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Neuro-Ophthalmology Around the World

Karl C. Golnik, MD, MEd

The International Council of Ophthalmology

The North American Neuro-Ophthalmology Society (NANOS) recently has become a member of the International Council of Ophthalmology (ICO). The ICO collaborates with ophthalmic societies and other organizations to enhance ophthalmic education and improve access to the highest quality eye care in order to preserve, restore, and enhance vision for the people of the world. The ICO represents and serves more than 100 national ophthalmic associations and 30 multinational ophthalmology subspecialty organizations.

The ICO is working to build a “World Alliance for Sight” by leading, stimulating, and supporting the efforts of ophthalmologic societies, eye departments, and related organizations worldwide to enhance ophthalmic education and eye care.

The ICO’s long history of providing ophthalmic education dates back to the first International Congress of Ophthalmology in 1857. Now called the World Ophthalmology Congress (WOC), the WOC is held every second year in a different region of the world. Member subspecialty societies are invited to participate in the development of the Scientific Program of the WOC.

The ICO leads and coordinates the efforts of international ophthalmology to increase support for eye care and prevention of vision loss worldwide. The ICO collaborates closely with the World Health Organization, the International Agency for the Prevention of Blindness, ophthalmologic organizations, and nongovernmental development agencies to support and implement initiatives like VISION 2020, the Global Initiative for the Elimination of Avoidable Blindness.

In an effort to internationally validate an ophthalmologist’s level of knowledge, the ICO offers examinations for ophthalmologists in training and practice. Since first established in 1995, more than 20,000 candidates have taken the examinations. In 2012, there were 3,327 ICO examinations taken in 130 test centers in 70 countries. The ICO examinations also enable teachers and trainers to evaluate their trainees’ performance by international standards.

One of the main efforts of the ICO is to improve the education of ophthalmologists. Since 2000, the ICO has awarded more than 600 fellowships, allowing promising young ophthalmologists from countries with an urgent need for modern eye care to bring acquired knowledge and skills back to their home country and take part in programs to preserve and restore vision. Working with committed partners, the ICO is improving the educational effectiveness of ophthalmology teachers by introducing them to principles of adult learning, curriculum development, teaching methods, and assessment tools. Collaborative efforts with member societies and other ophthalmologic organizations are creating beneficial educational opportunities and refining the most effective ways to teach residents, medical students, subspecialty fellows, practicing ophthalmologists, and allied eye care personnel.

In 2011, the ICO completed a revised ICO Residency Curriculum, working with more than 100 subspecialists from around the world, to offer an international consensus on what ophthalmology residents should be taught and provide a standardized content outline for ophthalmic training. Delivered online, it is intended to be translated and adapted, with the precise local detail for implementation left to each region’s educators. The Curriculum can be accessed at www.icoph.org/refocusing_education/courricula.html.
In 2012, the ICO initiated development of curricula for subspecialty fellowship training. The first 4 currently being drafted include Neuro-Ophthalmology, Cornea and External Diseases, Glaucoma, and Oculoplastic Surgery. Similar to the process for the ICO Residency Curriculum, the ICO involved the relevant member subspecialty societies in nominating a specialist to serve on these committees. To learn more about ICO programs, please visit http://icoph.org/downloads/2012Update-web.pdf.

**Regional and National Neuro-Ophthalmology Societies**

Besides NANOS, there are a number of other supranational and national neuro-ophthalmology societies, and the ICO hopes that they will follow the lead of NANOS and join the ICO to collaborate and facilitate achieving the goals listed above. The largest of the supranational societies is the Asian Society of Neuro-Ophthalmology (ASNOS) with more than 1,000 members. Established in 2002, members represent China, India, Indonesia, Japan, Malaysia, Philippines, South Korea, Taiwan, and Thailand. Scientific meetings are held every 2 years. The seventh Congress occurred in Bali Indonesia in August 2013. Notably, it had a special session called “Walsh-in-Asia”, a clinicopathologic case presentation conference in the style of the Frank B. Walsh Society Meeting. The official journal of ASNOS is Shinkei Ganka (Asian section) and the official Web site is http://www.shinkeiganka.com/asnos/index.html.

