulation, but CT with and without contrast or MRI with and without contrast is recommended as an initial diagnostic study. Thin-section pre- and post-contrast axial studies are indicated, but are not always routinely done, and therefore should be specifically requested in cases of suspected posterior scleritis; MRI, of course, would be done with fat saturation.

Trochleitis (Tychsen L, et al, 1984) presents with bilateral or unilateral severe ocular and periorcular ache, which may be variable in intensity and episodic. Often, pain is worsened by eye movement. The etiology is usually idiopathic but trochleitis can be associated with systemic autoimmune diseases. In some cases there is a history of migraine, and sometimes one phenomenon seems to trigger the other (Yangüela J, et al, 2002). Often, upon asking a patient if there is a region of greatest discomfort, they will point to the superomedial orbital rim. Clinical examination most often reveals significant tenderness at the trochlea. Paratrochlear corticosteroid injections are most often therapeutic. Relief can also be obtained with high dose NSAIDs. Some patients benefit from botulinum injections of the ipsilateral corrugator and procerus muscles.

Orbital myositis (Costa RM, et al, 2009) presents with pain which worsens with eye movement and is generally most painful in attempted movement in the direction of the inflamed muscle, sometimes with limitation of duction due both to pain, as well as thickening of the involved tendon. While in most cases there is chemosis and injection, which is most severe in the region of the tendon of the involved muscle, as well as periorbital edema and erythema, the early presentation of the disease may be pain, worsened on eye movement, as noted above, with little-to-no external evidence of inflammation. Pain on eye movement is a clinical indication of orbital disease. Myositis is usually evident with chairside ultrasonography, and should be confirmed, at least once by initial study via CT or MRI with and without contrast, with appropriate tailoring of the imaging study to emphasize viewing and analysis of the suspicious muscle. Some patients are found concurrently to have evidence of other auto-immune disease, or may demonstrate other autoimmunity later in life. Treatment is generally with high-dose corticosteroid, with appropriate taper, but tapering too rapidly often leads to recrudescence, prolongation of the course of disease and prolongation of use of corticosteroids. Some patients may benefit from steroid-sparing therapy and some benefit from radiotherapy.

Perioptic neuritis (Dutton JJ, et al, 1985) most often will present with optic neuropathy with pain on eye movement, but unlike optic neuritis, neuroimaging reveals thickening and enhancement of the optic nerve sheath, rather than inflammation within the optic nerve. Most often there is optic nerve head edema. Both the pain and vision are steroid responsive.

Optic neuritis / retrobulbar neuritis
In association with MS
In association with NMO
Vasculitic
Idiopathic

Diffuse orbititis: Rosai-Dorfman, Erdheim-Chester, amyloidosis, etc.

IgG4 disease - Orbital IgG4-related disease is characterized by IgG4-positive lymphoplasmacytic infiltrations in ocular adnexal tissues. Common presenting features include chronic noninflammatory lid swelling and proptosis. Patients often have a history of allergic disease and elevated serum levels of IgG4. Associated systemic IgG4-related lesions may be present. Systemic steroid therapy decreases the size of the lesions, but relapse often occurs when systemic steroid therapy is discontinued.

Orbital Apex – Superior Orbital Fissure – Cavernous Sinus inflammation:

Tolosa-Hunt Syndrome (the differential diagnosis, based on clinical presentation, examination and neuro-imaging often includes infection, neoplasm and sarcoidosis).

TUMORS

Ocular tumors: while intraocular tumors may present primarily with pain in a “quiet eye,” more often they are detected during evaluation of painless visual disturbance.

1. Primary
2. Secondary
   a. direct extension from contiguous structures;

Orbital tumors:

1. Primary
   a. Eyelid tumors.
   b. Lacrimal gland tumors (MALT or other lymphoma, pleomorphic adenoma, adenocarcinoma or adenoidcystic carcinoma)
Schwannoma
Cavernous hemangioma
Lymphangioma
Orbital varix
Optic Nerve Sheath Meningioma
Tumorous processes of orbital bone: fibrous dysplasia, aneurysmal bone cyst, chondrosarcoma, meningioma

2 Secondary
a. direct extension from contiguous structures;
b. metastatic: lymphoma, bladder (Krauss HR, et al, 1982), breast, lung, GI or prostate cancer. Metastases to the eye and orbit most often take hold and grow from within highly vascular tissues; most have a predilection for choroid, extraocular muscle or the marrow space of the greater wing of the sphenoid.

Cavernous sinus / skull base tumors:
1. Primary
   Meningioma
   Schwannoma
   Cavernous Hemangioma
2. Secondary
   a. direct extension from contiguous structures: nasopharyngeal carcinoma, angiofibroma, esthesioneuroblastoma, etc.
   b. metastatic.

INTRACAVERNOUS CAROTID ARTERY ANEURYSM (refer to Dr Digre’s manuscript)

SINONASAL DISEASE allergic, infectious (including fungal), mucocele, inflammatory disease, vasculitis, tumors.

REFERRED PAIN, not from eye, orbit or adnexae (refer to Dr Digre’s manuscript)

CONCLUSIONS
Eye pain in the “quiet” eye may or may not be a manifestation of disease of the eye or adnexa. The “quiet” eye, upon close inspection, may not be quiet. The neuro-ophthalmologist must be vigilant to consider these when symptoms, signs suggest the diagnosis. Once the diagnosis is made, then treatment can be directed at the underlying pathology. Of great importance, in addition to diagnosis and treatment, is pain management; if your therapeusis does not adequately reduce pain in timely fashion, compassion and standard of care dictate that referrals are made for pain management.

CME ANSWERS
1. c
2. b
3. a

REFERENCES
LEARNING OBJECTIVES

1. To review the clinical characteristics and disorders associated with photophobia
2. To provide an update on the pathophysiology of photophobia
3. To provide an approach to diagnosis and treatment of photophobia

CME QUESTIONS

1. Which of the following is true
   a. Uveitis is the most common ocular cause of photophobia
   b. The use of sunglasses indoors should be strongly discouraged in patients with photophobia
   c. Psychiatric disorder is the most common cause of photophobia in patients with a normal neuro-ophthalmic examination
   d. Approximately 50% of patients with blepharospasm suffer from light sensitivity

2. The intrinsically photosensitive retinal ganglion cells are also known as:
   a. Amacrine cells
   b. Bipolar cells
   c. Melanopsin cells
   d. Horizontal cells

3. Migraineurs are particularly sensitive to which wavelength?
   a. 425 nm
   b. 480 nm
   c. 550 nm
   d. 630 nm

KEYWORDS

1. Photophobia
2. Migraine
3. Blepharospasm
4. Melanopsin
5. FL-41 tint

INTRODUCTION

Photophobia, an abnormal intolerance to light, is associated with a number of ophthalmic and neurologic conditions. However, in the presence of a normal neuro-ophthalmic examination, the most common conditions associated with photophobia are migraine, blepharospasm, and traumatic brain injury. Recent evidence indicates that the intrinsically photosensitive retinal ganglion cells play a key role in the pathophysiology of photophobia. Although pharmacologic manipulation of intrinsically photosensitive retinal ganglion cells may be possible in the future, current therapies are directed at optical modulation of these cells.

WHY WE HATE PHOTOPHOBIA

In medicine we are taught that 80% of the time, one should be able to make a diagnosis based on the history alone. The practice of ophthalmology turns that dictum on its ear, as 80% of the time an ophthalmologist can make the correct diagnosis based on the examination alone, without any history. The ophthalmologist’s microscopes and lenses enable him or her to rapidly diagnose corneal ulcers, cataracts, glaucoma and macular degeneration. For this reason, ophthalmologists are understandably uncomfortable when a patient’s chief complaint is photophobia and the ophthalmic examination is entirely normal. However, armed with a bit of knowledge about the conditions that most commonly cause this symptom, neither the patient nor the neuro-ophthalmologist need despair.

CLINICAL PRESENTATION

The definition of photophobia is an abnormal intolerance to light, but no patient will ever walk into your clinic with
a chief complaint of abnormal intolerance to light. What they will tell you is that they are light sensitive in situations where most other people are not. Some patients will recognize that they are especially sensitive to artificial indoor lighting. The perspicacious patient will recognize that they are specifically sensitive to non-incandescent artificial indoor light. Computer monitors are another common source of discomfort for the photophobic patient. These patients tend to have less trouble with natural light from the sun, unless they are faced with glare from snow or other highly reflective surfaces.

Most patients with photophobia will have a normal eye and neurologic exam, but there are still a few signs to observe: It’s not uncommon for photophobic patients to be seen in the waiting room wearing sunglasses. If you walk into an exam lane and all the lights have been turned out, chances are your patient has photophobia. I can recall a patient seen in residency who sat with her long hair pulled over her eyes.

**CONDITIONS ASSOCIATED WITH PHOTOPHOBIA**

A number of ophthalmic and neurologic conditions are associated with photophobia (Table 1). However, most of these conditions are associated with additional signs and symptoms. Although not a neuro-ophthalmic condition, dry eye is one of the most commonly encountered conditions in an ophthalmic practice and is the most common ocular cause of photophobia. The majority of patients complain of itchy, dry, scratchy, burny eyes. Dry eye can sometimes be more challenging to diagnose when patients present with atypical symptoms. Useful examination tools include a careful evaluation of the tear film, tear film breakup time, corneal staining with fluorescein or rose bengal, and Schirmer test. In some neurologic conditions such as supranuclear palsy and Parkinson disease, severe dry eye syndrome is seen in nearly all affected patients. A subset of these patients may also complain of photophobia.

Chronic dry eyes can lead to corneal neuropathy, a condition also frequently associated with photophobia. Resolution of the pain after instillation of topical anesthetic drops in a patient with an otherwise unrevealing anterior segment evaluation should raise a suspicion for corneal neuropathy. Other causes of corneal neuropathy include zoster keratitis, diabetic neuropathy, and chemotherapy.

**OCULAR**

**Anterior segment**
- Dry eyes: the most common ocular cause
- Ocular inflammation (iritis, uveitis)
- Conjunctivitis
- Corneal diseases (corneal neuropathy, interstitial keratitis)
- Blepharitis
- Bilateral acute iris transillumination defects
- Pterygium

**Posterior segment**
- Vitritis, uveitis
- Photoreceptor dysfunction/retinal dystrophy (albinism, achromatopsia, cone dystrophy, retinitis pigmentosa)
- Alström syndrome
- Sjogren-Larsson syndrome

**OPTIC NERVE**
- Optic neuritis
- Papilledema

**CHIASM**
- Pituitary tumor (including apoplexy)
- Hypophysitis

**THALAMIC PATHOLOGY** (tumor, ischemia, hemorrhage)

**OCCIPITAL LOBE**
- Alteration in excitability (migraine)

**NEUROLOGIC**
- Migraine: the most common neurologic cause
- Blepharospasm
- Progressive supranuclear palsy
- Traumatic brain injury
- Meningeal irritation (meningitis, subarachnoid hemorrhage)

**PSYCHIATRIC**
- Agoraphobia
- Anxiety disorder (panic disorder)
- Depression

**MEDICATIONS**
- Barbiturates
- Benzodiazepam
- Chloroquine
- Methylphenidate
- Haloperidol
- Zoledronate

**OTHER**
- Hangover headache
- Neurasthenia (chronic fatigue)
- Fibromyalgia
- Measles
- Rabies
- Inflammatory bowel disease
- IFAP syndrome (ichthyosis follicularis, alopecia and photophobia)
- PPK (psoriasiform lesions and palmoplantar keratoderma)
- Trisomy 18
- Zinc deficiency with exocrine insufficiency

Table 1: Conditions associated with photophobia

(Digre KB, Brennan KC. Journal of Neuro-Ophthalmology: March 2012 - Volume 32 - Issue 1 - p 68-81)
If your patient has a normal neuro-ophthalmic examination, they are most likely to have one of three conditions: migraine, blepharospasm, or traumatic brain injury.

Migraine affects approximately 9% of men and 18% of women, making it the most common neurologic condition. Nearly all migraineurs report light sensitivity during a headache, but many will also tell you that certain kinds of light can trigger a migraine. A subset of these patients will report chronic light sensitivity, even when they don’t have a headache. Many patients with migraine are undiagnosed or misdiagnosed, so careful questioning may be required in order to identify migraines.

Similarly, nearly all patients with benign essential blepharospasm (BEB) have light sensitivity. Light makes their spasms worse and spasms make their light sensitivity worse. Many of these patients have chronic light sensitivity and addressing light sensitivity is a cornerstone of BEB treatment. Dry eye syndrome is almost universally seen in blepharospasm patients and aggressive dry eye therapy should be pursued.

The association between traumatic brain injury (TBI) and photophobia has gained more attention in recent years, not in small part due to the number of veterans returning from Iraq and Afghanistan with TBI. Patients with TBI can have several different visual complaints, but photophobia is one of the most common. These patients may also have migraine and/or chronic daily headache, so it’s not entirely clear if the photophobia is a primary or secondary symptom of their brain injury.

Photophobia has been reported in cohorts with panic-agoraphobia and depression. However, I have personally never encountered a patient who presented with photophobia due primarily to a psychiatric condition. Anxiety and depression are frequent comorbidities of migraine and some of these patients will of course also have photophobia.

PATHOPHYSIOLOGY
For years clinical researchers have hypothesized about the existence of a photophobia “transducer” in the eye. A bright light, such as directly viewing the sun, will elicit the sensation of pain in nearly everyone. This painful sensation is almost certainly a protective response and is probably shared by all vertebrates. Light induced pain discourages us from viewing intensely bright objects that could harm our retina. But how does light get transduced into a painful stimulus?

The answer appears to reside with the intrinsically photosensitive retinal ganglion cell (IPRGC), also known as a melanopsin cell. I consider the discovery of these cells to be one of the most important discoveries about retinal physiology in the last 50 years. About 10% of all retinal ganglion cells are IPRGCs. Unlike their cousins who send their axons to the lateral geniculate, these cells send their axons to the suprachiasmatic nucleus and the Edinger-Westphal nucleus. In the suprachiasmatic nucleus these cells entrain circadian rhythms. In the Edinger-Westphal nucleus they control the pupillary light response. More recently, these cells have also been shown to project to pain centers in the thalamus. This connection may be an integral part of the “photophobia pathway” (Figure 1). Perhaps this connection or this pathway has a pathologic gain in patients with certain neurologic conditions?

IPRGCs contain the photopigment melanopsin, a chromophore that is related to and probably an evolutionary forerunner of rhodopsin. Because they contain a photopigment, these cells are “intrinsically photosensitive”, meaning they can be stimulated by light in the absence of input from the traditional photoreceptors, rods and cones. The ability of these cells to become activated in the absence of input from photoreceptors likely explains the observation that some patients with photoreceptor degenerations (e.g. retinitis pigmentosa) can be exquisitely light sensitive. The action spectrum of IPRGCs peaks at 480 nm, midway between the action spectrum of green and blue cones. Although they are intrinsically photosensitive, IPRGCs are also stimulated by input from rods and cones, meaning that they can be activated by wavelengths other than 480nm.

PHOTOPHOBIA CIRCUITS
1. Ganglion cells project light-related signaling to the olivary pretectal nucleus (OPN; light green). OPN projections

Figure 1
activate superior salivatory nucleus (SSN; dark green), which via pterygopalatine ganglion, causes ocular vasodilation and activation of ocular trigeminal afferents (orange) which are heavily expressed on blood vessels. These afferents, with cell bodies in the trigeminal ganglion, project to trigeminal nucleus caudalis, thalamus and cortex. 2. Intrinsically photosensitive retinal ganglion cells (IPRGCs) project directly to thalamic neurons (blue) that also receive intracranial nociceptive afferent signal (yellow neurons in trigeminal ganglion and trigeminal nucleus caudalis). Thalamic neurons fire in response to light and pain stimuli. Their output projects diffusely to sensory and association cortex. 3. Melanopsin-containing, intrinsically photosensitive ganglion-like cells have been identified in rodent iris. These afferents may explain the fact that light can activate trigeminal blink reflex even after the optic nerve (through which circuits 1. and 2. pass) has been sectioned. Note that all three circuits may interact at different locations. (Digre KB, Brennan KC. Journal of Neuro-Ophthalmology: March 2012 - Volume 32 - Issue 1 - p 68–81).

TREATMENT
Our understanding of the photophobia “pathway” is in its infancy and much of its neurochemistry remains unknown. As this knowledge matures, pharmacologic modulation of photophobia may become possible. In the meantime, treatment of photophobia relies primarily on optical means of modulating the pathway.

A group in Birmingham, England formulated the optical tint FL-41 in 1989. The tint was formulated empirically for patients suffering from fluorescent light sensitivity. Different combinations of different color were tried until a specific combination seemed to be effective. Since then, FL-41 was shown to be helpful in alleviating migraine in a cohort of school children. Our group at Utah has also shown FL-41 to be effective in the treatment of benign essential blepharospasm.

