Pearls, Pitfalls and Advances in Neuro-Ophthalmology

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Optic Neuropathy

Causes
- Inflammatory
- Vascular
- Compressive/Infiltrative
- Toxic/Nutritional
- Hereditary
- Traumatic
- Elevated intracranial pressure
- Elevated intraocular pressure

Optic Neuropathy

Anterior Ischemic Optic Neuropathy
- Ischemia to the optic nerve head
- M:F 1:1
- Age: older than 50
- Diabetes, hypertension
- Painless
- Swollen disc
- Permanent visual loss
- Associated with giant cell arteritis

AION
“Disc at Risk”

- Small cup-to-disc ratio
  - c/d:0.8
  - c/d:0.5
  - c/d:0.1
AION vs. ON

<table>
<thead>
<tr>
<th>Age</th>
<th>Older (&gt;50)</th>
<th>Younger</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M = F</td>
<td>F &gt; M</td>
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<tr>
<td>Visual loss</td>
<td>Acute</td>
<td>Rapidly progressive</td>
</tr>
<tr>
<td>Pain</td>
<td>Infrequent</td>
<td>Frequent with EOM</td>
</tr>
<tr>
<td>Color Vision</td>
<td>Normal</td>
<td>Abnormal</td>
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<tr>
<td>Visual Field</td>
<td>Altitudinal defect</td>
<td>Central defects</td>
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<td>Optic Disc</td>
<td>Acute: edema</td>
<td>Normal or edema</td>
</tr>
<tr>
<td>MRI</td>
<td>Small c/d</td>
<td>Temporal pallor</td>
</tr>
<tr>
<td>Visual prognosis</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>HTN, DM, r/o GCA</td>
<td>Subsequent MS</td>
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</tbody>
</table>

Prognosis for visual recovery
Recognition of giant cell arteritis
Prognosis for multiple sclerosis
Treatment of demyelination
Risk of AION increased by 3.86 when taken within the week preceding the AION vs. when taken 7 weeks prior.

Risk of 2.36 when taken the day before vs. within the 29 days before.

Intravitreal injection of QPI-1007 (small interfering ribonucleic acid that blocks Caspase 2 apoptosis)

NAION 50-80 years old

Within 14 days of visual loss

USA

India, Israel, Italy, Germany, Australia, and China.

Giant Cell Arteritis

- Rule-out giant cell arteritis (ESR, CRP, platelets) in all > 50 yo patients with ischemic optic neuropathy

- Arteritic ION:
  - AION or PION
  - Systemic symptoms of GCA absent in 25%
  - Often with transient visual loss or diplopia
  - Bilateral if no treatment
  - Steroids emergently, then temporal artery biopsy
  - Poor visual prognosis
Perioperative Visual Loss
Ischemic Optic Neuropathy

- Anterior optic nerve
  - Acute: swelling of disc
  - > 6 wks: pallor of disc

- Posterior optic nerve
  - Acute: normal fundus
  - > 6 wks: pallor of disc

- Mechanism: ischemia
**Perioperative Visual Loss**

ASA Registry – Spine (n=93)

- **Unspecified ION**
- **CRAO**
- **AION**
- **PION**

- **60%** PION
- **11%** CRAO
- **9%** AION
- **20%** Unspecified ION

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**Risk Factors Associated with Ischemic Optic Neuropathy after Spinal Fusion Surgery**

**ABSTRACT**

- **Background:** Perioperative visual loss, a rare but dreaded complication of spinal surgery, is most commonly caused by ischemic optic neuropathy (ION). The authors sought to determine risk factors for ION in this setting.

- **Methods:** Using a multicenter case-control design, the authors compared 85 adult patients with ION from the American Society of Anesthesiologists Postoperative Visual Loss Registry with 315 adult control subjects without ION after spinal fusion surgery, randomly selected from 17 institutions, and matched by year of surgery. Preoperative medical conditions and perioperative factors were compared between groups.

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**Toxic Optic Neuropathies**

- **Ethambutol**
  - Dose-related
  - Early dyschromatopsia
- **Linezolid**
  - Dose-related
  - Mild disc edema
  - Peripheral neuropathy
- **Amiodarone**
  - Disc edema (mimics AION)
- **Cobalt-chromium metallosis**
  - Hip implants
- **Methanol and ethylene glycol**
Amiodarone-Associated Optic Neuropathy
A Nationwide Study

Hsi-Chen Cheng, MD,1,2 Huanyue Ye, MD,2,3 Ningle Huang, PhD,7 Ying-Jen Chao, MD, PhD,7
May-Yung Yen, MD,2,7 An-Chyung Wang, MD, PhD

Purpose: To investigate whether amiodarone use is associated with an increased risk of optic neuropathy.

Design: Retrospective population-based cohort study.