The European Society of Neuro-Ophthalmology (EUNOS) was founded in 1993 and conducts biennial clinical and scientific meetings. Beginning in 2012, shorter “update” meetings will take place in the off years. EUNOS has a membership of approximately 85 members from 28 countries. The main aims of the Society are to extend the knowledge of neuro-ophthalmology by promoting cooperation and communication among clinical neuro-ophthalmologists and vision scientists within Europe; to support the development of clinical neuro-ophthalmology in Europe by establishing training standards and syllabi and promoting the education of trainees through teaching courses; and to promote clinical research in neuro-ophthalmology and represent neuro-ophthalmologists in relevant European medical forums. Further information is available at www.eunosweb.org.

In Latin America, the Club Latinoamericano de Neuro-oftalmología (CLAN) was created in 1988. It initially was formed by a group of neurologists and ophthalmologists from Buenos Aires and Santiago. Membership now includes neuro-ophthalmologists from Argentina, Brazil, Chile, Columbia, Paraguay, Peru, Uruguay, Venezuela, and the United States. Scientific meetings have taken place once a year since 1988 to discuss trends and new developments between the members who also are active in national and international societies of neurology and ophthalmology. Members of CLAN also belong to supranational organizations, such as the ICO and the Pan American Association of Ophthalmology.

Other national neuro-ophthalmology societies including France, Israel, Australia/New Zealand, Japan, and South Korea have been described previously in this Journal (1–5).

The Neuro-Ophthalmology Society of the Philippines (NOSP) was founded in 2000 and is recognized by the Philippine Academy of Ophthalmology (PAO). The main objective of the society is to foster academic exchange and dissemination of knowledge in the realm of neuro-ophthalmology in the Philippines. This includes participation in the annual PAO Meeting by organizing instructional courses and basic course lectures being given by both invited international and local speakers and creation of a neuro-ophthalmology fellowship program. Currently, NOSP is creating a unique Philippine National Registry, ethambutol optic neuropathy. This initiative is designed to provide awareness and gather information nationwide on ethambutol toxicity and describe its clinical profile in the country. The ultimate goal is to establish official treatment guidelines on monitoring the visual parameters of patients on anti-tuberculosis medication and to help reduce the frequency of ethambutol optic neuropathy in the Philippines.

Thus, supranational and national neuro-ophthalmology societies are flourishing around the world. They serve to enhance training and provide advocacy for their members, which ultimately leads to improved patient care. Hopefully, the ICO can facilitate collaboration, communication, and provide mechanisms for these societies to realize their goals.

**REFERENCES**


**Editor’s Note:**


In his editorial, Dr. Golnik highlights the activities of neuro-ophthalmology around the world. The ICO is assuming an important role in facilitating and coordinating educational activities in ophthalmology, and an opportunity for neuro-ophthalmology to assert itself on the world stage.

In a similar fashion, the Journal of Neuro-Ophthalmology (JNO) serves as an important educational publication in neuro-ophthalmology throughout the world. Currently, 9 of our 26 editorial board members represent the international community. Sixty percent of our submissions come from outside North America. We have created a new section in the Journal
entitled “Worldwide Neuro-Ophthalmology”, which features neuro-ophthalmology activities in specific parts of the world. In addition, in “Neuro-Ophthalmology News,” we feature major meetings and other educational events taking place internationally. Probably no one more than William Hoyt, MD, recognized the importance of international education and collaboration. Many of his former fellows practice throughout the world and are training the neuro-ophthalmologists of the future. The JNO is committed to recognize and promote international neuro-ophthalmology and looks forward to expanding this role in the years to come.

Lanning B. Kline, MD
Editor-in-Chief
Baseline Retinal Nerve Fiber Layer Thickness and Macular Volume Quantified by OCT in the North American Phase 3 Fingolimod Trial for Relapsing–Remitting Multiple Sclerosis

Kimberly M. Winges, MD, John S. Werner, PhD, Danielle J. Harvey, PhD, Kimberly E. Cello, BS, Mary K. Durbin, PhD, Laura J. Balcer, MD, MSCE, Peter A. Calabresi, MD, John L. Keltner, MD

Background: Patients with multiple sclerosis (MS) demonstrate thinning of peripapillary retinal nerve fiber layer (RNFL) and decreased macular volume as measured by optical coherence tomography (OCT). To our knowledge, there are no previous reports from a large MS OCT database with strict quality control measures that quantitate RNFL and macula in patients with relapsing–remitting multiple sclerosis.