The transmission spectrum of FL-41, shown in Figure 2, has its minimum right around 480 nm, the very same wavelength at which IPRGCs are maximally stimulated. FL-41 was formulated more than 20 years before the discovery of IPRGCs and their action spectrum.

I don’t think the correlation between the action spectrum of IPRGCs and the transmission minimum of FL-41 is a coincidence. I think people with light sensitivity find 480 nm particularly annoying and they find a tint that blocks this wavelength especially comfortable. A study presented at the 2013 International Headache Congress concluded that migraineurs are particularly sensitive to 480 nm light compared to other wavelengths. Although FL-41 is not proprietary, it is difficult to find optical shops that carry it and know how to use it appropriately. The Moran Optical Shop (http://healthcare.utah.edu/moran/patient_care/optometry/optical_shops.php) is one of the few retail outlets that is a reliable source. The tint can also be purchased from Brain Power Incorporated (www.callbpi.com) and Phantom Laboratories (www.phantomresearch.com).

Theoretically, one should be able to create an optical filter that specifically blocks 480 nm light. Such a filter, termed a “notch filter” because of the shape of the transmission spectrum, cannot be easily produced using tints. Tints are organic dyes. Plastic spectacle lenses are dipped into a warm bath of the dye and the plastic absorbs the dye, giving the lens a particular shape and transmission spectrum. This process is used to tint spectacle lenses with FL-41. By contrast, one can design a notch filter using thin film technology. This technology involves the sequential deposition of ultra-thin layers of metal oxides onto substrate lenses. The composition, thickness, and order of the layers imbue the lens with particular optical properties. This technique is used to make modern day anti-reflective coatings that have become ubiquitous in spectacle lens manufacture. This technique is also used to produce mirror coatings on sunglasses that have enjoyed a recent resurgence in popularity. In collaboration with a University of Utah engineer who is familiar with this technology and a Florida company that specializes in the design and manufacture of these coatings, I have developed a thin film coating that specifically blocks 480 nm light. I am currently testing this coating in migraine patients to determine if it reduces migraine frequency and severity.

Don’t forget to diagnose and treat dry eye syndrome aggressively in photophobic patients. A discussion of dry eye syndrome and its treatment is beyond the scope of this manuscript. The mainstays of treatment are over-
the-counter artificial tears, punctual occlusion, topical cyclosporine (Restasis), and oral omega-3 supplements. A significant subset of dry eye patients also has blepharitis and meibomian gland dysfunction that must also be treated appropriately.

Finally, the use of sunglasses indoors must be strongly discouraged. By wearing dark glasses indoors, patients are dark-adapting their retinas, aggravating their sensitivity to light. Encourage these patients to transition to the use of FL-41 for indoor light sensitivity. There is no need to restrict the use of sunglasses outdoors in these patients.

CONCLUSIONS
Patients with photophobia need not be a source of frustration. The majority of these patients have migraine or a migraine predisposition and recognition and treatment of the underlying illness is critical. Concrete measures can be taken to aid in their treatment: Ban the use of sunglasses indoors, use FL-41 tinted spectacles, and address their dry eye syndrome. Don’t forget the treatment that is administered by ear: Words of comfort. Most of these patients have been to multiple physicians and have not been given a diagnosis or any hope of getting better. Just telling them that they have a recognized condition and that treatments are available can be incredibly therapeutic.

CME ANSWERS
1. b
2. c
3. b

REFERENCES
LEARNING OBJECTIVES
1. Recognize the signs, symptoms and history associated with the presentation and diagnosis of somatoform disorders;
2. Differentiate neurological and non-neuroanatomical presentations;
3. Discuss the diagnosis of somatoform disorders with patients and families to enable acceptance of treatment;
4. Recognize the treatment options available for patients with somatoform disorders.

CME QUESTIONS
1. The clinician should address which of the following issues in a person suspected of having a somatoform disorder:
   a. The patient’s understanding of the disorder
   b. The presence of current psychiatric symptoms
   c. The impact of the symptoms on the patient’s life, work, and family
   d. Past psychiatric history
   e. All of the above
2. The gold standard for diagnosing psychogenic nonepileptic seizures is:
   a. Serum prolactin
   b. Routine EEG
   c. History alone
   d. Video EEG capturing a typical event
3. Which of the following therapies has the least successful outcomes for patients with somatoform disorders:
   a. Group therapy
   b. Cognitive behavioral therapy
   c. Supportive therapy
   d. Interpersonal therapy

KEYWORDS
1. Neuropsychiatry
2. Somatoform disorders
3. Conversion disorder
4. Examination
5. Treatment

INTRODUCTION
A century ago, neurology and psychiatry were practiced in a unified framework as neuropsychiatry. In the early 20th century, divisions occurred in the fields and lines were drawn between those who evaluated and treated patients with epilepsy, strokes, and migraines, and those with anxiety, depression, and schizophrenia. These divisions resulted in a dichotomous view of the brain/mind and influenced how we assessed the two patient populations.

Every medical specialty has patients who overlap the boundaries of its practice. These patients require a broadened perspective in their assessment. General neurologic training focuses its teachings on the elemental neurological exam, and psychiatric training focuses on the mental status exam. Many times, one approach is used at the exclusion of the other. How to best assess at bedside the borderlands of neurology and psychiatry (attention, alertness, cognition, memory, motivation), truly can be a gray zone.

The future of neurology and psychiatry has been and will be largely influenced by two major areas of interface – neuroscience discovery in the past 20 years and during the decade of the brain, and by the practical needs of society as felt in the growing elderly population. Neuroscience continues to yield greater advances in diagnosis and treatments for brain/mind diseases. As the population ages, we will have to confront increasing needs for effective and safe neurobehavioral management in patients with greatly prevalent neurodegenerative disorders.

In this session we review the literature on one of the most challenging and sometimes frustrating patient population, those with somatoform symptoms. It is here, where medically unexplained symptoms present,
that a combined neurologic-psychiatric perspective is essential for diagnosis and management. To make the presentation both academically informative and clinically applicable, an overview of each of the disorders in the somatoform disorders (SDs) classifications is reviewed. The DSM-IV classifications included: Somatization Disorder, Undifferentiated Somatoform Disorder, Conversion Disorder, Pain Disorder, Hypochondriasis, Body Dysmorphic Disorder, and Somatoform Disorder Not Otherwise Specified. A comparison to the DSM-5 will be discussed [1, 2]. A number of these disorders are often encountered in medical and neurological clinical settings. Examples of the examination in patients in the clinic with somatoform disorders are given to aid in discerning distinguishing characteristics and semiology of the presentations.

Of equal importance is the discussion of patients who present with medically unexplained symptoms that diagnostically are not a somatoform disorder in nature. Examples include Factitious disorder and Malingering. Brief mention is also made of current diagnoses including chronic fatigue syndrome, fibromyalgia, chronic Lyme, and multiple chemical sensitivities, which have elements of chronic fatigue syndrome, fibromyalgia, chronic Lyme, and multiple chemical sensitivities, which have elements of somatoform disorders. The descriptive overview is followed by presenting diagnostic and treatment research in somatoform disorders that is found in the literature and that we are conducting at Brown Medical School/Rhode Island Hospital.

The key points that will be discussed in the presentation are as follows:

1. There is a plethora of observational, phenomenological and diagnostic information on Somatoform disorders.
2. There is no serologic or imaging lab test that will definitively diagnose somatoform disorders. Nonepileptic seizures (NES), however, are diagnosed with video EEG, the gold standard for NES diagnosis.
3. We have only a small but growing body of controlled data on somatoform disorders treatments.
4. Anxiety and depression occur commonly in patients with somatoform disorders.
5. Reviewing the extant literature on somatoform disorders treatment suggests that improved outcomes may be obtained with intensive, multimodal treatment of patients with somatoform disorders.

A SUMMARY OF SOMATOFORM DISORDERS
[based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)] [3]

**Somatization Disorder**
Diagnostic features
Multiple and recurring somatic complaints that begin before the age of 30 years and occur over several years, resulting in medical treatment or impairment of important areas of functioning (i.e. socially, occupationally, etc.).

**Undifferentiated Somatoform Disorder**
Diagnostic features
Undifferentiated Somatoform Disorder is the category for somatoform presentations of one or more persistent physical complaints that last for 6 months or more. These somatoform presentations do not meet the criteria for Somatization Disorder, lacking the number of symptoms, the age of onset, and the timeline.

**Conversion Disorder**
Diagnostic features
Conversion symptoms are changes or deficits in voluntary motor or sensory functioning that are not are explained by structural anatomical pathways or physiological mechanisms and are not intentionally produced. Motor symptoms or deficits include impaired balance, coordination, gait, paralysis or paresis, aphonia, dysphagia, urinary symptoms or seizures. Sensory symptoms include anesthesia or dysesthesia, diplopia, amaurosis, deafness and hallucinations. Psychological factors are judged to be associated with the symptoms or deficits.

**Pain Disorder**
Diagnostic features
Key features of Pain Disorder are that the pain itself is grave enough to warrant clinical attention and is the primary focus of the clinical presentation. Psychological factors are judged to play a significant role in the onset, severity, exacerbation, or maintenance of the pain. Subtypes are described that best characterize the factors involved in the etiology and maintenance of the pain. These include “associated with psychological factors,” “associated with both psychological factors and a general medical condition,” and the final subtype, “associated with a general medical condition,” which is not considered a mental disorder.

**Hypochondriasis**
Diagnostic features
Individuals with Hypochondriasis are preoccupied with unwarranted concerns of having a serious disease despite multiple medical reassurances and a negative work up. The preoccupation is based on a misinterpretation of one or more bodily sign or symptom, which could include bodily function, with minor physical abnormalities, or with vague and ambiguous physical sensations.

**Body Dysmorphic Disorder**
Diagnostic features
Individuals with Body Dysmorphic Disorder are preoccupied with thoughts concerning imagined or slight defects in their appearance. Such individuals may become extremely self-conscious and avoid work, school, and other public settings. Areas of concern include hair thinning, acne, wrinkles, scars, vascular markings, pale or plethoric complexion, swelling, facial asymmetry or disproportion, or hirsutism. Size or shape of other facial or bodily areas are also common preoccupations. The thoughts may dominate their lives, spending hours a day thinking about their “defect.”
Somatoform Disorder Not Otherwise Specified

Diagnostic features

‘Somatoform Disorder Not Otherwise Specified’ is the category for somatoform symptoms that do not meet the diagnostic criteria of any specific Somatoform Disorder. An example of a disorder in this category is Pseudocyesis, (i.e. a false belief of being pregnant associated with objective signs of pregnancy, such as abdominal enlargement, reduced menstrual flow, amenorrhea, subjective sensation of fetal movement, nausea, breast engorgement and secretions, and labor pains at the expected date of delivery).

Factitious Disorder

Diagnostic features

An individual with Factitious Disorder is psychologically driven to assume a sick role, thus feigning psychological or physical symptoms with no external motives. Symptoms or signs may be fabricated subjective complaints, self-inflicted conditions, exaggeration or exacerbation of preexisting general medical conditions, or any combination of these. The judgment that a particular symptom is intentionally produced is made both by direct evidence and by excluding other causes of the symptom. An individual may deny taking medication for an illness even though blood tests state otherwise (e.g. hematuria in a person with an elevated coag panel found to have anticoagulants in his possession). They may present their history with dramatic flair, but with extreme vagueness and inconsistency. Some may engage in pathological lying about the symptoms (i.e., pseudologica fantastica). Once recognized and confronted, inpatients with Factitious Disorder, (also known as, “Munchausen’s syndrome”) may deny allegations or abruptly leave against medical advice.

Factitious Disorder Not Otherwise Specified (including by Proxy)

Diagnostic features

Disorders with factitious symptoms that do not classify as Factitious Disorder are categorized as ‘Factitious Disorder Not Otherwise Specified’. An example of a ‘Factitious Disorder Not Otherwise Specified’ is factitious disorder by proxy, when an individual indirectly assumes a sick role by intentionally producing a feigned physical or psychological condition on another person, such as a sibling or child, who is under that person’s supervision. As with Factitious Disorder, there is no external incentive involved.

Malingering

Diagnostic features

Malingering IS NOT a psychiatric condition but refers to the exaggeration or feigning of physical and psychological illness to achieve personal motives, such as avoiding obligations at work, school, or the military. Individuals may also resort to malingering to obtain drugs, financial compensation, win a law suit or avoid jail time.

Advances in somatoform diagnostic research

Diagnostic Measures

A common concern with diagnoses in the Diagnostic and Statistical Manual of Mental Disorders–IV is that psychiatric diagnoses have no physiologic correlates. While aggregate data on depression and anxiety states have revealed alterations in the hypothalamic-adrenal-pituitary (HPA) axis, [4, 5] these findings are not applicable to the diagnosis of individuals with major depressive disorders or post traumatic stress disorders. NES are the neuropsychiatric exception to this rule, with diagnosis validated by a physiologic measure—the gold standard, video EEG, which has excellent interrater reliability [6], and with adjunctive differentiation from epilepsy using serum prolactin assay [7].

Neuroimaging studies in somatoform disorders

A study of 11 patients with NES and 12 healthy controls comparing resting state fMRI revealed stronger connectivity values between areas involved in emotion (insula), executive control (inferior frontal gyrus and parietal cortex) and movement (precentral sulcus) [8].

Structural neuroimaging (morphometric MRI) in 10 patients with conversion disorder compared to healthy controls revealed smaller mean volumes of the left and right basal ganglia and smaller right thalamus in the conversion patients [9]. Studies using SPECT and functional MRI have identified the anterior cingulate gyrus and the orbitofrontal cortex as potentially mediating the hypothesized attention and inhibition findings seen in patients with sensory and motor conversion disorders [10, 11]. Bilateral vibrotactile stimulation in three patients with sensory conversion disorders resulted in activation of the contralateral primary somatosensory region (S1), but no contralateral activation was present during unilateral stimulation of the affected limb [12].

Other case reports and small sample-size functional neuroimaging studies in patients with conversion disorders have been appearing in the literature increasingly [13, 14], but it is premature to “localize the conversion lesion.” Sensory gating may be affected in conversion disorders such as PMD [15]. Further studies of functional neuroimaging examining striatothalamicortical circuits controlling sensorimotor function and attention may yield insights into the neural and effective connectivity in NES and other somatoform disorders.

Management

Treatment of SDs involves a team approach and consists of correct diagnosis, presentation, acute and chronic management. Along with diagnosing the presentation, identifying the associated comorbidities is important for treatment. Most psychopathology underlying SDs is often due to one of two issues: psychosocial developmental environment or prior trauma and abuse. In recent years, research has focused on psychopathology of the disorder, classification of the diagnosis, and development of outcome measures. This focus on psychopathology has led to the development of targeted treatment strategies that can be tested in hypothesis driven studies.

The treatment team involves the clinician to whom the patient presents (which is typically symptom matched to
the medical specialty for the organ, e.g. chest pain to the ER/cardiologist, or seizure to the ER/neurologist). Once the appropriate tests have confirmed the absence of an anatomic/physiologic cause, a mental health professional (psychiatrist/psychologist) is called in to “rule out conversion.” If the consult is not obtained in the inpatient setting, many times, outpatient follow up does not occur. If the diagnosis is established and clearly conveyed to the patient and the family, outpatient follow up can be established, where therapy can be initiated. The clinician to whom the patient presented should continue to follow the patient as they are being treated by the mental health provider for continuity of care and to mitigate unnecessary further testing.

Different types of treatment strategies have been used for management of SDs, including group therapy, family therapy, cognitive behavioral therapy (CBT), antidepressants, and rehabilitation [16]. Behavioral modification has been used, as opposed to utilizing a cognitive or psychodynamic approach, in some populations, with the hypothesis that psychogenic neurological events are a “reinforced” behavior, especially in the intellectually deficient subpopulation. Recently, specific treatments have been studied in systematic, controlled trials for the management of SDs [17]. One type of therapy that has been used for various psychological and psychiatric disorders, including SDs, medically unexplained symptoms and conversion disorders, is CBT [18]. CBT is a form of psychotherapy that can be administered as a time-limited treatment to help a patient become aware of their dysfunctional thoughts and to maximize function by practicing new ways to think about their symptoms and learning new ways to respond to them.

CONCLUSION
Patients with somatoform symptoms remain a conundrum in the neurologic and the psychiatric clinic. There may be a number of interventions that may be effective, but in the absence of adequately powered phase III trials, we do not know what the best treatment for somatoform disorders are [19]. The challenges in the difficult neuropsychiatric population with somatoform disorders, many times having comorbid neurological and psychiatric disorders, were described in a study examining methodology for NES treatment trials [20]. Building on data from smaller sampled studies[21], a multi-site randomized controlled trial for NES revealed improvement in patients treated with an NES workbook [22]. The advances made in NES from utilizing a multidisciplinary approach [23], and results from these trials will possibly have implication for other somatoform disorders’ treatments.