Participants: Patients newly treated with amiodarone between 2006 and 2008 were identified from the
Taiwan National Health Insurance Research Database. For each case patient, the study also included 4 age- and
gender-matched control subjects who did not receive amiodarone treatment.

Methods: Cox multivariate regression analysis was used to assess the association between amiodarone and
the occurrence of optic neuropathy.

Main Outcome Measures: Hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: The analysis included 6,718 amiodarone-treated patients and 24,700 controls. The mean age was
66.7 years and 65.4% of subjects were male. The mean follow-up was 668 days. During the observation period,
optic neuropathy developed in 17 amiodarone-treated patients (0.3%) and 30 control patients (0.1%; P = 0.006).

Multivariate Cox regression analysis showed that amiodarone-treated patients had a 2.06-fold increased risk of optic
neuropathy (HR, 2.06; 95% CI, 1.15–3.60; P = 0.02). After stratification by gender, amiodarone use remained a
significant factor for optic neuropathy development among male subjects (HR, 3.20; 95% CI, 1.44–6.90;
P = 0.01), but not among female subjects (HR, 1.24; 95% CI, 0.38–4.37; P = 0.81). Among amiodarone-treated
patients, male gender was associated with a nearly 3-fold increased risk of optic neuropathy development,
compared with female gender (HR, 2.91; 95% CI, 0.84–9.01; P = 0.08). We also detected a trend of increased
cumulative incidence of optic neuropathy with longer treatment duration (>41 vs. ≤41 days; HR, 3.46; 95% CI,
0.99–12.07; P = 0.05). However, higher daily dose did not increase the risk of optic neuropathy (HR, 0.96; 95% CI,
0.81–1.00; P = 0.67).

Conclusions: These results demonstrated a higher risk of optic neuropathy in patients treated with amiodarone,
especially in males and possibly in patients with longer duration of treatment. Ophthalmology 2010;122:2503–
2509 © 2010 by the American Academy of Ophthalmology.

Optic Neuropathy
Causes

- Inflammatory
- Vascular
- Compressive
- Toxic/Nutritional
- **Hereditary**
- Traumatic
- Elevated intracranial pressure
- Elevated intraocular pressure

Optic Neuropathy
Hereditary

- Maternal/Mitochondrial (Leber’s)
- Autosomal dominant (Kjer’s)

Optic Neuropathy
Hereditary

Visual system involvement in patients with
Friedreich’s ataxia

Axonal Neuropathy with Optic Atrophy Is
Caused by Mutations in Mitofusin 2
Ann Neurol 2005;57;2–21
Hereditary Optic Neuropathies

Treatment

• Genetic counseling
• Symptomatic
• Disease-modifying
  • Mitochondrial diseases
• Hereditary optic neuropathies
• Idebenone (900mg/d)
• Gene therapy (ongoing clinical trials)

Leber Hereditary Optic Neuropathy

Treatment – Idebenone?


Leber Hereditary Optic Neuropathy

Gene delivery to mitochondria by targeting modified adenovassociated virus suppresses Leber’s hereditary optic neuropathy in a mouse model


Optimized Allotopic Expression of the Human Mitochondrial ND4 Prevenst Blindness in a Rat Model of Mitochondrial Dysfunction


Safety and Tolerability Study

• Intravitreal injection of rAAV2/2-ND4 in one eye of 9 patients (3 groups escalating doses) with LHON (11778) and chronic visual loss

• Excellent systemic safety and tolerance
  • No vector shedding
• Good local tolerance with mild AE’s
• Mild ↑IOP (23-34) and ocular inflammation:
  • Treatment responsive and reversible
• No unexpected adverse events
Rescue & Reverse Studies

• Two, simultaneous, parallel Phase III clinical trials of intravitreal gene therapy for the treatment of LHON, occurring at 7 study sites worldwide (Atlanta, Los Angeles, Philadelphia, Paris, London, Munich, Bologna)

• Goal is to randomize 36 patients for each study over 1 year with 2-year followup

From a Patient’s Perspective

• Social media growth makes it easier for LHON patients and families to connect
  – Global LHON Facebook (2,500+ members)
  – Clinical database (3,400+ entries)
• Website and social media facilitate study trial recruitment with just a “click”
Probability of Improvement vs Time Since Injury

Time Since Injury (months)

0 1 2 3 4 5 6

Probability of Improvement

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7

95% CI

[Image]
Underdiagnosis of Posterior Communicating Artery Aneurysm in Noninvasive Brain Vascular Studies
 Valerie I. Elmaleh, MD, Patricia A. Hudgings, MD, Beau B. Bruce, MD, Nancy J. Newman, MD, Valerie R. Biousse, MD

Background: Despite advances in modern neuroimaging techniques, such as computed tomographic angiography (CTA) or MRI, intracranial aneurysms remain an important source of morbidity and mortality. Magnetic resonance imaging (MRI) remains the diagnostic modality of choice for detecting intracranial aneurysms, but the sensitivity of MRI in detecting small aneurysms is limited. The aim of this study was to determine the prevalence of small aneurysms in patients with posterior communicating artery (PComA) aneurysms, as detected on follow-up MRI scans.