Methods: The University of California Davis OCT Reading Center gathered OCT data at baseline as part of the North American phase 3 trial of fingolimod (Gilenya). Average RNFL thickness (RNFLT) and macular volume (TMV) were measured using time domain OCT (TD-OCT). RNFL quadrants, clock hours, and macular subfields were included. With strict quality control and accounting for signal strength differences, scans were categorized as “reduced” or “not reduced” for each field, based on being less than 5th percentile for age-matched controls derived from the normative database in the scanner software. Patients were deemed “abnormal” if at least 1 eye had reduced values for a given parameter. Patients with abnormalities in corresponding RNFL and macular subfields were compared by cross-tabulation.

Results: The TD-OCT data were prospectively collected from 939 of the 1,083 trial patients, 712 of whom met all final quality and data inclusion criteria. Of the final cohort, 242 (34.0%) demonstrated reduced (less than 5th percentile) average RNFLT in at least 1 eye. One hundred seventy-eight (25.0%) patients had reduced TMV. One hundred twenty-eight (18.0%) demonstrated both reduced TMV and RNFLT in the same eye, whereas 42 (5.8%) had reduced TMV and RNFLT in both eyes. Of the 242 patients with reduced average RNFL thickness, 128 (52.9%) also had reduced TMV. Fifty patients had reduced TMV in the absence of reduced RNFLT in at least 1 eye, a cohort prevalence of 7.0%. Quadrant and subfield analysis showed a predominance of temporal and inferior RNFL thinning, with inferior macular thinning corresponding best to RNFL thinning.

Conclusion: RNFL and macular thinning/volume loss is common at baseline in relapsing–remitting multiple sclerosis, as measured by TD-OCT. When the RNFL is thin, the macular volume is reduced in more than half of the patients. There is a population of reduced TMV without any reduction in RNFLT. Documenting the prevalence and distribution of these structural abnormalities supports recent reports and suggests new retinal areas to probe for functional vision changes in MS.

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Retinal nerve fiber layer (RNFL) degeneration and the resulting optic nerve atrophy is a widely accepted measure of disease burden in patients with multiple sclerosis (MS) (1,2). It is thought that both anterograde
and retrograde transsynaptic axon degeneration may be responsible for the loss of neural tissue in the brain and the eye affecting both the white and gray matter (3). It is evident both in magnetic resonance imaging lesion burden and on pathological specimens showing gliosis and neuronal loss, in addition to retinal ganglion cell axon degeneration (4–7).

Optical coherence tomography (OCT) has gained increasing popularity in quantifying RNFL thickness (RNFLT) as a measure of axon disease in the MS population. Both time domain and spectral domain platforms are reproducible and reliable in quantifying these changes (1,8–12). Furthermore, peripapillary RNFL thinning correlates over time with clinical measures of low-contrast letter acuity and contrast sensitivity, as well as the expanded disability score and disease duration, giving clinicians an objective way to follow disease burden (9,12–15). Even patients with MS without a history of optic neuritis have shown thinner RNFL than controls (16,17), providing evidence that at baseline, patients with MS have abnormal optic nerves.

It is now recognized that macular volume is reduced in MS vs normal eyes, and some studies have shown that macular volume loss is associated with RNFL loss (18,19). Approximately 34% of the macular volume is made up of ganglion cells and their axons, so it may be expected that macular volume loss would follow RNFL loss (8). However, OCT evidence of macular thinning has recently been demonstrated even in the absence of RNFL thinning, with new evidence of inner and outer macular atrophy (20). Thus, in early MS, there are significant fundamental structural changes of the retina that can be quantified in vivo.

The purpose of our study was to use the largest known quality-controlled database of time domain OCT (TD-OCT) in a phase 3 MS trial to describe and map the baseline thickness and/or volume of the RNFL and macula in the relapsing–remitting MS population.

**METHODS**

In this retrospective observational study, OCT data were collected from all screening TD-OCT scans performed for FREEDOMS 2, the phase 3 North American trial of fingolimod (Gilenya), a sphingosine 1-phosphate receptor modulator that is the first Food and Drug Administration–approved oral treatment in the relapsing–remitting MS population (21,22). Institutional review board approval was obtained at University of California Davis for this substudy.