CME ANSWERS
1. e
2. d
3. c

REFERENCES

Portions of this syllabus were used for the publication: LaFrance Jr WC, Somatoform disorders. Semin Neurol 2009;29(3):234-246.
LEARNING OBJECTIVES
1. At the end of the session, the attendee will have gained knowledge about epidemiology of patients with non-organic visual loss
2. At the end of the session, the attendee will have reviewed the common presentations of patients with non-organic loss of vision
3. At the end of the session, the attendee will have gained knowledge on the psychological profile of patients with non-organic loss of vision

CME QUESTIONS
1. A non-organic cause of visual field loss can be ruled out if:
   a. Visual field defects are reproducible
   b. Reliability indices of the visual field are good
   c. a. + b.
   d. None of the above
2. Which visual field defect is generally not suggestive of a non-organic etiology?
   a. Homonymous defect
   b. Central scotoma
   c. Bitemporal defect
3. Which statement is not correct regarding non-organic loss of vision?
   a. Unilateral involvement is common in children
   b. Psychiatric disturbances are more frequent in adults
   c. There is a predominance of women in adults

KEYWORDS
1. Non-organic
2. Loss of vision
3. Visual field
4. Visual acuity

INTRODUCTION
The non-organic nature of signs and symptoms in some patients has been recognized for almost 4000 years by the ancient Egyptians. Hippocrates coined the term hysteria as he believed that the misplacement of a wandering uterus was responsible for such manifestations. Other terms were given by famous physicians like Jean-Martin Charcot (“La belle indifférence”), Sigmund Freud (conversion syndrome), or Jozef Jules François Félix Babinsky (pithiatism). Homer’s description of a warrior who lost sight upon seeing an enemy may have been the first case of non-organic visual loss (NOVL). However, the first report of NOVL in the medical literature was written by Albrecht von Graefe in 1855 who described two techniques to demonstrate the non-organicity of visual loss in some patients.

EPIDEMIOLOGY OF NON-ORGANIC MANIFESTATIONS
The true incidence of non-organic signs and symptoms is not known and varies depending on medical specialty. It represents 1-4% of all diagnoses in a general hospital and can be as high as 30% of neurological patients. Between the early twentieth century and its end no drastic change in the incidence of non-organic manifestations occurred and this was demonstrated in different countries, namely UK, Greece, and Switzerland. However, a change in the spectrum of clinical manifestations occurred, as a net decrease of the dramatic manifestations of hysteria was observed, whereas an increase of more minor manifestations was noted by these authors.

The incidence of NOVL was reported to be 5.25% amongst adults and 1.0-3.08% in the pediatric population. Recent epidemiological studies are lacking and it is generally accepted that NOVL accounts for 1-5% of diagnoses amongst ophthalmological patients. NOVL can occur in patients at any age, and from both sexes. For any age group there is a female predominance with even a higher proportion of girls in the younger group (≤ 14 years-old). Children tend to present more frequently with bilateral symmetric visual loss and adults can either present monocular or binocular loss of vision.
Triggering factors may be present but are not always found. They include physical trauma, conflicts at school or home, environment stressors, prescription of glasses to a sibling or friend, or, rarely but more worrying, physical or sexual abuse. (Bain, Catalano, Kathol, Lim, Mouriaux, Rada) Mouriaux reported that a rather trivial precipitating factor could be disclosed in 64% of their pediatric patients. (Mouriaux) During periods of extreme stress, such as wars, there is an increased incidence of NOVL, usually manifesting as bilateral and severe loss of vision, resulting from either malingering or a true conversion syndrome. Such an example of NOVL during wartime is provided by Corporal Adolf Hitler who, at the end of the first World War, was able to avoid active duties claiming bilateral blindness after gas exposure. (Maranho-Filho)

The true prevalence of psychosocial disturbances in patients with NOVL is not known. Not only does it vary between adults and children, but it varies markedly from publication to publication. Psychological/psychiatric disturbances were present in 27% of children and significant home/school stress was uncovered in another 31%. (Taich) Sixty percent of children were reported to have social problems (school, family, exams). (Bain) Similarly, family problems, difficulty in school and mild psychological problems were prominent in a series of 58 children, but no serious psychiatric disorder was disclosed. (Toldo)

The incidence of true psychiatric disorders, for which psychiatric management is necessary, is overall low, and lower in the pediatric group. Mantyjarvi reported that 8% of their cohort presented psychiatric disturbances. (Mantyjarvi) In Clarke's experience and from a series of 54 children with NOVL, most were emotionally stable and did not have a specific psychologic conflict. (Clarke) Catalano believed that psychiatric referral was not necessary for children with NOVL, but underlined that the possibility of evidence of sexual or physical abuse should be sought in any case. (Catalano) In adults, Kathol et al reported no evidence of psychiatric syndrome or personality disorder in almost 50% of their cases, and advised psychiatric referral only if non-organic symptoms other than visual were detected. (Kathol) Lim et al reported an incidence of psychiatric problems in 18% of children, whereas the incidence was 39% in adults. (Lim)

The psychological mechanisms leading to NOVL may be psychogenic, unconscious, or deliberate and conscious. Patients with NOVL have been categorized by Thompson as ranging on a spectrum of "deliberate malingers", "worried impostors", "impressionable exaggerators", and "suggestible innocents". NOVL in all these patients result from a mixture of fraud and suggestibility, the extremes being mostly fraud (deliberate malingers) and mostly suggestibility (suggestible innocent). (Thompson HS) As a general rule, true malingers are more difficult to handle (as they are worried to be discovered as non-organic) and fortunately represent a minority of NOVL patients. However, depending on cultural background, countries, and socio-economic situations, the psychomechanisms of NOVL can vary. For example, in California, Keltner et al reported that 86% of 59 adults with NOVL were malingers seeking financial gain, faking or exaggerating their symptoms consciously. Noteworthy, 56% of these 59 patients were unemployed. (Keltner)

Coexisting organic disease is always a possibility and exhaustive investigations are necessary to rule out that possibility. Amongst published series, the frequency of functional overlay averages 22%, ranging from 5% to 54%. (Bain, Behrmann, Kathol, Keltner, Krill, Lim, Schlaegel, Scott, Yasuna) Underlying pathologies included amblyopia, keratoconus, congenital or acquired optic neuropathies, congenital or acquired retinopathies. (Lim)

The fear of the physician is to mistakenly diagnose NOVL when a real pathology was responsible of the visual loss. Such a misdiagnosis carries potential medico-legal implications. The rate of misdiagnosis appears to be overall low (2-3%), most likely reflecting the caution that physicians adopt when facing a suspicion of NOVL. (Kathol, Krill, Lim) Occult retinopathies (early Stargardt's disease, cone dystrophy) and hereditary optic neuropathies (Leber's hereditary optic neuropathy) are the most frequent causes of misdiagnoses. (Lim)

**CLINICAL PRESENTATION**

NOVL can manifest as decreased visual acuity, altered visual field, or dyschromatopsia. Examination frequently reveals a combination of these. Around two-thirds of NOVL patients present a combination of decreased VA and altered VF; less frequently they present either isolated VA loss or VF loss. (Barris, Keltner) Dyschromatopsia is rarely a primary complaint in NOVL but abnormal color vision results can be found in up to 50% of cases. (Keltner, Toldo, Yamade)

**Visual acuity loss**

VA loss can vary from minimal to complete blindness and can affect one or both eyes. Sometimes discrepant results between near and distance VA are present in NOVL patients, hinting at the non-organic cause of visual loss. When visual loss affects only one eye and is profound, the situation is relatively easy to handle. More difficult is the presence of moderate and bilateral symmetrical loss of VA.

Many tests can be used to diagnose NOVL, and it is not the purpose of this paper to review them all. Excellent reviews and textbooks provide an exhaustive list and explanations of these techniques. (Walsh & Hoyt) A selection of the tests frequently used in patients with either monocular or binocular non-organic loss of visual acuity is listed in the Table. Recently, Mojon and Flueckiger designed a very useful test for detection of NOVL. It is a pocket optotype chart in which the optotype minimal angle of resolution is independent of its size; patients with organic visual loss identify correctly all the optotypes whereas non-organic patients tend to stop at the large optotypes. (Mojon)

When VA is decreased, mERG, pattern ERG, EOG and pattern VEP are the most useful tests. Results of these tests are often
considered as objective and reliable, but it is worth keeping in mind that results of VEPs can be altered by the patient, voluntarily or not. (Morgan, Uren) Normal VEP results are very helpful, but abnormal results are less reliable.

The past 15 years have seen the revolution and evolution of optical coherence tomography (OCT). With OCT, the physician can now appreciate in vivo whether the anatomy of either the retina or the optic nerve is intact. Measurement of the retinal nerve fiber layer thickness, assessment of the macular thickness, and, more recently, evaluation of the ganglion cell layer are invaluable tools for the investigation of NOVL.

The mimickers of non-organic loss of VA are the followings: keratoconus, amblyopia, subtle maculopathies, and early optic neuropathies. The following are the most common mimickers of NOVL with tips on how to diagnose them:

- Keratoconus: decreased VA, normal color vision, no RAPD. Normal OCT, abnormal corneal topography;
- Occult maculopathy: decreased VA, sometimes abnormal color vision, no RAPD. Possibly metamorphopsia, possibly abnormal VEP, abnormal macular OCT, abnormal pERG or mERG;
- Early Leber’s hereditary optic neuropathy: decreased VA, abnormal color vision, absence of RAPD at the early stage, abnormal VEP, abnormal pERG, normal mERG.

**Visual field loss**

Distinctive and various patterns of VF loss are present in NOVL. The patterns of VF loss can also vary according to the technique of perimetry that was used. Keane reviewed his own experience of 454 non-organic patients and found 142 patients with non-organic visual field loss. Whereas the majority (91/142) exhibited tubular fields, a surprising 36% displayed hemianopias. This high number of hysterical hemianopias was explained by the confrontational technique of counting fingers which encourage the patient to choose one side. On the other hand, centripetal testing (tangent screen, Goldmann perimetry) tends to produce constriction of VF. (Keane) Nowadays, as most patients are examined with computerized static perimetry, the most apparent significant “loss” by subjective perimetry. (Hood).

When VF is decreased, full-field ERG and multifocal VEP are the most useful electrophysiological tests. A diffuse retinopathy will produce a significant alteration of the full-field ERG. Multifocal VEP provides an objective mean of assessing the VF. By analyzing the cortical potentials, it is possible to demonstrate the preservation of VF despite apparent significant “loss” by subjective perimetry. (Hood). Multifocal VEP offers a great potential for investigating NOVL. However, due to the lack of available commercial software, the technique of multifocal VEP is not widely used.

Sometimes NOVL is diagnosed in a patient harboring a real but subtle organic disorder. Hereafter are listed the most common medical conditions producing constricted VF which could be confused with NOVL with tips on how to diagnose them:

- Vitamin A deficiency: history, decreased VA, dyschromatopsia, night-blindness, abnormal full-field ERG;
- RP sine pigmento: constricted VF, night-blindness, abnormal full-field ERG;
- Paraneoplastic retinopathy: constricted VF, night-blindness, photopsias, abnormal full-field ERG.

**VISUAL PROGNOSIS - RECOVERY**

Overall, the rate of improvement or full recovery of visual function varies from 40% to more than 90%. Better prognosis is achieved in the pediatric group with full recovery reaching more than 90% in three series. (Catalano, Mouriaux, Toldo) Catalano et al reported visual improvement within 24 hours in one-third of cases, and in 75% within two months. The recovery rate in adults is lower, averaging 40-50%.

(Behrmann, Friesen, Kathol, Lim, Sletteberg) The exception

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The finding of either central or arcuate scotomas imply
Keane, McLeod, Smith, Stewart, Thompson JC) As a rule, the physician needs to realize that “reproducible” and “reliable” do not mean “true”. When the patient presents with severe constriction of VF, a very useful technique is the confrontation VF examination. This simple technique can demonstrate non expansion of VF diameter with increasing examination distance or can disclose a much larger VF than by computerized perimetry. Kinetic Goldmann VF examination remains the best examination tool in experienced hands. Demonstrating to the patient that his/her kinetic manual VF is larger than its computerized static counterpart can be of great help, and usually contributes to reassure the patient on his actual VF. Microperimetry disclosed a larger VF than previously measured in one case. Microperimetry can potentially help to assess NOVL patients. (Shimamoto) Pineles et al used a reversed Galilean telescope in a computerized kinetic perimeter and tested patients with constricted VF of both organic and non-organic nature. Patients with organic constricted VF had a normal VF “expansion” while viewing through the telescope, while NOVL patients with constricted VF did not, exhibiting a tubular field of vision. (Pineles)
was the series reported by Keltner, where the improvement rate was only 9%, most likely due to the very high percentage of malingerers. (Keltner)

**CONCLUSIONS**

Neuro-ophthalmologists are in a favorable position when confronted with a patient suspected of NOVL. The physician has knowledge of both the anatomy and the physiology of the visual pathways, whereas the rules governing this specific sensory system are usually not known by the patient. This provides the physician with a certain advantage when investigating NOVL. Further, the use of objective techniques such as electrophysiology and OCT certainly helps the physician to diagnose NOVL with more confidence.

The diagnosis of NOVL is not easy and its consequences can be severe for the patient (this labeling will stick to the patient for several years). Facing a patient suspected of NOVL, the goals of the physician are the following:

a. It is necessary to exclude the possibility of any organic cause which could at least partially explain the loss of vision;

b. It is mandatory to demonstrate that the visual function of the patient is superior to what the patient claims;

c. The patient should be informed that his visual potential is unaltered and it should be possible to recover it;

d. Most patients with NOVL need to be reassured without any other therapy. However, some patients may benefit from temporary “external support” in order to help them recover. Psychiatric management remains episodic.

In order to achieve these goals, an empathetic approach is usually most effective; confronting the patient is rarely beneficial.

Table – Selection of tests that are useful for demonstrating the non-organic nature of VA loss

<table>
<thead>
<tr>
<th>Test</th>
<th>Unilateral VA loss</th>
<th>Bilateral VA loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prism test</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Pupils</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>*Red-green duochrome test</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>*Polarized test</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Rocking mirror test</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Optokinetic drum</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>*Titmus stereoscopic test</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mojon test</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fogging</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Touch both indexes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Electrophysiology</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*These tests are used with both eyes seeing

**CME ANSWERS**

1. d
2. b
3. a

**REFERENCES**

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LEARNING OBJECTIVES
1. The attendee will be familiar with the common presentations of non-organic ocular motor disturbance
2. The attendee will be able to distinguish these psychogenic manifestations from similar organic neuro-ophthalmic syndromes using specific examination techniques
3. The attendee will be able to distinguish pharmacologic mydriasis from parasympathetic pupillary palsy using clinical features and pharmacologic testing

CME QUESTIONS
1. Voluntary nystagmus is usually accompanied by which of the following:
   a. Vertical gaze palsy
   b. Ptosis
   c. Convergence
   d. Pupillary dilation
2. Reported causes of convergence spasm include which of the following:
   a. Myasthenia
   b. Botulism
   c. Wernicke's encephalopathy
   d. Radiation therapy
3. Conditions that may mimic non-organic convergence spasm include which of these:
   a. Ocular neuromyotonia
   b. Posterior fossa tumor
   c. Myasthenia
   d. Midbrain stroke
   e. All of the above
4. The most helpful feature for distinguishing Adie tonic pupil from pharmacologic mydriasis is:
   a. Light-near dissociation
   b. Segmental sphincter palsy
   c. Conjunctival blanching
   d. Response to weak pilocarpine

KEYWORDS
1. Convergence spasm
2. Spasm of the near triad
3. Pseudomyopia
4. Voluntary nystagmus
5. Pharmacologic mydriasis

INTRODUCTION
Somatoform neuro-ophthalmic disorders most commonly affect afferent visual function. When eye movements, lids or pupils are involved, the diagnosis may be challenging. In many such cases the variable nature of the abnormality in question suggests the correct diagnosis but great care must be taken because certain organic disorders may be similarly intermittent. For each of the non-organic syndromes described below, one or more "look-alike" conditions are also described, including features that help distinguish them from the non-physiologic variety.

EYE MOVEMENTS
Gaze palsies
Non-organic conjugate (horizontal or vertical) gaze palsies are most often seen as an incidental finding in a patient with other non-organic visual disturbance(s) or in a patient who is especially anxious about the examination. In the latter, adopting a reassuring and non-threatening manner and moving the fixation target further back from the patient may be sufficient to produce normal versions. In other cases, observing random eye movements during other parts of the visit (like during the history) will reassure the examiner that eye movements are in fact full.

The Lookalike: some eye movement disorders produce a dissociation between saccadic and pursuit movements. This can create the impression of inconsistency and thus be mistaken for a non-organic eye movement disorder. The key is to recognize that the variability in range of motion is related to the type of eye movement tested. In most such cases there is more limitation to saccades (as tested by voluntary re-fixations) than to pursuit movements (a common feature in patients with Progressive Supranuclear Palsy). Similar dissociation of eye movements is seen in...
some cases of internuclear ophthalmoplegia in which adduction is preserved for convergence movements but not for conjugate lateral gaze and in cases of ocular motor apraxia (congenital or acquired) in which reflex movements accomplish what cannot be done with voluntary gaze.