Methods: We retrospectively reviewed the records of all patients with PComA aneurysms undergoing serial MRI scans at our institution from 2001 to 2015. A total of 527 patients were included in the study.

Results: A total of 1,374 serial MRI scans were performed in these patients. A total of 527 aneurysms were identified, with a mean size of 5.6 mm and a maximum size of 20 mm. The sensitivity of MRI in detecting small aneurysms was found to be significantly lower than that of digital subtraction angiography (DSA).

Conclusions: MRI should not be relied upon as the sole diagnostic tool for detecting small aneurysms. Combined imaging with DSA should be considered to improve diagnostic accuracy.

Prognosis of Ocular Myasthenia Gravis
Retrospective Multicenter Analysis
Lina Nagi, DO, Jean Levison, MD, Khadeja Alhassani, MD, Wayne T. Combs, MD, Eric R. Egginger, DO, MSME

Original Investigation
Clinical Utility of Acetylcholine Receptor Antibody Testing in Ocular Myasthenia Gravis
JAMA Neurol 2015; 72: 1177

Cranial E. Peeler, MD, Lindsey B. DeLott, MD, Lina Nagi, DO, Jean Levison, MD, Eric R. Egginger, DO, MSME, Wayne T. Combs, MD

Results: A total of 284 patients were included in the study. The median age at onset was 56 years (range, 20-81 years). The most common presenting symptom was ptosis, followed by diplopia and ophthalmoparesis. The median duration of symptoms at presentation was 18 months (range, 1-108 months). The best visual acuity at presentation was 20/40 (range, 20/20-20/200).

Conclusions: Acetylcholine receptor antibody testing is a useful diagnostic tool in the evaluation of ocular myasthenia gravis. However, the diagnostic yield is lower in patients with mild or asymptomatic disease.

Ability of an Upright-Supine Test to Differentiate Skew Deviation From Other Vertical Strabismus Causes
Agnis M. F. Wong, MD, PhD, Francis Caiazzo, MD, John Calpas, OCIO, Manoharanandam Chandramohan, HRSc

Objective: To determine the sensitivity and specificity of a new upright-supine test to differentiate skew deviation from trochlear nerve palsy and other causes of vertical strabismus in a large number of patients.

Methods: The study consisted of 125 consecutive patients who underwent treatment from January 1, 2003, through December 31, 2010, for vertical strabismus of various causes: skew deviation (52 patients), trochlear nerve palsy (56 patients), restrictive (14 patients), and other causes (e.g., myasthenia gravis and childhood strabismus) (20 patients). Twenty healthy participants served as controls. The deviation was measured by the prism and alternate cover test using a near target at 19 in both the upright and supine positions. A vertical strabismus that was corrected by 50% or more from the upright to supine position was considered a positive test result.

Results: The upright-supine test was positive in 20 of 25 patients with skew deviation (sensitivity, 80%) but negative in all patients with trochlear nerve palsy, restrictive, or other causes (specificity, 100%).

Conclusions: The upright-supine test is highly specific for differentiating skew deviation from other causes of vertical strabismus. This test could be added as a fourth step of the 3-step test, and if the result is positive, neuroimaging should be considered.
A Simple Flashcard Test to Detect Concussions


ABSTRACT
Objective: The aim of our study was to evaluate whether wearing sunglasses the "sunglasses sign" can be used by neuro-ophthalmologists to predict organic visual loss (OVL), in their patients.

Methods: We prospectively collected information on all new patients seen by us over 2 years. The study period included 377 patients, 27.1% were patients wearing sunglasses. The probability of wearing sunglasses for OVL was 0.003 (95% CI 0.003 to 0.005). The probability that a patient walking into our office that had OVL was 0.003 (95% CI 0.003 to 0.005); increased to 0.003 (95% CI 0.003 to 0.005) in office patients with organic ophthalmologic disorders.

Results: Among the 377 consecutive new patients seen in our clinic during the study, 24 patients were sunglasses, among whom 7 (22.2%) had organic visual loss. During the study period, 37 patients were diagnosed with NOVL, among whom 27 (73.0%) were sunglasses. The sensitivity of wearing sunglasses for NOVL was 0.003 (95% CI 0.003 to 0.005). The probability that a patient walking into our office that had NOVL was 0.003 (95% CI 0.003 to 0.005); increased to 0.003 (95% CI 0.003 to 0.005) in office patients.

Conclusion: The "sunglasses sign" in a patient without an obvious ophthalmologic reason to wear sunglasses is highly suggestive of nonorganic visual loss. Neurology 2008;70:1–1.