**Patients**

Patients were recruited for FREEDOMS 2 based on the following inclusion criteria: men or nonpregnant women, 18–55 years of age, a diagnosis of MS as defined by 2005 revised McDonald criteria, a relapsing–remitting course with at least 1 documented relapse during the previous 1 year or 2 documented relapses during the 2 years before randomization, and an expanded disability status scale score of 0–5.5 inclusive (Novartis Protocol for North American Phase 3 Fingolimod Clinical Trial NCT00355134, 2006). During randomization, those patients in whom a suspicion of macular edema by dilated ophthalmoscopy or OCT (increased central foveal thickness or cystic changes in the fovea) failed screening and were not randomized into the study.

**Optical Coherence Tomography**

OCT scans were collected at the time of randomization and in follow-up over the 2-year study, using a single alignment and capture on the time domain platform (Stratus OCT; Carl Zeiss Meditec, Inc, Dublin, CA). Fast RNFLT protocols measured A-scans in a nominal 1.73-mm radius circle of peripapillary RNFL. Data for average RNFLT, 4 quadrants, and 12 clock hours were collected. The left eye from a sample MS patient with reduced RNFLT is shown in Figure 1A. Total macular volume (TMV) and the 9 Early Treatment Diabetic Retinopathy Study (ETDRS) sectors were also collected, using fast macular thickness protocols to measure A-scans over the 1-mm central fovea, 4 quadrants of the 1- to 3-mm inner macular ring, and 4 quadrants of the 3- to 6-mm outer macular ring (23). The same MS patient as in Figure 1A is shown in Figure 1B with reduced macular thickness.

Data from both eyes of each subject were submitted to the study sponsor and to a centralized review by masked investigators at the University of California Davis OCT Reading Center. As published previously, scans were excluded from the final database if they met any of the following criteria: signal strength less than 7 (except in the case of a few clearly visible fovea or optic nerve scans with correct centration), exported data missing, extra scans, decentered scans, wrong scans or scanner used, or they required redraw by the technician due to segmentation artifact (24).

Only patients with complete data for both eyes were included in the final OCT analysis. Measurements for each eye were categorized as “reduced” (less than 5th percentile of normal limits) or “normal, not reduced” (within or above normal limits) based on the manufacturer’s normative database of age-matched controls (25). Study analysts were masked to all clinical information beyond gender, date of birth, and eye that was measured. Thus, the number of patients with a history of optic neuritis or glaucoma was unknown.

**Analysis**

Percentages of age-matched individuals who had abnormal results in a given field were graphed and summarized (See Supplemental Digital Content, Figure 1, http://links.lww.com/WNO/A81). Scans from reduced and normal eyes were also plotted according to measured field of interest (See Supplemental Digital Content, Figure 2, http://links.lww.com/WNO/A82, and Figure 3, http://links.lww.com/WNO/A83). Average OCT
thicknesses were measured in micrometers ± one standard deviation (SD; type 1 error rate set at 0.05). Based on retinal ganglion cell axon distribution in the fundus, cross-tabulations of anatomically corresponding RNFL and macula quadrants were created. McNemar test was used to compare proportions of patients who had thinning in an RNFL quadrant and the corresponding outer or inner sector of the macula. Linear repeated-measures

FIG. 1. Left eye of a patient with relapsing-remitting multiple sclerosis. A. Fast retinal nerve fiber layer thickness (RNFLT) protocol shows reduced RNFLT. B. Fast macular thickness protocol reveals reduced total macular volume and macular sector thickness. ETDRS, Early Treatment of Diabetic Retinopathy Study; OCT, optical coherence tomography; OS, left eye; TMV, total macular volume.
regression models, assuming an exchangeable correlation structure to account for the intercorrelation between eyes from the same person, were used to compare signal strength and mean thicknesses between reduced eyes and not reduced eyes (26). Models for mean thicknesses included signal strength as a covariate to ensure that differences were not due to differences in signal strength.

RESULTS

One thousand eighty-three patients were enrolled in the clinical trial. The OCT Reading Center received 18,733 scans from 939 patients at 96 sites. From this database, 2,880 high-quality representative OCT scans determined by the above strict quality control criteria (24) were selected. Only patients with complete data of each eye’s macula and RNFL were used, representing 1,434 eyes in 717 patients. Across the 1,434 eyes, the average signal strength was 8.1 ± 1.5 for RNFL and 7.7 ± 1.5 for TMV. During final analysis, total average RNFLT and TMV were missing in five patients, but all subfield measures for these patients were included.