**Convergence spasm**

Most convergence spasm occurs as a component of the near triad, accompanied by pupillary constriction and accommodation. The large majority of such patients do not have an underlying organic cause, although cases due to brain disease have been described [See Table 1]. When convergence spasm does occur as a manifestation of brain disease it is most often due to midbrain dysfunction and is accompanied by other signs of midbrain disturbance such as up-gaze palsy and poorly reactive pupils with or without light-near dissociation.

The determination that intermittent esotropia is due to convergence spasm is usually based on the observation of miosis while the eyes are converged. The associated induced myopia can often be observed during retinoscopy. In addition, the limitation of abduction induced b convergence spasm often disappears under monocular viewing. Treatment is often challenging [See Table 2].

**Look-alike:** variable esotropia may occur with myasthenia but the lateral rectus is not a favorite target in this disease and is therefore uncommon. Ocular neuromyotonia, when it affects the medial rectus, also produces variable esotropia. In such examples of this uncommon disorder, failure of medial rectus relaxation following adduction causes persistent esotropia upon returning to primary position, worse on contralateral gaze, lasting from seconds to minutes. The trick to diagnosing this condition is recognizing that the variable esotropia is not random or voluntary but precipitated by gaze in a particular direction. Diagnosis may be more challenging in cases in which contractions also occur spontaneously and in those with a refractory period after contraction. A helpful clue for diagnosing this syndrome is recalling that it usually occurs after radiation therapy for a skull base tumor. Dramatic response to carbamazepine is characteristic.

**Look-alike:** accommodative spasm occasionally occurs in isolation, not accompanied by miosis and convergence. The most common form of isolated accommodative spasm, also termed pseudomyopia, is peripheral, i.e. due to ciliary spasm as from inflammation, corneal abrasion or trauma. Uncommonly, pseudomyopia is due to central nervous system disease, usually severe head injury. Accommodative spasm due to head trauma usually affects young adults (perhaps because of their more robust accommodative amplitudes) and can persist for years. The basis for such spasm is unclear, most likely due to disinhibition of putative brain stem accommodation centers. Cases are usually managed by supplying the manifest (non-cycloplegic) refraction (or at least part of it) or with cycloplegic drops and near glasses.

**Look-alike:** acute acquired comitant esotropia (AACE) usually arises from temporary occlusion of the visual axis that disrupts fusion of a pre-existing esophoria. Occasional cases are due to brain disease, the most worrisome being a posterior fossa tumor.

**NYSTAGMUS**

Some normal subjects can voluntarily induce saccadic oscillations, termed “voluntary nystagmus”. The ability to produce such movements is found in 5 – 8% of the population and sometimes runs in families. These eye movements are conjugate and are usually confined to the horizontal plane with frequencies ranging from 3 – 42 Hz and amplitudes from 0.5 to 35 degrees. Eye movement recordings in such individuals indicate that these ocular oscillations are more similar to ocular flutter and opsoclonus than to nystagmus and the alternative term “psychogenic flutter” has been proposed. In most individuals with this talent, saccadic oscillations are accompanied by convergence and fluttering of the eyelids and the presence of these features should suggest the correct diagnosis.

**EYE LID CLOSURE**

Voluntary ptosis does not usually occur in isolation but is found more often in the setting of other non-organic visual/ocular symptoms following trauma or other inciting incident. While this condition may simulate levator weakness, more often it takes the form of orbicularis spasm; at times the patient presents a picture of both levator weakness and orbicularis spasm which is especially helpful in confirming its non-organic basis. It is difficult to sustain voluntary ptosis in a consistent fashion; the twitchiness of the apparently ptotic lid is a helpful feature but must be distinguished from the lid twitches of myasthenia and from aberrant regeneration involving the levator. It is difficult to sustain voluntary ptosis and upgaze at the same time and so observation of lid position on upward gaze is a helpful examination technique.

**The Lookalike:** patients with Essential Blepharospasm, as in other forms of dystonia, often have tricks they can use to improve their symptoms. For example, some patients find that opening their mouth helps them keep their eyes open. Such oddities of basal ganglia function may give the impression of a non-organic movement disorder. In addition, patients with blepharospasm may be worse under scrutiny and with bright lights. Thus, with “casual conversation”, as when engaged in the history-taking, they may not exhibit much in the way of unwanted eyelid closure.

**PUPILLARY DILATION**

Pharmacologic instillation with a cholinergic agent produces pupillary dilation that may be suspected based on the very large degree of dilation and a history of access to a mydriatic agent. Trauma to the pupillary sphincter and anterior chamber inflammation are ruled out by biomicroscopy, the demonstration of normal ocular motility rules out a third nerve palsy. The non-organic basis for this form of mydriasis is typically confirmed by its lesser response to pilocarpine compared to the fellow eye.
The Lookalike: an acute post-ganglionic parasympathetic palsy (Adie's pupil) produces a similarly dilated and poorly reactive pupil to light. Characteristic light-near dissociation and super-sensitivity to weak cholinergic agents are later developments and therefore not helpful for diagnosis in the acute setting. In contrast to pharmacologic mydriasis, an Adie pupil at any stage should show a strong miotic response to 1-2% pilocarpine. The most helpful feature for distinguishing pharmacologic mydriasis from an Adie's pupil is the segmental nature of the sphincter palsy in the latter.

Table 1. Organic Causes of Convergence Spasm

- Diphenylhydantoin intoxication
- Wernicke's encephalopathy
- Head trauma
- Chiari I malformation
- Syphilis
- Labyrinthine lesions

Table 2. Reported Treatment Options for Spasm of the Near Triad

- Cycloplegic eye drops and reading glasses
- Anti-anxiety medication
- Placebo eye drops
- Counseling
- Glasses with opaque inner third
- Amytal interview

CME ANSWERS

1. c
2. c
3. e
4. b

REFERENCES

LEARNING OBJECTIVES
1. Understanding commonly employed imaging modalities in non-organic disorders
2. Understand limitations of current literature concerning non-organic disorders
3. Understand limitations of current functional imaging techniques in understanding non-organic disorders

CME QUESTIONS
1. fMRI may employ paradigms with activation epochs interspersed with inactivity to elicit BOLD responses indicative of brain activation. True/false
2. Functional imaging is a consistent and reliable method to diagnose functional disorders. True/false
3. fMRI has the potential to teach us about neural networks involved in specific tasks and compensation for disease. True/false

KEYWORDS
1. Functional MRI
2. Functional disorders
3. Positron emission tomography

INTRODUCTION
Many of neuro-ophthalmology’s most challenging conditions are rooted in sub-structural pathology. Functional imaging has the potential to unravel many of these brain mysteries by illustrating regional metabolic (inferred activity) differences within the brain at rest and during specific tasks. Within this context, functional imaging (PET, SPECT or fMRI) may teach us about functional disorders – either conversion or malingering. Group data in these disorders has provided interesting, but varied and at time disparate results. Despite the promise and potential (and at times hype), functional imaging at present does not have the ability to assist in the diagnosis of individual patients.

QUESTION: Can imaging reliably & objectively diagnose functional disorders?

BACKGROUND
Functional disorders are common in clinical practice; indeed, it has been estimated that 20% of outpatient neurologic encounters harbor unexplained medical symptoms (Mace 1991). Such disorders are also common in ophthalmology clinics, where 1-5% of patients manifest medically unexplained visual loss (Kathol 1983, Sletteberg 1989), and such impairments run a chronic course in up to 50% of patients (Barris 1992). Accordingly, neuro-ophthalmology is often the crossroads for functional disorders within these specialties. Despite their frequency, these disorders are poorly understood.

When exploring the neurobiology of a particular disease, investigators establish disease-specific requirements and employ certain tools. Such methodology is best exemplified by conditions such as progressive supranuclear palsy (PSP). PSP has an established case definition, and a described course. A case of PSP in Europe would share these features with a case documented in North America, and patients visiting several clinics would receive the same diagnosis at each, assuming similar criteria were applied. MRI features such as midbrain atrophy have been well described and do not vary among imaging centers. The applicable genetics have been elucidated in familial forms. The pathology inclusive of tau protein accumulation is well documented. Within this framework, we can begin to understand the neurobiology of this tauopathy: why the protein accumulates, what dysfunction does it cause in the favored locations, and potential interventions to reverse the disease.

This well established model couldn’t be applied to current day understanding of functional conditions. These disorders do not have established, agreed-upon diagnostic criteria, and the same functional patient may receive several different diagnoses from different physicians based on a similar symptom set. The final word on many functional disorders belongs to the psychiatrists, who use the DSM as a codified bible (ironically, most of the functional disorders are seen outside of psychiatry clinics). Even within this context, the diagnostic rules have changed. While DSM-IV included diagnoses of somatization disorder, hypochondriasis, pain...
disorder, and undifferentiated somatoform disorder, these have been removed from DSM-V. The latter dispenses with the DSM-IV arbitrary symptom count for somatization disorder, instead renaming this ‘somatic symptoms disorder’ with an emphasis on maladaptive thoughts and behaviors. DSM-V’s somatic symptoms disorder can also accompany organic medical disorders. The criteria for conversion disorder have been modified to emphasize the importance of the neurological exam and the exclusion criteria of psychological factors at the time of diagnosis. These criteria will continue to morph with time and increasing medical knowledge. It is worth remembering the long list of medical diagnoses that have been considered factitious or functional in the past but which now are accepted as clearly organic and have well-explained pathophysiologic basis. Gowers’ 1893 textbook classified Parkinson’s disease, chorea, torticollis, epilepsy and narcolepsy as functional because at the time there was no autopsy-visible lesion to stamp them “organic”. commonplace disorders such as blepharospasm were also thought to be functional in the recent past. There are no current traditional imaging, genetic or other biomarkers at present that help in diagnosis or prognosis. Tissue samples are normal, and autopsy fails to establish the histological features indicative of functional disorders. New knowledge regularly creates old fools.

THE EVIDENCE/SCIENCE:
Functional imaging is very difficult to do in the target population for several reasons. First, we cannot agree on clear diagnostic criteria for the diagnosis – this would make it virtually impossible to design a workable multicenter trial. Second, this population is very difficult to recruit – attesting to this fact is that the largest published series of functional visual patients studied with functional imaging to date is 8. Additional difficulties confounding the literature include the heterogeneity of the functional groups – visual, motor, sensory, movement disorder symptoms, with further variable within these groups (e.g., one or both eyes, degree of claimed visual loss, duration of symptoms, etc.). Adding to these problems is the variability of imaging equipment and protocols, a problem that could be overcome with elements of standardization, but a situation that renders the current literature difficult to assess. Since the 1990s, protocols continue to undergo refinement and improvements (Tiihonen 1995).

fMRI
Functional MRI (fMRI) has many advantages pertaining to functional imaging and has become the imaging tool of choice. The technology when used during an activation task involves the use of BOLD (blood oxygenation level dependent). Although there are numerous small series or single cases concerning motor or sensory functional deficits, there are very few such cases with visual symptoms.

Becker et al reported an interesting case single of a 25-year old male with functional “complete” visual loss OU (Becker 2013); these authors were able to study the subject during and after episodes of visual loss. An unaltered visual cortical response to checkerboard stimulation was observed during functional blindness; however, more complex visual stimuli such as faces or objects produced hypofunction in the occipital lobes with hyperfunction in the postcentral gyrus bilaterally and right superior temporal lobe. Extraction of the emotion-specific activity revealed increased activity in the left medial frontal gyrus and anterior cingulate cortex plus bilateral angular gyrus (hypothesized to be involved in moral reasoning and emotional regulation).

The largest study involving visual stimuli with medically unexplained visual loss was reported by Werring et al in 2004 (Werring 2004). These investigators recruited 5 patients with unexplained visual loss fulfilling DSM-IV criteria for conversion disorder. Among this cohort, 4/5 had bilateral visual field defects, and the duration of symptoms ranged from 2-10 years. Monocular whole field 8hz red photic stimulus was used to elicit fMRI responses with 20-second epochs alternating with darkness. The control group consisted of 7 healthy volunteers. Patients demonstrated reduced visual cortex activation, with increased activation of the left inferior frontal cortex, left insula-claustrum, bilateral striatum and thalami, left limbic regions and left posterior cingulate cortex. This visually-based example fits the general functional imaging model as described below.

Stone et al studied the fMRI findings in a group of 4 conversion weakness patients compared to healthy controls simulating weakness. During attempted ankle plantar flexion, both the conversion patients and the controls showed less activation of the responsible motor cortex compared to plantar flexion on the normal side; conversion patients showed activation in the basal ganglia, insula, lingual gyri and inferior frontal cortex; however this was not present in controls feigning weakness. Controls (but not conversion patients) activated contralateral supplementary motor areas when moving the “weak” side (Stone 2007). Employing a different paradigm, Voon et al studied 8 patients with conversion tremor compared to volunteers feigning tremor; conversion tremor demonstrated hypoactivation of the right temporoparietal junction, and less connectivity between right temporoparietal junction, sensorimotor regions (sensorimotor cortex and cerebellar vermis) and limbic regions such as the cingulate and ventral striatum (Voon 2010).

“Common” Pattern: hypofunction of primary cerebral area with hyperfunction of other areas; the hyperfunctioning regions may have inter-individual variability and have been reported to involve a large variation of regions. In addition, while group differences may be present (conversion vs feigned symptoms vs asymptomatic with history of conversion), the ability of the technology to distinguish an individual patient’s conversion vs. organic diagnosis is limited and suspect because of the variability of findings, very small magnitude of signal changes elicited by fMRI, and unknown meaning of these areas of activation (causal, consequence or compensation).
SPECT
Single photon emission computerized tomography lacks sufficient resolution to address detailed issues of functional localization and has been largely supplanted by PET or more commonly, fMRI. Nonetheless, this imaging modality ushered in future functional imaging studies in non-organic disorders (Tiihonen 1995).

PET
Positron emission tomography is a useful method for functional imaging but has several drawbacks. It is labor intense and expensive, requiring a cyclotron near or on-site to generate radioactive metabolites; perhaps most importantly, PET involves ionizing radiation which limits the enthusiasm of healthy volunteers. (Vuilleumier 2005; Spence 2000). Functional imaging studies of functional disorders utilizing PET have focused on non-visual symptoms. Vuilleumier et al studied 7 patients with functional sensorimotor syndrome using PET; decreased contralateral basal ganglia activation was evidenced during the symptoms, which resolved upon recovery. Spence et al studies 3 patients with unilateral weakness compared to 4 volunteers simulating unilateral weakness with PET; patients displayed left dorsolateral prefrontal hypoactivation when attempting to move the limb, while feigned weakness was associated with right dorsolateral prefrontal cortex (regardless of side).

COMMONALITIES
Although patients and protocols vary widely, there are some common themes buried within the functional imaging literature concerning non-organic disorders. Hypoactivation is commonly seen in the expected cortical regions for a given task (e.g., motor strip with functional paralysis) with hyperactivation in other areas; the specifics of these “other” areas varies widely but has included RIGHT anterior cingulate and orbitofrontal cortex, parietal operculum, supplementary motor areas, ventral premotor cortex; LEFT inferior frontal cortex, insula-claustrum, thalamus, cerebellum, supplementary motor areas, limbic structures, posterior cingulate cortex, inferior parietal cortex; and BILATERAL striatum, thalami, putamen, cerebellum. (Burgmer 2006; Stone 2007; Voon 2010a)

LIE DETECTION: AN ILLUSTRATIVE EXAMPLE
There are now two private corporations that sell fMRI assessment as a method for lie detection, No Lie MRI (http://www.noliemri.com/) and the Cephos Corporation (http://cephosdna.com/); however, fMRI (similar to traditional lie detector tests) are not admissible in US courts.

ANSWER: Can imaging reliably & objectively diagnose functional disorders? Not yet, but stay tuned...

REFERENCES
7. Slettenberg O, Bertelsen T, Hovding G. The prognosis of patients with hysterical visual impairment. 67, 159-163, 1989

CME ANSWERS
1. True
2. False
3. True
LEARNING OBJECTIVES

1. Recognize the signs, symptoms and history associated with the presentation and diagnosis of somatoform disorders;
2. Differentiate neurological and non-neuroanatomical presentations;
3. Discuss the diagnosis of somatoform disorders with patients and families to enable acceptance of treatment;
4. Recognize the treatment options available for patients with somatoform disorders.

CME QUESTIONS

1. The clinician should address which of the following issues in a person suspected of having a somatoform disorder:
   a. The patient’s understanding of the disorder
   b. The presence of current psychiatric symptoms
   c. The impact of the symptoms on the patient’s life, work, and family
   d. Past psychiatric history
   e. All of the above

2. The gold standard for diagnosing psychogenic nonepileptic seizures is:
   a. Serum prolactin
   b. Routine EEG
   c. History alone
   d. Video EEG capturing a typical event

3. Which of the following therapies has the least successful outcomes for patients with somatoform disorders:
   a. Group therapy
   b. Cognitive behavioral therapy
   c. Supportive therapy
   d. Interpersonal therapy

KEYWORDS

1. Neuropsychiatry
2. Somatoform disorders
3. Conversion disorder
4. Examination
5. Treatment

INTRODUCTION

Somatoform disorders (SD) present in adults and children with a combination of neurologic signs, underlying psychological conflicts and comorbid psychiatric disorders. The majority of SD do not have a laboratory test to confirm the diagnosis. The exception to the rule is in psychogenic nonepileptic seizures (PNES), where the gold standard of video electroencephalography and adjunctive tests are used in establishing the diagnosis of PNES.

After establishing the diagnosis, engaging patients in treatment is essential for symptom control. Patients and families of patients with SD sometimes refuse to accept the diagnosis and to follow recommendations for treatment. Other barriers arise when the mental health professionals to whom they are referred fail to agree with the neurologist’s diagnostic impression. The role of the neurologist, mental health providers and other clinicians in the diagnosis and management of these patients will be discussed, and common obstacles that preclude treatment will be reviewed.

I. Diagnosis of somatoform disorders
   A. epidemiology
   B. semiology
   C. work up

II. Management of Somatoform disorders
   A. Treatment modalities
   B. Presentation of the Diagnosis
   C. Acute Treatment
   D. Maintenance Treatment

III. Future Directions
CME ANSWERS

1. e
2. d
3. c

REFERENCES

ONSITE REGISTRATION HOURS (located in the Rio Mar Foyer)

- Friday: 4:00 p.m. – 8:00 p.m.
- Saturday: 7:00 a.m. – 8:00 p.m.
- Sunday: 6:30 a.m. – 5:30 p.m.
- Monday – Thursday: 6:30 a.m. – 12:30 p.m.

SOCIAL FUNCTIONS

SATURDAY, MARCH 1

Catamaran Sail and Snorkel - $140 (Buffet lunch included) 9:00 a.m. – 4:00 p.m.

The group will board for a relaxing sail aboard a splendid catamaran to one of the nearby coral reefs. When the boat anchors you may choose to snorkel among live reef and hundreds of colorful types of fish which you can hand feed or, relax on the pristine beaches and crystal clear waters of the Caribbean Sea.

Opening Reception 6:30 p.m. – 8:00 p.m.

Please join us for the Opening Reception in the Ocean Terrace. All are welcome to attend the opening reception, which features complimentary cocktails and heavy hors d’oeuvres.

SUNDAY, MARCH 2

Members-in-Training Program and Reception 5:30 p.m. – 6:30 p.m.

New to neuro-ophthalmology? All students, residents and fellows are encouraged to attend!

MONDAY, MARCH 3

WIN Luncheon 12:15 p.m. – 1:30 p.m.

Join your female colleagues for the Women in Neuro-Ophthalmology (WIN) Luncheon & Meeting. A lunch selection will be available for purchase in your registration for $35; however, all are welcome to attend even without the purchase of a lunch.

Young Neuro-Ophthalmologist Forum: Career GPS 2.0: 3:00 p.m. – 5:00 p.m.

Finding your path, avoiding the potholes (NEW FORMAT!)

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

Topics include: How to negotiate your first contract (academic and private practice), Demystifying academic promotion: from assistant to associate professor, a hands-on CV workshop: how to put your best foot forward on paper (bring your CV), and neuro-ophthalmology 2014: how to blend your neuro-ophthalmic career with pediatrics, oculoplastics, clinical research and more! Because you asked, we will also work to provide additional networking opportunities with fellowship directors and prospective employers during the latter half of the forum!
TUESDAY, MARCH 4

Rainforest Tour - $70 *(boxed lunch included)*
12:15 p.m. – 5:00 p.m.
Explore El Yunque - the only tropical rainforest in the United States Forest System encompassing 28,000 acres and reaching an elevation of 3,526 feet. The certified and professional guide will lead you along well marked trails and paths as you embark on an adventure through the vast Palo Colorado forest which receives over 200 inches of rainfall a year and nourishes over 240 species of trees and a variety of animals including the endangered Puerto Rican parrot. Wear comfortable shoes and loose fit clothing that you would not mind getting dirty or wet; don’t forget your camera!

Old San Juan Historical Tour - $75 *(boxed lunch included)*
12:15 p.m. – 6:00 p.m.
Fall in love with the beautiful cobblestone streets, and colorful buildings that date back to the 16th and 17th century, when Puerto Rico was under Spanish possession. With its abundance of shops, historic places, museums, open air cafés, restaurants, gracious homes, tree-shaded plazas, and its old beauty and architectonical peculiarity, “Old San Juan” is a main spot for local and international tourism. Consisting of 400 restored buildings from the 16th- and 17th-century Spanish colonial period, this area in San Juan is steeped in history with an old-world and romantic European charm.

Poster Session
6:00 p.m. – 9:30 p.m.
This year’s Poster Session will include a reception and dinner buffet. Event is complimentary for attendees but guests must purchase tickets. Tickets are available for purchase for $50 per person. The buffet will open at 6:00 p.m. Authors will present their posters between 6:45 p.m. and 8:15 p.m. Odd numbered posters: 6:45 p.m. – 7:30 p.m., Even numbered posters: 7:30 p.m. – 8:15 p.m.

WEDNESDAY, MARCH 5

Annual NANOS Reception and Banquet
6:45 p.m. – 12:00 a.m.
Buses will depart from the El Yunque Foyer at 6:45 p.m. to bring attendees to the Coco Rio which is located in the Rainforest. Join your colleagues for a fun, casual evening of socializing, dining and dancing at the NANOS Annual Reception and Banquet. Guests and children are welcome. Event is complimentary for attendees but guests must purchase tickets. Tickets are available for purchase for $100 per person. Comfortable shoes are highly recommended. Buses will bring guests back to the hotel as they fill throughout the evening. Last bus will depart at 11:45 p.m. Since the event is in the rainforest, driving separately is strongly discouraged.

BIOLUMINESCENT BAY KAYAK TOURS
Saturday, March 1 and Monday, March 3 – 8:30 p.m. – 11:59 p.m. - $89 – SOLD OUT
Thursday, March 6 – 5:30 p.m. – 9:00 p.m. *(boxed meal included)* - $104 and 8:30 p.m. – 11:59 p.m. - $89
Buses will depart from the El Yunque Foyer. Visit one of the most amazing natural phenomenon’s of the world! As you paddle your way through the mystical mangrove channels, you will be introduced to the Pyrodinium Bahamans, microscopic plankton capable of producing natural light when the water is disturbed. Watch how every stroke of your paddle leaves behind a glowing swirl of blue light, and fish light up their path like shooting stars in the water. You can bring your own towel or one can be rented for $10.

GUEST MEETING LOUNGE AREA
Sunday, March 2 – Thursday, March 6—No set hours; between 9-11 am is recommended.
Relax and enjoy the company of other guests in the Gazebo, located in “La Playa Beach Event Area” of the Wyndham Rio Mar Resort.
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Cannon, Carlow, Daroff, Glaser, Hoyt

1976 SANTA FE, NEW MEXICO
Cannon, Carlow, Daroff, Glaser, Hoyt, Schatz

1977 PURGATORY, COLORADO
Appenleider, Bicknell, Cannon, Daroff, Glaser, N. Newman (CA), Schatz

1978 PURGATORY, COLORADO
Bicknell, Cannon, Daroff, Glaser, Schatz, Snyder, A.E. Walker, Wray

1979 JACKSON HOLE, WYOMING
Bicknell, Cannon, Daroff, Glaser, Schatz, Van Dyk, Wilson, Younge

1980 SANTA FE, NEW MEXICO
Bicknell, Cannon, Daroff, Glaser, Hoyt, Schatz

1981 PARK CITY, UTAH
Carlow, Cobbs, Corbett, Dell’Osso, Ellenberger, Glaser, Kennerdall, Sanborn, Savino, Seigel, Schatz, Thompson, Wilson, Wirtschafter, Younge, Zaul

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1983 BIG SKY, MONTANA

1984 SNOWBIRD, UTAH

1985 SUNSHINE VILLAGE, ALBERTA

1986 WHISTLER, BRITISH COLUMBIA

1987 NORTHSTAR, CALIFORNIA

1988 CRESTED BUTTE, COLORADO

1989 CANCUN, MEXICO

1990 STEAMBOAT SPRINGS, COLORADO

1991 PARK CITY, UTAH

1992 RANCHO BERNARDO INN, SAN DIEGO

1993 BIG SKY RESORT, BIG SKY, MONTANA

1994 TAMARACK RESORT, DURANGO, COLORADO

1995 EL CONQUISTADOR, TUCSON, ARIZONA

1996 SNOWBIRD RESORT, SNOWBIRD, UTAH

1997 KEYSTONE RESORT, KEYSTONE, COLORADO

1998 BUENA VISTA PALACE RESORT, ORLANDO, FLORIDA
# NANOS Archives

## Past Officers and Board Members

<table>
<thead>
<tr>
<th>Year</th>
<th>President</th>
<th>Vice-President</th>
<th>Treasurer</th>
<th>Secretary</th>
<th>Member-At-Large</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-1982</td>
<td>Thomas J. Carlow, M.D.</td>
<td>Joseph Bicknell, M.D.</td>
<td>Donald Seelinger, M.D.</td>
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<td>1983-1985</td>
<td>Thomas J. Carlow, M.D.</td>
<td>Peter Savino, M.D.</td>
<td>Carl Ellenberger, M.D.</td>
<td>Robert Daroff, M.D.</td>
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<td>1992-1994</td>
<td>James A. Sharpe, M.D.</td>
<td>Steven E. Feldon, M.D.</td>
<td>Steven E. Feldon, M.D.</td>
<td>Robert Daroff, M.D.</td>
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<tr>
<td>1994-1996</td>
<td>Steven E. Feldon, M.D.</td>
<td>Jonathan Wirtzschafter, M.D.</td>
<td>Alfredo A. Sadun, M.D.</td>
<td>Robert Daroff, M.D.</td>
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<td>2000-2002</td>
<td>Neil R. Miller, M.D.</td>
<td>Kathleen Digre, M.D.</td>
<td>Larry Frohman, M.D.</td>
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<td>2002-2004</td>
<td>Kathleen Digre, M.D.</td>
<td>Larry Frohman, M.D.</td>
<td>Steven E. Feldon, M.D.</td>
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<tr>
<td>2004-2006</td>
<td>Larry Frohman, M.D.</td>
<td>Deborah I. Friedman, M.D.</td>
<td>Nancy J. Newman, M.D.</td>
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<td>2006-2008</td>
<td>Deborah I. Friedman, M.D.</td>
<td>Preston C. Calvert, M.D.</td>
<td>Andrew Lee, M.D.</td>
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<td>2008-2010</td>
<td>Anthony C. Arnold, M.D.</td>
<td>Preston C. Calvert, M.D.</td>
<td>Larry Frohman, M.D.</td>
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<td>2010-2012</td>
<td>Preston C. Calvert, M.D.</td>
<td>Leah Levi, M.D.</td>
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<tr>
<td>2014 Annual Meeting Syllabus</td>
<td>Jonathan D. Trobe, M.D.</td>
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RESIDENT FELLOW AWARD RECIPIENTS
Separate awards are given to the best work by a medical student, resident or fellow. Eligible candidates include any medical student, resident or individual in a fellowship program who is the first (presenting) author of work done as a student, resident or fellow respectively. Judging for the awards is based upon the candidate’s platform or poster presentation at the annual NANOS meeting.

1983  Big Sky
   David Zackon
   Vertical Supranuclear Gaze Palsy and Intrathoracic Carcinoid Tumor

1984  Snowbird
   Mary Stefanyszyn
   Optic Nerve Tumor in a Child

1985  Sunshine Village
   Paul Ranalli
   Ocular Motor Syndrome of the Superior Cerebellar

1986  Whistler
   William Fletcher
   Big Blind Spot Syndrome without Optic Disc Edema Artery

1987  Lake Tahoe
   Steven Gross
   A Child with Aminoaciduria and Retinal Degeneration

1988  Crested Butte
   Jonathan Horton
   Ocular Dominance Columns in Human Visual Cortex

1989  Cancun
   Karl Golnik
   Acute Visual Loss in a Young Male

1990  Steamboat Springs
   Jonathan Horton
   Occipital Visual Field Defects Respecting the Horizontal Meridian: Hallmark of Extrastriate Cortical Lesions

1991  Park City
   Constance Fry
   Is there Value in Evaluating Carotid Artery Patency in Patients with Anterior Ischemic Optic Neuropathy

1992  Rancho Bernardo
   Ikyle Smith
   Heteroplasmy in Leber’s Hereditary Optic Neuropathy

1993  Big Sky
   Kimberly Peele
   The Role of Peripheral Visual Fields in IIH

1994  Durango
   Aki Selky
   Variability of the Relative Afferent Pupillary Defect:
   Effect of Stimulus Number, Duration, and step Size on the Confidence Limit Using Pupillography

1995  Tucson
   Erkan Mutlukan
   Red Color Desaturation, Brightness Perception Asymmetry and Light Detection Threshold Elevation in Optic Neuropathy: How Do They Inter-Relate?

1996  Snowbird
   Nurhan Torun
   Initial and Sinusoidal Vestibulo-Ocular Reflex Following Focal Brainstem Lesions

1997  Keystone
   John M. Khoury
   Can Humphrey Perimetry 24-2 Be Substituted for 30-2

1998  Orlando
   Valerie Biassus, M.D.
   Neuro-Ophthalmologic Manifestations of 145 Patients with Extracranial Internal Carotid Artery Dissections

1999  Snowmass
   John Kerrison, M.D.
   Congenital Motor Nystagmus Linked to Xq26-q27

2000  Mt. Tremblant
   Agnes Wong, M.D.
   Effects of Abducens Nerve Palsy on Listing’s Law During Saccades and Fixation

2001  Rancho Mirage, CA
   Gabriella Szatmary, M.D.
   Can Sita Fast Be Used as a Reliable Alternative to Goldman Perimetry in Neuro-Ophthalmic Practice?

2002  Copper Mountain
   Nicholas T. Monsul, M.D.
   Dibutyryl Cyclis AMP Promotes Optic Nerve Regeneration

2003  Snowbird
   Nitza Goldenberg-Cohen, M.D.
   Defining the Retinal and Optic Nerve Response to Anterior Ischemic Optic Neuropathy (AION) Using a Mouse Model

2004 Orlando
• Fellow: Guy V. Jirawuthiworavong, M.D., M.A.
  Frequency of Antiretinal Antibodies in Normal Human Serum
• Resident: Gregory F. Wu, M.D., Ph.D.
  Visual Function and Disease Phenotype in Multiple Sclerosis
• Student: A Quantitative Approach to Identifying Non-Organic Contributions to Field Defects Using the Multifocal Visual Evoked Potential (mfVEP)
2005 Copper Mountain
- Fellow: Gabrielle R. Bonhomme, M.D.
  Isolated Pediatric Optic Neuritis: Brain MRI Abnormalities and Risk of Multiple Sclerosis
- Resident: Clare Fraser, M.B.B.S
  Multifocal Visual Evoked Potentials in the Differential Diagnosis of Acute Optic Neuritis
- Student: Christopher Rodarte, B.A.
  A Quantitive Approach to Identifying Delayed Latencies in the Multifocal Visual Evoked Potential (mfVEP)

2006 Tucson
- Fellow: Gregory Wu, M.D., Ph.D.
  Regional MRI Abnormalities and Visual Dysfunction in Patients with Multiple Scerosis
- Resident: Clare Fraser, M.B.B.S.
  One Year Multiple Sclerosis Conversion Rates for Patients with Multifocal Visual Evoked Potential (MVEP) Latency Delay
- Student: Michael D. Richards
  Duration of Binocular Decorrelation Predicts the Intensity of Fusion Maldevelopment (Latent) Nystagmus in Strabismic Macaque Monkeys

2007 Snowbird
- Fellow: Christopher C. Glisson, D.O.
  Clinical Characteristics Associated with Neuromyelitis Optica (NMO) Antibody Seropositivity
- Resident: Melissa W. Ko, M.D.
  Assessment of Visual Dysfunction in Parkinson’s Disease
- Student: Bryn Burkholder
  Low-Contrast Letter Acuity Loss Over Time in Multiple Sclerosis Correlates with Reductions in Retinal Nerve Fiber Layer Thickness and Macular Volume by OCT

2008 Orlando
- Fellow: Thomas N. Hwang, M.D., Ph.D.
  Reconstitution of Light-Evoked Responses through a Mechanism of NMDA Receptor Mobility across the Cell Membrane in a Tiger Salamander Model
- Resident: Sashank Prasad, M.D.
  Cross-Modal Language Processing in the Visual Cortex of the Congenitally Blind
- Student: Matt Schlenker
  The Translational Vestibulo-Ocular Reflex in Patients with Skew Deviation

2009 Lake Tahoe
- Fellow: Divya Aggarwal, M.D.
  Melanopsin Retinal Ganglion Cells: A New Class of Cells in Human Retina
- Resident: Daniel Barthelmes, M.D., FEBO
  Retinal Hemorrhages in High Altitude Mountaineers
- Student: Sally C. Chang
  MS Functional Composite Scores with a Visual Component Added Capture Axonal Loss in Patients with Multiple Sclerosis