Average RNFL Thickness vs Total Macular Volume

Table 1 summarizes results of total average RNFLT and TMV. Of 712 patients, 242 (34.0%) had reduced average RNFLT. TMV was reduced in 178 (25.0%) patients. Average RNFLT and TMV were reduced in the same eye of 128 (18.0%) patients. Of the 242 patients with reduced average RNFLT, 128 (52.9%) also demonstrated reduced TMV. Fifty (18.0%) patients. Of the 242 patients with reduced average RNFLT, 128 (52.9%) also demonstrated reduced TMV. Fifty (18.0%) patients. Of the 242 patients with reduced average RNFLT, 128 (52.9%) also demonstrated reduced TMV. Fifty (18.0%) patients.

Of the 712 patients with average RNFLT and TMV available for both eyes, 153 (21.5%) demonstrated bilaterally reduced values for one or both categories: bilateral RNFLT in 115 individuals, bilateral TMV in 80 individuals, and bilateral RNFLT and TMV in 42 patients. Twenty-one patients had bilaterally reduced TMV without RNFLT reduction in either eye.

### TABLE 1. Patients with abnormal TMV vs abnormal average RNFLT in at least one eye

<table>
<thead>
<tr>
<th>RNFLT</th>
<th>TMV</th>
<th>RNFLT</th>
<th>TMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, n (%)</td>
<td>Abnormal, n (%)</td>
<td>Normal, n (%)</td>
<td>Abnormal, n (%)</td>
</tr>
<tr>
<td>420 (59.0)</td>
<td>114 (16.0)</td>
<td>534 (75.0)</td>
<td>128 (18.0)</td>
</tr>
<tr>
<td>50 (7.0)</td>
<td>178 (25.0)</td>
<td>470 (66.0)</td>
<td>242 (34.0)</td>
</tr>
</tbody>
</table>

RNFLT, retinal nerve layer thickness; TMV, total macular volume.

**RNFL and Macular Subfield Thickness**

Figure 1A (See Supplemental Digital Content, http://links.lww.com/WNO/A81) summarizes the percent of patients with reduced RNFLT in at least one eye by quadrants and clock hours. RNFLT was most often reduced in the temporal quadrant (34.3% of the patients) and in clock hours 2 (41.7%) and 7 (52.7%). Reduced eyes had significantly lower signal strength for all RNFL measures (Table 2), but even after accounting for these differences, the average RNFL values were significantly different between normal and thin eyes (Table 3, \( P < 0.001 \) for all RNFL measures). Figure 1B (See Supplemental Digital Content, http://links.lww.com/WNO/A81) summarizes the percent of patients with reduced macular thickness in at least one eye by ETDRS subfield. TMV was 5.97 ± 0.20 mm³ for normal eyes and 6.83 ± 0.38 mm³ for reduced eyes. In general, the frequency of reduced thickness in the inner quadrants was higher than that in the outer quadrants. The highest frequency of macular thinning was found in the inner temporal (37.4%) and inner inferior (34.9%) subfields. The lowest frequency regions of thinning were the central 1-mm fovea (7.8%) and the outer nasal quadrant (2.5%). Reduced eyes had significantly lower signal strength for TMV and the outer quadrants (Table 4), but even after accounting for these differences, all macular values were significantly different between normal and thin eyes (Table 5; \( P < 0.001 \) for all macular measures).

RNFL quadrants and macular sectors that corresponded anatomically are compared in Table 6. The percentage of patients with thinning in the RNFL quadrant that were also thin in the macula quadrant is also presented. The highest frequency of concurrent thinning in RNFL and macula quadrants occurred in the superior RNFL and inner temporal macula (17.1%). Thinning of the inferior RNFL was associated with the inner temporal macula (16.9%), inner inferior macula (16.5%), and outer inferior macula (15.5%). In most cases, percentages between inner and outer macula quadrant and RNFL were significantly different (\( P < 0.001 \), McNemar test).