2010 Tucson
- Fellow: Robert Avery, D.O.
  Reference Range of Cerebrospinal Fluid Opening Pressure in Children
- Resident: Patrick Yu-Wai-Man, M.D.
  Multi-System Neurological Disease is Common in Patients with OPA1 Mutations
- Student: Jonathan Frandsen
  Macular Carotenoids in Patients with Photophobia

2011 Vancouver
- Fellow: Jennifer Graves, M.D.
  Visual Pathway Axonal Loss in Patients with Benign Multiple Sclerosis
- Resident: Patrick Yu-Wai-Man, M.D., Ph.D.
  Efficacy and Safety of Idebenone in Patients with Leber’s Hereditary Optic Neuropathy (LHON): Results of a 6-Month Randomized, Placebo-Controlled Trial (RHODOS)
- Student: Joyce Ho
  In Vivo Imaging of Murine Experimental Anterior Ischemic Optic Neuropathy

2012 San Antonio
- Fellow: Patrick Yu-Wai-Man, BMedSci, MBBS, PhD, MRCOphth
  Mitofusin 2 (MFN2) mutations cause mitochondrial DNA instability in Charcot-Marie-Tooth disease
- Resident: Karen Schmitt, M.D.
  Transmeningeal Drug Delivery to the Optic Nerve
- Student: Mithu Storoni
  The Use Of Magnetic Resonance Imaging To Distinguish Between NMO Spectrum And MS Related Optic Neuritis Based On The Appearance Of The Visual Pathways

2013 Snowbird
- Fellow: Kimberly Winges, MD
  The Ganglion Cell Layer Across the Vertical Meridian in Hemianopsia: I Get No Respect!
- Resident: Cynthia Yu-Wai-Man, MBBS, FRCOphth
  Extraocular muscle atrophy and central nervous system involvement in chronic progressive external ophthalmoplegia – a structural and spectroscopic magnetic resonance study
- Student: Ali S. Saber Tehrani
  Quantitative video-oculography for diagnosing stroke at the bedside in acute vertigo: an “ECG” for the eyes

NANOS RECOGNITION AND AWARDS
PRESENTED AT THE ANNUAL NANOS BANQUET DURING THE ANNUAL MEETING
(CONTINUED)
THE THOMAS AND SUSAN CARLOW YOUNG INVESTIGATOR AWARD
This award was established to encourage and recognize basic or clinical research in neuro-ophthalmology by a NANOS candidate or active member. The originality, scientific merit and neuro-ophthalmic interest of a developing investigator’s total body of work combined with a representative new research manuscript will be considered as criteria to determine the award recipient. The award is selected by the Research Committee during the Annual Meeting and need not be given annually. It is not open to NANOS Fellows.

1997    Leonard A. Levin, M.D., Ph.D.
        Induction of Gene Expression after Retinal Ganglion Cell Anatomy

1998    Jason J.S. Barton, M.D.
        Ocular Tracking of Step-Ramp Targets by Patients with Unilateral Cerebral Lesions

1999    Wolf Lagreze, M.D.
        Neuroprotection with Memantine, Cerestat and Riluzole in a Rat Model of Acute Retinal Ischemia

2000    Sean Donahue, M.D.
        Skew Deviation and Inferior Oblique Palsy

2002    Valérie Biousse, M.D.
        The Eyes of Mito-Mouse

2003    Agnes M.F. Wong, M.D., Ph.D.
        Early Versus Delayed Correction of Infantile Strabismus in Macaque Monkeys: Effects on Cerebral Ocular Motor Circuits

2004    John B. Kerrison, M.D.
        Candidate Gene Analysis in X-linked Congenital Nystagmus

2005    Steven F. Stasheff, M.D., Ph.D.
        Alterations in Spontaneous and Light Evoked Ganglion Cell Activity During Retinal Degeneration in Roll Mice

2006    None

2007    Fiona Costello, M.D., FRCP
        Retinal Nerve Fiber Layer Measurements in Optic Neuritis: Determining the Role of OCT in Predicting Visual Recovery and the Future Risk of MS

2008    Kenneth Shindler, M.D.
        Orally Administered SIRT1 Activator SRT501 is Neuroprotective for Retinal Ganglion Cells and Suppresses and Neurological Dysfunction in a Mouse Model of Multiple Sclerosis

2009    Michael S. Salman, Ph.D., MRCP
        Characteristics of the Cerebellar Dysplasia in Type II Malformation as Revealed by Ocular Motor Functions

2010    None

2011    Y. Joyce Liao, M.D., Ph.D.
        Laser-Assisted Transplantation of Stem Cells into the Adult Eye

2012    Beau B. Bruce, M.D., M.S.
        Non-mydriatic Ocular Fundus Photography Read by Emergency Department (ED) Physicians: FOTO-ED Study

2013    Robert A. Avery, D.O.
        Hand-Held Optical Coherence Tomography During Sedation Detects Visual Acuity and Visual Field Loss in Young Children with Optic Pathway Gliomas

THOMAS CARLOW DISTINGUISHED SERVICE AWARD
This award is given by the Executive Board to those who have provided a sustained and substantial service to the North American Neuro-Ophthalmology Society. It is named after, and honors, the NANOS Founder, Thomas Carlow, who contributed an immeasurable amount of his time and energy founding and then nurturing NANOS.

2000    Susan Carlow
        Thomas J. Carlow, M.D.
        Robert B. Daroff, M.D.
        Joel S. Glaser, M.D.
        William F. Hoyt, M.D.
        David L. Knox, M.D.
        Norman J. Schatz, M.D.

2002    Ronald M. Burde, M.D.

2004    James A. Sharpe, M.D.
        H. Stanley Thompson, M.D.
        Jonathan D. Wirtschafter, M.D.

2005    Steven E. Feldon, M.D., MBA

2006    None

2007    John B. Selhorst, M.D.
        Neil R. Miller, M.D.

2008    Kathleen B. Digre, M.D.

2009    Mark J. Kupersmith, M.D.

2010    Larry Frohman, M.D.

2011    John L. Keltner, M.D.

2012    Deborah I. Friedman, M.D., M.P.H.

2013    None

WILLIAM F. HOYT LECTURE

2001    Thomas J. Carlow, M.D.
        Oculomotor Ophthalmoplegic Migrane: Is it Really Migrane?

2002    H. Stanley Thompson, M.D.
        The Vitality of the Pupil: A History of the Clinical Use of the Pupil as an Indicator of Visual Potential.

2003    Simmons Lessell, M.D.
        The Neuro-Ophthalmic Complications of Radiation

2004    Creig S. Hoyt, M.D.
        What Do We Really Know About Amblyopia?

2005    Neil R. Miller, M.D.
        Advances in the Diagnosis and Management of Optic Nerve Sheath Meningiomas

2006    None

2007    Joel S. Glaser, M.D.
        Romancing the Chiasm

2008    Peter J. Savino, M.D.
        Evaluation of the Retinal Nerve Fiber Layer: Descriptive or Predictive

2009    Norman J. Schatz, M.D.
        The Troubles I’ve Seen

2010    Jonathan Trobe, M.D.
        Papilledema: The Vexing Issues

2011    Steven A. Newman, M.D.
        Interventional Neuro-Ophthalmology, an Addition Not an Oxymoron

2012    Alfredo A. Sadun, M.D., Ph.D.
        Are We There Yet? Has Neuro-Ophthalmology Reached the Paradigm Shift?
NANOS RECOGNITION AND AWARDS
PRESENTED AT THE ANNUAL NANOS BANQUET DURING THE ANNUAL MEETING
(CONTINUED)

WILLIAM F. HOYT LECTURE (CONTINUED)
2013  Nancy J. Newman, M.D.
Neuro-Ophthalmology in Review: Around the Brain With 50 Fellows

BEST FRANK B. WALSH SESSION PAPER PRESENTATION
BY A FELLOW
2004  Margaret M. Wong, MBBS, FRCS, FRCOphth
Frozen Eyes and Muscle Cramps
2005  Kevin M. Barrett, M.D.
An Obvious Case of Giant Cell Ateritis
2006  Jennifer T. Scruggs, M.D.
A 68 Year-Old Woman with New Onset Vertical Diplopia and Pain
2007  Thomas N. Hwang, M.D., Ph.D.
A Case of Bilateral Optic Nerve Atrophy
2008  Beau Bruce, M.D.
What?!?
Thomas Hwang, M.D.
My Orbits Are Melting
2009  Sashank Prasad, M.D.
Hear No Evil, See No Evil
2010  Rebecca Stacy, M.D.
A Bitter-Sweet Diagnosis
2011  Clare Fraser, M.D.
Bad Eyes, Bad Walking and Bad Judgment
2012  Lindsey DeLott, M.D.
CSEye
2013  Chantal J. Boisvert, M.D.
OMG, I can’t C

PILOT GRANT RESEARCH AWARD
The NANOS Pilot Research Grant Program provides a one-year, non-renewable source of funding to help principal investigators generate preliminary data that will lead to additional funding from other national agencies or foundations.

2007  Deborah M. Grzybowski, M.D., Ph.D.
An in-vitro model of CSF outflow through the arachnoid membrane for IIH
2008  Kimberly Cockerham, M.D., F.A.C.S.
Thyroid Eye Disease Clinical Manifestations Measurements: Comparing Clinical Examination with Laboratory Values of Thyroid Antibodies and Magnetic Resonance Imaging
Nitza Goldenberg-Cohen, M.D.
Intraocular Injection of Growth Factors to Enhance Differentiation of Bone Marrow Derived Stem Cells Following Ischemic Injury
2009  Prem S. Subramanian, M.D., Ph.D.
Pilot Study to Measure Diplopic Fields and the Correlation of Diplopic Field Characteristics with Visual Function Quality

FIGHT FOR SIGHT/NANOS POSTDOCTORAL FELLOWSHIP AWARD
This award was established by Fight for Sight (FFS) and the North American Neuro-Ophthalmology Society (NANOS) to fund a Summer Student Fellowship for ophthalmology residents or fellows interested in pursuing neuro-ophthalmology research.

2008  Arun Sundaram, M.D.
Saccadic Roles of the Human Subthalamic Nucleus and Globus Pallidus
2009  Zoë Williams, M.D.
Diffusion tensor magnetic resonance imaging of the optic nerve in patients with congenital and acquired optic disc elevation
2010  Karen E. Schmitt, M.D.
In vitro determination of the potential of a novel nanosponge to penetrate optic nerve dura and arachnoid mater for delivery of a fluorescent marker, a surrogate for various neuroprotective drugs
2011  None
2012  None
2013  Linus Da-Shih Sun, M.D., Ph.D.
Quantitative Eye Movements to Evaluate Corollary Discharge

DANIEL M. JACOBSON LECTURE
2008  James J. Corbett, M.D.
Familial Idiopathic Intracranial Hypertension
2009  Robert B. Daroff, M.D.
Reflections and Advice from an Aging Academic
2010  Deborah I. Friedman, M.D., M.P.H.
IIH with Dan, and Beyond
2011  Kathleen B. Digre, M.D.
Neuro-ophthalmologic Disorders in Pregnancy
2012  Jonathan Trobe, M.D.
The Lasting Scientific Contributions of Dr. Daniel Jacobson
2013  H. Stanley Thompson, M.D.
Neuro-Ophthalmology at Iowa
ARTICLES OF INCORPORATION NORTH AMERICAN NEURO-OPTHALMOLOGY SOCIETY
(A Non-Profit Corporation)

BYLAWS

ARTICLE I - OBJECTIVES
The North American Neuro-Ophthalmology Society (NANOS), also called the Society, exists for and is dedicated to the following purposes:

1) Support for those principles, policies and practices that seek the attainment of the best in neuro-ophthalmologic patient care.

2) The pursuit of excellence in medical education, especially as it concerns the neuro-ophthalmologic sciences.

3) The pursuit of scientific and clinical knowledge in fields related to neuro-ophthalmology.

4) The communication of scientific and scholarly information through scientific meetings and publications.

5) Provision for communication with other groups and their representation for neuro-ophthalmologic opinion to best achieve and preserve the purposes of the Society.

6) The advancement of clinical neuro-ophthalmology.

ARTICLE II - MEMBERSHIP

Section 1 - Classes of Membership
Membership in NANOS shall consist of ten classes: Fellow, International Fellow, Active Member, International Active Member, Candidate, International Candidate, Associate Member, Honorary Member, Senior Fellow Member and Senior Member. There shall be no restriction regarding the number of members in any given category. All candidates for membership and all members shall be in compliance with the NANOS ethics statement. Violation of the NANOS ethics statement will render an applicant ineligible for membership.

Section 2 - Fellows may be elected only from among physicians nominated by the Membership Committee:

1) who have been certified in Neurology by the American Board of Psychiatry and Neurology, or in Neurosurgery by the American Board of Neurosurgery, or in Ophthalmology by the American Board of Ophthalmology, or in Neurology by the American Osteopathic Board of Neurology and Psychiatry, or in Ophthalmology by the American Osteopathic Colleges of Ophthalmology and Otolaryngology, Head and Neck Surgery, or in Neurology, Neurosurgery or Ophthalmology by the Royal College of Physicians and Surgeons of Canada; and

2) whose chief interest is directed toward practice, teaching or research in Neuro-Ophthalmology; and

3) who have been Active Members of NANOS for no less than three years; and

4) who have attended no less than five annual NANOS or Frank Walsh meetings in five separate calendar years; and

5) who have demonstrated special achievement in clinical Neuro-Ophthalmology; and

6) who have completed a year of Neuro-Ophthalmology Fellowship or have practiced clinical Neuro-Ophthalmology or have performed research in Neuro-Ophthalmology for three years. An exception may be the election of certain other members of unusual accomplishment, at the discretion of the Executive Board of NANOS upon recommendation by the Membership Committee.

Section 3 - International Fellows may be elected only from among physicians outside the United States and Canada upon nomination by the Membership Committee:

1) whose chief interest is directed toward practice, teaching or research in Neuro-Ophthalmology; and

2) who have been International Active Members of NANOS for no less than three years; and

3) who have attended no less than five annual NANOS or Frank Walsh meetings in five separate calendar years; and

4) who have demonstrated special achievement in clinical Neuro-Ophthalmology; and

5) who have completed a year of Neuro-Ophthalmology Fellowship or have practiced clinical Neuro-Ophthalmology or have performed research in Neuro-Ophthalmology for three years. An exception may be made for the election of certain other members of unusual accomplishment, at the discretion of the Executive Board of NANOS upon recommendation by the Membership Committee.

Section 4 - Active Members may be elected from among physicians nominated by the Membership Committee who have been certified in Neurology by the American Board of Psychiatry and Neurology, or in Neurosurgery by the American Board of Neurosurgery, or in Ophthalmology by the American Board of Ophthalmology, or in Neurology by the American Osteopathic Board of Neurology and Psychiatry, or in Ophthalmology by the American Osteopathic Colleges of Ophthalmology and Otolaryngology, Head and Neck Surgery, or in Neurology, Neurosurgery or Ophthalmology by the Royal College of Physicians and Surgeons of Canada.

Section 5 - International Active Members may be elected from among physicians outside the United States and Canada upon nomination by the Membership Committee:

1) who have graduated from a foreign medical school recognized by the World Health Organization (WHO) and who show evidence of having passed the requirements for license to practice medicine in their home country or country of residence; and

2) who have completed postgraduate training in Neurology, Ophthalmology or Neurosurgery who are certified by the licensing authority in their country or by an internationally-recognized agency that grants accreditation in these specialties,
Section 6 - Candidate Members may be elected from among physicians nominated by the Membership Committee:

1) who have graduated from a recognized School or College of Medicine in the United States or Canada, or College of Osteopathic Medicine in the United States, or a foreign medical school and are in a fellowship program in neuro-ophthalmology of at least 12 months duration, or a residency in ophthalmology or neurology or a similar field in the United States or Canada, and

2) who are engaged in postgraduate studies directed toward qualification to be certified in Neurology by the American Board of Psychiatry and Neurology, or in Neurosurgery by the American Board of Neurosurgery, or in Ophthalmology by the American Board of Ophthalmology, or in Neurology by the American Osteopathic Board of Neurology and Psychiatry, or in Ophthalmology by the American Osteopathic Colleges of Ophthalmology and Otalaryngology, Head and Neck Surgery, or in Neurology, Neurosurgery or Ophthalmology by the Royal College of Physicians and Surgeons of Canada.

The duration of Candidate Membership status may not extend beyond seven (7) years from the date the Candidate Member began postgraduate training, except that a Candidate Member may, upon written request and authorization from the NANOS Board, extend his/her Candidate Membership due to active military service for a period of time, equal to the time such Candidate Member spent in active duty military service during the Candidate Membership period. In no event shall a Candidate Member be allowed to maintain Candidate Membership status for a period of more than ten (10) years.

Candidate Members shall be transferred to Active Membership upon certification in Neurology by the American Board of Psychiatry and Neurology, or in Neurosurgery by the American Board of Neurosurgery, or in Ophthalmology by the American Board of Ophthalmology, or in Neurology by the American Osteopathic Board of Neurology and Psychiatry, or in Ophthalmology by the American Osteopathic Colleges of Ophthalmology and Otalaryngology, Head and Neck Surgery, or in Neurology, Neurosurgery or Ophthalmology by the Royal College of Physicians and Surgeons of Canada. The transfer of status from Candidate Member to Active Member will automatically occur after written receipt of notification from the appropriate board or entity and subsequent independent confirmation by NANOS that the Candidate Member has satisfactorily completed the required training program. International Candidate Members shall be transferred to International Active Membership upon completion of a postgraduate training program in Neurology, Ophthalmology or Neurosurgery which is recognized by the licensing authority in their country or by an internationally recognized agency that grants accreditation in these specialties. The transfer of status from International Candidate Member to International Active Member will automatically occur after written receipt of notification from the appropriate board or entity and subsequent independent confirmation by NANOS that the International Candidate Member has satisfactorily completed the required training program. International Candidate Members who are ineligible for International Membership may apply for election to Associate Membership at the end of their period of eligibility for Candidate Membership.

Section 7 - International Candidate Members may be elected from among physicians outside the United States and Canada upon nomination by the Membership Committee:

1) who have been recognized specialists in Neuro-Ophthalmology in their country for at least five years; and

2) have achieved distinction in clinical practice, teaching or research.

The duration of International Candidate Membership status may not extend beyond seven (7) years from the date such International Candidate began postgraduate training, except that an International Candidate Member may, upon written request and authorization from the NANOS Board, extend his/her International Candidate Membership due to active military service for a period of time, equal to the time such International Candidate Member spent in active duty military service during the initial International Candidate Membership period. In no event shall an International Candidate Member be allowed to maintain International Candidate Membership status for a period of more than ten (10) years.

International Candidate Members shall be transferred to International Active Membership upon completion of a postgraduate training program in Neurology, Ophthalmology or Neurosurgery that is recognized by the licensing authority in their country or by an internationally recognized agency that grants accreditation in these specialties. The transfer of status from International Candidate Member to International Active Member will automatically occur after written receipt of notification from the appropriate board or entity and subsequent independent confirmation by NANOS that the International Candidate Member has satisfactorily completed the required training program. International Candidate Members who are ineligible for International Membership may apply for election to Associate Membership at the end of their period of eligibility for Candidate Membership.

Section 8 - Associate Members may be elected upon nomination by the Membership Committee from among the following:

1) Physicians who have graduated from any medical school recognized by the World Health Organization (WHO), who show evidence of having passed the requirements for license to practice medicine in their home country or country of residence and who are practicing in clinical specialties of Neurology, Neurosurgery or Ophthalmology.

2) Persons, including physicians or holders of an advanced degree, practicing or engaged in non-clinical fields relating to Neuro-Ophthalmology.

Section 9 - Honorary Fellows may be elected upon nomination by the Membership Committee from among distinguished persons including physicians in clinical Neuro-Ophthalmology or cognate fields and other holders of an advanced degree. Nominating for this category must bear the signature of two sponsors who must be Fellows.

Section 10 – Senior Fellow Members may be elected upon nomination by the Membership Committee from among Fellows who are the age of 65 or older, disabled, or are fully retired from the active practice of clinical Neuro-Ophthalmology or research.

Section 11 – Senior Members may be elected upon nomination by the Membership Committee from among Active or Associate Members who have been Society Members for a period of no less than five years, are the age of 65 or older, disabled, or are fully retired from the active practice of clinical Neuro-Ophthalmology or research.

Section 12 - Voting and Holding Office in NANOS

Only Members in the following classes of Membership are entitled to vote on any matter in person or by proxy during any Annual or Special Business Meeting of the Society or by electronic voting, as provided in Article III, section 6: Fellows, International Fellows, Active Members, International Active Members, Senior Fellow Members, and those Senior Members who had voting privileges in their most recent previous category of Membership. NANOS Fellows and Members who have the right to cast votes in person or by proxy or electronically will...
be designated as “eligible voters” and the group of eligible voters may be referred to as the “Voting Membership” in these Bylaws and in official Society documents. Voting privileges may be suspended at the discretion of the Executive Board if an eligible voter is found to be in violation of the NANOS ethics statement.

The only classes of Members entitled to hold any elected office in NANOS shall be Fellows and Senior Fellows. Violations of the NANOS ethics statement will render Members ineligible for holding an elected NANOS office until otherwise decided by the Executive Board. Elected officers found to be in violation of the NANOS ethics statement may be removed from office at the discretion of the Executive Board.

Section 13 - Procedure for Application to Membership

Application for membership shall be made in writing on the application form provided by the Executive Office, supplying in detail all information required, and signed as the name is to appear in the membership records.

Application for Fellowship must include the written recommendation of two Fellows. Application for International Fellowship must include a written recommendation from two Fellows or International Fellows. Application for International Membership must include a written recommendation from two Fellows, International Fellows or International Members. Applications for other classes of membership must bear the signature of two sponsors who are Fellows in NANOS.

Completed applications will be forwarded to the Membership Committee for review to assure applicants meet the criteria for membership. Recommendations regarding either approval or rejection for all categories of membership must be approved by a two-third vote of the eligible voters in attendance at the annual meeting.

Section 14 - Fees, Dues and Assessments

1) The dues, assessments, and other fees for each class of membership shall be established annually by the Executive Board.

2) Annual dues shall be established on the basis of the fiscal year. The dues for a year shall be payable on the first of January for the fiscal year beginning January 1 of that year and shall be considered delinquent if not paid by March 15 of the current fiscal year. Assessments and fees shall be payable at the time or times that the Executive Board shall determine.

3) Assessments, or other fees shall be payable by Honorary Members, Senior Fellow Members, or Senior Members at the discretion of the Executive Board.

Section 15 - Termination of Membership

Policies regarding late or non-payment of dues, including penalties and suspension or termination of membership, shall be established by the Executive Board.

Section 16 - Disciplinary Action

The Executive Board shall have the duty to consider disciplinary action for any violation of the NANOS Ethics Statement or for any professional misconduct on the part of any Member of NANOS for which similar disciplinary action has been taken by a State, County, or official governmental Board of Medical Examiners, Board of Professional Medical Responsibility, or like body. Such disciplinary action may be in the form of censure, suspension or expulsion from NANOS; and if the Member be an Officer of NANOS, that Member shall be removed from office regardless of whether the Member is otherwise censured, suspended or expelled. For purposes of this section, the word “censure” means that the individual shall be advised in writing that his or her professional conduct is not consistent with the objectives of NANOS and that such conduct should be changed; the word “suspended” means that the individual shall be advised in writing that his or her privileges as a Member of NANOS have been temporarily suspended or terminated until the professional misconduct has been corrected to the satisfaction of the State Board of Medical Examiners, Provincial, or other professional bodies supervising professional conduct; “expulsion” means that the Member shall be advised that the Member’s membership in the Society is terminated. A Member suspended or terminated, as a result of disciplinary action, may apply to have Membership reinstated after a period of one year.

ARTICLE III - MEETINGS AND VOTE OF FELLOWS AND MEMBERS

Section 1 - Annual Meetings

Annual Meetings of the Society shall be held each year at the place or places and on the date or dates designated by the Executive Board. The primary purpose of the Annual Meetings shall be to provide educational courses and forums for the presentation of scientific papers. There shall be not less than one (1) business session at each annual meeting of NANOS, run according to the Order of Business as provided in Article III, Section 4.

Section 2 - Special Meetings

Special scientific and business meetings of NANOS may be called by the Executive Board for the times and places it may designate.

Section 3 - Notice

Notice of each Annual Meeting of the Society shall be given to all Society members, as provided in Article VI, Section 2, not less than 90 days prior to the date on which the meeting is to begin. Notice of special scientific and business meetings of the Society shall be given, as provided in Article VI, Section 2, at least 30 days prior to the date on which the meeting is to begin.

Section 4 - Order of Business

The order of business at the annual business meeting shall be:

1) Reading of minutes of preceding meeting
2) Reports of Officers and Executive Board
3) Reports of Committees
4) Unfinished Business
5) New Business
6) Report of Nominating Committee and Elections, if not performed by electronic vote.

Section 5 - Quorum

At any annual or special business meeting of the Society, a quorum shall consist of not less than 10% of the voting membership, except as required by further provisions in these Bylaws.

Section 6 - Vote

If a quorum is present, a majority vote of the eligible voters present shall be required to constitute an action by the eligible voters on any
matter, unless otherwise provided by applicable law, the Articles of Incorporation, or these Bylaws. A member may vote either in person or by proxy executed in writing and signed by the member. Every proxy shall be dated, but need not be sealed, witnessed or acknowledged. No proxy shall be valid after 11 months from its date, unless otherwise provided in the proxy. At all meetings of members, the proxies shall be filed with and verified by the Secretary of the Society.

The Voting Members may vote electronically on special matters as approved by the Executive Board. For purposes of electronic voting, the entire Voting Membership shall be deemed present during the voting process. Notice of special matters subject to electronic vote shall contain a detailed explanation of the matters to be voted on by the Voting Membership and shall be provided electronically to all Voting Members as provided in Article VI, Section 2. An adequate time period will be offered to submit an electronic vote, and the dates for submitting an electronic vote will be clearly stated. Appropriate security measures will be employed to ensure a fair and accurate balloting process.

Section 7 - Standing Rules

The Standing Rules of the Society are contained in the document attached to these Bylaws in effect on the effective date of the adoption of the Bylaws. The Standing Rules of NANOS may be amended or revised from time to time as provided therein, but may not be inconsistent with the Articles of Incorporation or Bylaws of NANOS.

Section 8 - Parliamentary Authority and Rules of Order

The deliberations of NANOS, its Executive Board, and all committees shall be governed by the rules contained in the then current edition of Robert’s Rules of Order Revised (Robert’s Rules) except in instances where Robert’s Rules are contrary to or otherwise inconsistent with the Articles of Incorporation, Bylaws, Standing Rules, or the customary practices and procedures of NANOS. In such event the Articles of Incorporation, Bylaws, Standing Rules, or the customary practices and procedures of NANOS shall govern.

ARTICLE IV – EXECUTIVE BOARD

Section 1 - Elected Board Members of the Society shall be:

1) Officers: President, President-Elect, Vice-President, Treasurer, and Secretary.
2) Other Members of the Board – of which there will be five (5).
3) Immediate Past President – serves on the Board for two (2) years following President term.

- Non-elected, non-voting members of the Board shall be:

1) The founder, Dr. Thomas Carlow, until such a time as he indicates he no longer wishes to serve on the Board or can no longer serve;
2) The Executive Vice President of the Society, when such a person has been appointed by the Board;

Section 2 - Election

Election of Officers shall be held by electronic vote during even-numbered years. Officers shall serve a term of two (2) years, commencing on July 1 following the Annual Meeting at which they were elected. Other Members of the Executive Board (not Officers) shall serve a term of three (3) years, or until a successor is elected, commencing on July 1 following the Annual Meeting at which they were elected. The immediate Past President shall serve a term of two (2) years immediately following the term of President.

When there is only one candidate running for office, the affirmative vote of a majority of the Eligible Voters present and voting shall be required for the election to any office. When there are two or more candidates for one office, a plurality vote of the Eligible Voters present and voting shall be sufficient for the election to that office. If a tie occurs, there shall be a runoff election between just the two tied members. If in the runoff election, the tie is not broken, then the Executive Board shall vote to break the tie. If the tie is not broken at the level of the Executive Board, then the Executive Vice President shall be asked to cast a vote as the Board re-votes.

Each member may vote for only one candidate for each office or Board seat.

With exception of the President, President-Elect, and immediate Past President, the Members of the Board may be nominated for consecutive terms in the same office. The terms of Board Members and Officers shall be staggered so that the term of half of the Board Members and Officers will expire during any single election year.

One Fellow will be designated Parliamentarian by the Chair of the Executive Board. The Parliamentarian shall be responsible for ensuring adherence to the stated Parliamentary Authority and Rules of Order during all Executive Board and Annual Business Meetings.

Section 3 - Nominations

Prior to each electronic vote or Annual Meeting at which elections are to be held, the Executive Board, acting on the recommendation of the Nominating Committee, shall nominate Fellows of NANOS for each vacancy that occurs on the Executive Board. NANOS Members shall be notified of the names of all nominees at least thirty (30) days prior to the electronic vote or Annual Meeting. In the event of death or withdrawal from candidacy of any of these nominees, the Executive Board shall designate a substitute nominee at any time before the election and shall announce that designation before the election. In addition, nominations for positions on the Executive Board may be made from the Voting Membership, provided that at least thirty (30) days before the date of the election, a written petition, signed by twenty (20) or more eligible voters, has been filed with the Chair of the Executive Board together with a signed statement by the nominee setting forth willingness to serve if elected.

Section 4 - President

The President shall preside at all business sessions of the membership of NANOS; shall act as chief spokesman of NANOS to the public, the press, legislative bodies, the medical community at large and federal, state, and local governmental and private agencies and organizations; shall work with the Chair of the Executive Board to ensure that basic NANOS policies and programs are formulated and executed; shall not serve consecutive terms as president; is responsible for making appointments to replace members rotating off standing committees; and may create ad hoc committees and appoint NANOS representatives to civic, professional, and governmental organizations as may be required to execute the business and affairs of NANOS.

Section 5 - President-Elect

The President-Elect shall automatically become the President of NANOS upon expiration of the President’s term; shall, in the absence or disability of the President, have and perform the duties and responsibilities of the President; shall in the event of a vacancy in the office of President,
however occurring, fill the vacancy in the office of President for the unexpired portion of the President’s term and also serve a full term as President; shall assist the President in the performance of his or her duties whenever requested to do so; and shall have all other duties and responsibilities that the President or the Executive Board may determine.

Section 6 - Vice President

The Vice President shall, in the event of a vacancy in the office of both the President and the President-Elect, however occurring, have and perform the duties of the President; shall have all other duties and responsibilities that the President or Executive Board may determine.

Section 7 - Treasurer

The Treasurer shall serve as Chair of the Finance Committee; ensure that NANOS maintains accurate financial records; review NANOS expenditures and financial status on a regular basis to ensure overall financial integrity; submit the financial accounts of NANOS to an annual independent audit; submit annual state and federal tax returns to the Internal Revenue Service; develop and present financial recommendations to the Executive Board; and perform other duties assigned by the President or Executive Board.

Section 8 - Secretary

The Secretary shall ascertain that records are maintained for all business meetings and Executive Board meetings of NANOS; ensure that copies of the minutes of each meeting are provided to the President and other Officers and Directors as appropriate; maintain current copies of the Association Rules and Bylaws for use by the President and the Executive Board; perform other duties assigned by President or Executive Board.

Section 9 - Members of the Executive Board (other than Officers)

Members of the Board shall have all duties and responsibilities that the President or the Executive Board may determine.

Section 10 - Immediate Past President

The Immediate Past President shall be a member of the Executive Board and shall have all duties and responsibilities that the President or the Executive Board may determine.

Section 11 - Vacancies

In the event of incapacitation, withdrawal, demise, resignation or removal of any Officer or Member of the Executive Board, except the President-Elect, the President, with a majority approval of the Executive Board, shall appoint a successor who will hold the appointed office until a successor has been elected.

In the event of incapacitation, withdrawal, demise, resignation or removal of the President-Elect, the Nominating Committee shall be reconvened to name a nominee for that position to present for election by the voting membership of NANOS at the next annual business meeting.

Section 12 - Removal from Office

Any Member of NANOS elected by the Voting Membership may be removed from office by the affirmative written ballot of two-thirds of the Board Members whenever, in their judgment, the removal will serve the best interests of NANOS. Ratification of removal from office of such Member must be approved by a majority vote of eligible voters in attendance at the next Annual Meeting.

ARTICLE V - EXECUTIVE BOARD

Section 1 - Authority

The Executive Board shall manage all the business and affairs of NANOS. The Chair of the Executive Board will be a current member of the Executive Board and will be elected every two (2) years by a majority vote of the Members of the Board. The Executive Board shall have all powers and responsibilities conferred upon the Board of Directors of a nonprofit corporation by the State of New Mexico, as now or hereafter amended, except as those powers or responsibilities may be limited by the Articles of Incorporation or these Bylaws. The Executive Board shall have the final responsibility and authority for all actions and policies that are recommended or adopted by any and all standing and ad hoc committees, sections, representatives to professional and governmental organizations, agents, and employees; and no action or policy shall be the action or policy of NANOS unless and until it is adopted, ratified, or approved by the Executive Board.

The Executive Board shall appoint, when in its opinion the affairs of NANOS justify such action, an Executive Vice-President, who shall function in the usual capacity of such office when those functions are not contrary to the Articles of Incorporation and Bylaws of the Society. The Executive Board shall determine the duties and salary, if provided, of such an Executive Vice-President and policies pertaining to that office. The Executive Vice-President is a non-voting member of all NANOS Committees and may be appointed as a voting member of Committees at the discretion of the President.

Section 2 - Members of the Executive Board

The members of the Executive Board shall number not more than eleven (11) elected members and shall consist of all the Officers and other Members of the Board elected by the voting membership. The Executive Vice-President and the Editor of the Journal of Neuro-Ophthalmology shall be non-voting “ex officio” members of the Executive Board. The founder of the Society, Dr. Thomas J. Carlow, shall sit as a non-voting ex-officio member of the Executive Board, until he notifies the Executive Board in writing of his resignation.

Section 3 - Meetings

The Executive Board shall meet during the Annual Meeting. Special Meetings of the Executive Board may be called by the President or at the written request of four (4) Members of the Board addressed to the Secretary at no less than twenty (20) calendar days’ notice in advance of the proposed special meeting.

Section 4 - Notice

Notice of each Meeting of the Executive Board shall be given, as provided in Article VI, Section 2, by the Executive Vice-President, or, if such position is vacant, by a designee of the Executive Board, not less than fifteen (15) calendar days prior to the date on which the meeting is scheduled to be held. The matters to be discussed and voted upon at any duly called meeting of the Executive Board shall not be limited to those set forth in the Notice of the Meeting.

In the event that an electronic vote shall be held for the Election of Executive Board members, the Voting Membership shall be notified of the names of all nominees at least thirty (30) days prior to the date on which the vote is to be held, as provided in Article IV, Section 3.

Section 5 - Quorum

Five (5) Voting Members of the Executive Board shall constitute a quorum for the purposes of transacting Executive Board business and affairs on behalf of NANOS.
Section 6 - Manner of Acting

A majority vote of the Executive Board Members present and voting at a meeting at which a quorum is present shall be the act of the Executive Board, unless the vote of a larger number is required by applicable law, the Articles of Incorporation, or these Bylaws.

Section 7 - Written Action

Any action that the Executive Board could take at a duly called meeting of the Board may be taken by a written action signed by two-thirds of the Board Members. The same written action need not be signed by all Board Members, and each may sign a separate counterpart of the written action, but all Board Members shall be notified in writing at least twenty (20) calendar days in advance of the matter to be voted on.

Section 8 - Telephone Conference

Any action that the Executive Board could take at a duly called meeting of the Board may be taken during a telephone conference of the Board Members. A quorum must participate in the telephone conference in order to transact business. A notice of two (2) business days is required to all Executive Board members in order to schedule a telephone conference of the Board for the purpose of transacting NANOS business.

ARTICLE VI - MISCELLANEOUS

Section 1 - Fiscal Year

The fiscal year of NANOS shall be from January 1 to December 31.

Section 2 - Notice and Waiver of Notice

Notice is deemed given by a Fellow or member of NANOS to NANOS or to an Officer of NANOS when it is in writing and mailed or delivered to NANOS or to the Officer at the principal executive office of NANOS. In all other cases, notice is deemed given to a Fellow or Member of NANOS when it is communicated to the Fellow or Member orally, in person or by telephone, or in writing by mail, fax, email, telegram or otherwise delivered to the person at the person’s last known address. Notice by mail is deemed to be given when it is deposited with the official government postal authority with sufficient postage affixed. Whenever any notice is required to be given by law, the Articles of Incorporation, or these Bylaws, a waiver of the notice may be executed, whether before, during, or after the time stated therein, and the waiver shall constitute the equivalent of receiving the notice.

Section 3 - Indemnification

To the full extent permitted by any applicable law, any person who is or was a director, officer, employee or agent of NANOS shall be indemnified by NANOS against any and all liability and reasonable expense incurred by reason of the person being or having been a director, officer, employee or agent of NANOS, or by reason of any action taken or not taken in the course and scope of the person’s service as such director, officer, employee or agent of NANOS, in the event that such person was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, wherever brought, whether civil, criminal, administrative or investigative, other than an action by or in the right of the corporation. Such person shall be entitled to reimbursement by the Society of reasonable expense in advance of the final disposition of a proceeding in accordance with, and to the full extent permitted by, any applicable law.

The rights of indemnification provided in this section shall not limit, but shall be in addition to, any other right to which such director, officer, employee or agent may otherwise be entitled by contract, law or statute, or otherwise; and in the event of such person’s death, such rights shall extend to such person’s heirs, legal representatives, or successors. The foregoing rights shall be available whether or not the claim asserted against such person is based upon matters which antedate the adoption of this section.

NANOS, its Directors and Officers, shall be fully protected in making any determination under this section, or in making, or refusing to make any payment under this section, in reliance upon the advice of counsel.

NANOS may, to the full extent permitted by applicable law, purchase and maintain insurance on behalf of any person who is or was a Member of the Executive Board, an officer or employee of this corporation or a Member of a Committee of this corporation against any liability asserted against such person in such capacity.

If any provision of this section shall for any reason be determined to be invalid, the remaining provisions hereof shall not be affected thereby but shall remain in full force and effect.

ARTICLE VII - AMENDMENTS

These Bylaws may be amended, altered or repealed by the vote of at least two-thirds of the eligible voters, either by physical presence at a meeting or by electronic ballot of all of the eligible voters, provided that any proposed amendment 1) has been submitted in writing to the Executive Board and 2) notice thereof has been provided to each Fellow and other Voting Member at least one month prior to the date on which it will be voted upon. Bylaw amendments may be proposed only by Members of NANOS who are eligible voters as defined by these Bylaws. These Bylaws shall be subject to a complete review every ten years.

ARTICLE VIII - PUBLICATIONS

Section 1 - Publications Committee

The Publications Committee shall maintain liaison between the Executive Board of NANOS, and the Publisher and Editor of the Journal of Neuro-Ophthalmology. Members of the Publications Committee shall be appointed by the President each cycle to serve a two-year term, and may be reappointed for two additional terms to serve a maximum of six years. At least one (1) member of the Publications Committee shall be a Member of the Executive Board of NANOS.

Section 2 - Journal of Neuro-Ophthalmology

1) The governance of affairs of the Journal of Neuro-Ophthalmology is the responsibility of the Executive Board of NANOS. The Executive Board of NANOS shall report on the affairs of the Journal of Neuro-Ophthalmology to the membership each year at the time of the annual meeting. This report may be either by a member of the Executive Committee or by the Editor, or by the Chair of the Publications Committee, whichever is deemed appropriate to the Executive Board.

2) The Editor shall be appointed by the President upon recommendation of the Publications Committee for a term of four (4) years, renewable once. The Executive Board shall have the option, at its discretion, of extending the Editor’s term for one additional one (1) year term to allow the Board time to locate and obtain a new Editor. An individual nominated for editorship of the Journal of Neuro-Ophthalmology must be a Member of the Society at the time he/she assumes the editorship.
The Editor shall serve at the pleasure of the Executive Board, and will be a non-voting, “ex officio” member of the Board. The Editor may be asked to step aside by the Executive Board with two (2) months notice. This period may be lengthened or shortened by mutual assent of the Executive Board and Editor.

The Editor is accountable directly to the Executive Board. The Editor will prepare an annual report to the Executive Board. The Editor will report annually to the Executive Board through the Publications Committee, or as frequently as events may dictate. There shall be a broad range of editorial autonomy; however, it should be understood that the Editor will share major business and financial decisions with the Executive Board. Major business and financial decisions include but are not limited to such matters as the choice of a publisher, the frequency of the publication, and similar business and financial matters. The Editor, with the advice of the Editorial Board, shall have complete and final authority over all editorial content, selection, modification, and quality matters. Working relationships with the publisher shall be completely within the authority of the Editor. Editorial operations shall not be subject to direct review by the Executive Board or by the membership of NANOS.

3) Members of the Editorial Board shall be approved by the Executive Board of NANOS upon recommendation of the Editor. The terms of Members of the Editorial Board will be determined by the Editor and shall not exceed five (5) years. The Editor shall have authority to recommend the appointment of Associate Editors and Editors for specific topics whose terms on the Editorial Board will be determined by the Editor, but shall automatically expire when the Editor vacates his position. When appropriate, the Editor will recommend Corresponding Editors from other countries who will be regular members of the Editorial Board and have similar responsibilities.

4) The Publications Committee will meet annually with the Editor, and the publisher, examine the product in order to review editorial and publishing practices and prepare an advisory report to the Executive Board of NANOS. The Executive Board of NANOS shall in turn advise the Editor of the findings. A function of the Publications Committee will be to provide constructive criticism.

The Publications Committee shall also be responsible for advising the Executive Board of NANOS in regard to the selection of the Editor. In relation to this duty, the Publications Committee shall poll the entire membership of NANOS to solicit nominations for the position of Editor.

5) Relationship to NANOS: The Journal of Neuro-Ophthalmology will serve as the official journal of NANOS.

6) Budgetary commitments between the publisher and NANOS are the responsibility of the Executive Board of NANOS. Contractual relations with the publishers shall be made by the President as recommended by the Chair of the Publications Committee with the approval of the Executive Board. Financial considerations of the Journal of Neuro-Ophthalmology shall be part of the regular reporting function to the Executive Board of NANOS by the Chair of the Publications Committee. The Editor shall be reimbursed by NANOS and the publisher for all secretarial and clerical expenses of maintaining the Editor’s office. In addition, the Editor shall be provided with an honorarium, to be determined by the Publications Committee and approved by the Executive Board of NANOS. The Executive Board of NANOS will be responsible for negotiating these fiscal matters with the publisher and the Editor.

7) Subscriptions to the Journal of Neuro-Ophthalmology will be provided to all dues-paying Members of NANOS.

ARTICLE IX - USE OF THE SOCIETY NAME, INITIALS AND LOGO

Regulation of the use of the Name of the Society (North-American Neuro-Ophthalmology Society), its initials (NANOS) and its Logo shall be determined by the Executive Board. Use of these without written consent of the Board is strictly prohibited. Penalties for unapproved use of the Society name, initials and logo shall be determined by the Executive Board.

STANDING RULES OF THE NORTH AMERICAN NEURO-OPTHALMOLOGY SOCIETY

I. CREATION OF STANDING COMMITTEES OF NANOS

Standing Committees of NANOS may be created by a majority vote of the Executive Board. These Standing Committees shall provide the ongoing functions vital to the Society on a long term basis. The scope of responsibility of each Standing Committee shall be established by the President on the advice of the Executive Board.

II. EXISTING STANDING COMMITTEES OF NANOS

The Chair of a Standing Committee shall be appointed by each new President when taking office. Chairpersons of all Standing Committees, except for the Nominating Committee whose Chair shall be the Board Chair, shall be appointed by the President to serve a two-year term, and may be re-appointed for two additional terms to serve a maximum of six years. An incoming President, at his/her sole discretion, may elect to extend the maximum term of an outgoing Committee Chair to allow such outgoing Committee Chair to serve in the capacity of a member of such committee for one additional two-year term.

Members of the Nominating Committee shall include one Past President of NANOS, two Chairpersons of Standing Committees, three Executive Board Members, and three additional Members who will be Fellows of NANOS, but not members of the Executive Board. The Executive Vice-President, when such a person has been appointed by the Board, is a non-voting member of the Nominating Committee unless appointed as a voting member by the Board Chair. The Committee is selected by the Board Chair and the Committee Members are vetted by the Executive Board.

With exception of the Nominating Committee, whose Members are selected by the Board Chair, Members of Standing Committees shall be subject to re-approval as each new President takes office. Members of Standing Committees shall serve for a maximum of six years, or three two-year terms, and terms of membership shall be staggered so that no more than one-third of the Committee Members have terms ending in the same year. As provided by Article IV, Section 4, the President is responsible for making appointments to replace Members rotating off Standing Committees.

III. STANDING COMMITTEES OF NANOS

Archives - Compiles, researches and maintains the written archives of NANOS.

Audit – Reviews annual independent audit and presents recommendations to the Executive Board.

Bylaws - Develops and recommends changes in the NANOS bylaws to the Executive Board.

Continuing Medical Education - Develops and maintains a continuing medical education program for all NANOS meetings; develops recommendations and monitors all activities related to NANOS continuing medical education activities.
Education - Develops and maintains an effective educational program for the NANOS Annual Meeting; develops recommendations and monitors activities related to other educational issues of importance to NANOS.

Ethics – Serves to facilitate awareness and discussion of ethical issues that may arise in the practice of Neuro-ophthalmology and to educate, consult, and advise on ethical issues.

Executive – Serves to advise the Executive Board in the management of all the business and affairs of NANOS. Consists of 3-7 members, including the President, Past President, President-elect, Treasurer, Executive Vice President, when such a person has been appointed by the Board, and up to three (3) additional Board members.

Finance - Prepares yearly budget for review and approval of Executive Board; supervises investments and accounts; reviews existing fiscal policies and develops recommendations for improving the financial status of NANOS.

International Relations - Develops and recommends policies and procedures for fostering cooperative relationships between NANOS and physicians and organizations outside the United States and Canada.

Membership - Assures that proper membership status is provided for all present and potential NANOS members; recommends methods for strengthening membership activities within NANOS.

Nominating - Nominates a slate of Executive Board members consistent with NANOS Bylaws for election as allowed by the voting membership of NANOS.

Professional Standards – Addresses issues concerning professional standards for neuro-ophthalmology, especially the training requisite to be recognized by NANOS as a neuro-ophthalmologist and advises the Board and membership on matters pertaining to these issues. The Chair of this Committee represents NANOS on these issues to relevant external agencies, specialty boards and associations.

Publications - Advises the Board on the selection of an Editor of the Journal of Neuro-Ophthalmology, meets annually with the Editor and the publisher, and prepares an advisory report to the Executive Board; roles of the Publications Committee are described in Article VIII.

Research - Promotes and facilitates research endeavors in neuro-ophthalmology, and advises the Board in the selection of recipients of specific NANOS research awards.

Walsh - Develops and recommends policies for structure, format and operation of the Frank B. Walsh Session; develops and maintains an effective educational program for the Frank B. Walsh Session; coordinates planning with the NANOS staff.

IV. CREATION OF AD HOC COMMITTEES OF NANOS

Ad Hoc Committees may be appointed as the need arises by the President to carry out a specific task that is not the assigned function of an existing Standing Committee of NANOS. The Ad Hoc Committee's charge and date of expected report should be specified by the President, The Ad Hoc Committee and Members of all Ad Hoc Committees shall be appointed at the discretion of the President.

Ad Hoc Committees shall submit to the President reports as deemed appropriate by the President. The Chair of each Ad Hoc Committee shall be responsible for all reports.

V. COMMITTEE LONGEVITY

Standing Committees will continue to exist indefinitely at the discretion of the Executive Board. When, in the judgment of the Executive Board, a Standing Committee is no longer necessary, it may discharge the Standing Committee by majority vote of all Executive Board Members.

Ad Hoc Committees are discharged automatically 1) upon the acceptance of their final report by the Executive Board or 2) upon completion of the current President's term of office. Ad hoc committees may be discharged at any time by the President.

VI. REPRESENTATIVES TO CIVIC, PROFESSIONAL, AND GOVERNMENTAL ORGANIZATIONS FROM NANOS

Representatives shall be appointed by the President to the following organizations and to all others as deemed necessary:

American Academy of Neurology
American Society of Neuroimaging
American Academy of Ophthalmology
Canadian Neurological Society
Canadian Ophthalmological Society
International Neuro-Ophthalmological Society
International Perimetry Society
World Federation of Neurology

A position taken or expressed by a representative shall not be deemed the position of NANOS unless and until it is adopted, ratified, or approved by the Executive Board.

Representatives shall submit to the Executive Board an annual report and special reports as deemed appropriate by the representatives or as requested by the President.

VII. ELIGIBILITY REQUIREMENTS FOR COMMITTEE MEMBERS AND REPRESENTATIVES

All Members of NANOS Committees and NANOS representatives to organizations shall be NANOS Fellows, Senior Fellows, or Active Members. Exceptions to this include the International Relations Committee, Membership Committee, and Patient Education Subcommittee, on which International Members may serve.

Other classes of NANOS Membership may, upon receipt of approval from the NANOS Board, be appointed by the President to serve on NANOS Standing Committees and NANOS Ad Hoc Committees and NANOS representatives to organizations.

Nonmembers of NANOS may, with the specific approval of the President, serve as consultants on committees; however, they shall not vote on matters of administration or policy affecting NANOS.

VIII. ANNUAL AND SPECIAL REPORTS OF STANDING COMMITTEES, SPECIAL COMMITTEES, AND REPRESENTATIVES TO ORGANIZATIONS

Standing Committees, Ad Hoc Committees, and representative to organizations shall submit to the Executive Board an annual report and such special reports, from time to time, as deemed appropriate by the Committee, representatives or the Executive Board.

The chair of each committee and representative to each organization shall be responsible for submitting all reports. All reports shall be in writing.

IX. AMENDMENTS AND REVISIONS

These Standing Rules may be amended or revised by the Executive Board of NANOS.
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