**DISCUSSION**

Our study demonstrated baseline thinning of the RNFL reduced macular volume in the largest quality-controlled data set of OCT from a phase 3 MS trial cohort to date. In this population, about one third of the patients had RNFL thinning at baseline and one-quarter of patients had reduced TMV. Average RNFLT and TMV were collectively reduced in 18.0%. When the RNFLT was reduced, the macular volume was reduced in over half of the patients (52.9%). In other words, individuals with RNFL reduction were much more likely to have TMV reduction.
In total, macular volume was reduced in the absence of RNFL reduction in 7.0% of the trial cohort. Additionally, many subfields of RNFL and macula were abnormal, with the inferior RNFL and inferior and temporal macula showing the most collectively reduced values. There is no doubt that a significant fraction of this cohort had objective

**TABLE 2.** Signal strength differences in reduced and not reduced eyes for retinal nerve fiber layer thickness

<table>
<thead>
<tr>
<th>RNFL Region</th>
<th>Average Signal Strength of Reduced Eyes (SD)</th>
<th>Average Signal Strength of Not Reduced Eyes (SD)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average thickness RNFL</td>
<td>7.75 (1.54)</td>
<td>8.31 (1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superior average RNFL</td>
<td>7.86 (1.52)</td>
<td>8.25 (1.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior average RNFL</td>
<td>7.71 (1.51)</td>
<td>8.29 (1.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temporal average RNFL</td>
<td>7.79 (1.56)</td>
<td>8.27 (1.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nasal average RNFL</td>
<td>7.78 (1.45)</td>
<td>8.23 (1.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clock hour 1†</td>
<td>7.79 (1.59)</td>
<td>8.27 (1.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clock hour 2</td>
<td>7.89 (1.48)</td>
<td>8.27 (1.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clock hour 3</td>
<td>7.75 (1.51)</td>
<td>8.30 (1.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clock hour 4</td>
<td>7.76 (1.62)</td>
<td>8.27 (1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clock hour 5</td>
<td>7.69 (1.56)</td>
<td>8.23 (1.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clock hour 6</td>
<td>7.76 (1.50)</td>
<td>8.24 (1.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clock hour 7</td>
<td>7.93 (1.50)</td>
<td>8.25 (1.49)</td>
<td>0.007</td>
</tr>
<tr>
<td>Clock hour 8</td>
<td>7.73 (1.58)</td>
<td>8.29 (1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clock hour 9</td>
<td>7.75 (1.57)</td>
<td>8.26 (1.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clock hour 10</td>
<td>7.78 (1.57)</td>
<td>8.25 (1.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clock hour 11</td>
<td>7.70 (1.57)</td>
<td>8.30 (1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clock hour 12</td>
<td>7.89 (1.54)</td>
<td>8.20 (1.47)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*Includes all normal eyes of individuals with both eyes not reduced.
†Clock hours are standardized such that left eyes have been flipped to correspond with right eye orientation, that is, 9-o’clock position corresponds to the temporal quadrant and 3-o’clock position corresponds to the nasal quadrant.

(128 of 242 patients, 52.9%) than individuals without RNFL reduction (50 of 470 patients, 10.6%). In total, macular volume was reduced in the absence of RNFL reduction in 7.0% of the trial cohort. Additionally, many subfields of RNFL and macula were abnormal, with the inferior RNFL and inferior and temporal macula showing the most collectively reduced values. There is no doubt that a significant fraction of this cohort had objective

**TABLE 3.** Distribution of RNFL thinning by quadrant and clock hour in relapsing–remitting multiple sclerosis patients with at least one eye affected

<table>
<thead>
<tr>
<th>RNFL Region</th>
<th>Percent of Patients With at Least One Eye &lt;5% Normal Thickness, %</th>
<th>Average Value of Reduced Eyes, μm (SD)</th>
<th>Average Value of Not Reduced Eyes, μm (SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average thickness RNFL</td>
<td>34.0†</td>
<td>73.3 (8.2)</td>
<td>100.1 (9.9)</td>
</tr>
<tr>
<td>Superior average RNFL</td>
<td>28.3</td>
<td>86.2 (11.1)</td>
<td>123.9 (15.2)</td>
</tr>
<tr>
<td>Inferior average RNFL</td>
<td>26.6</td>
<td>85.4 (10.9)</td>
<td>126.2 (16.6)</td>
</tr>
<tr>
<td>Temporal average RNFL</td>
<td>34.3</td>
<td>41.1 (6.1)</td>
<td>68.4 (11.8)</td>
</tr>
<tr>
<td>Nasal average RNFL</td>
<td>17.6</td>
<td>46.8 (6.2)</td>
<td>81.1 (17.0)</td>
</tr>
<tr>
<td>Clock hour 1†</td>
<td>27.6</td>
<td>70.3 (11.7)</td>
<td>118.8 (21.1)</td>
</tr>
<tr>
<td>Clock hour 2</td>
<td>41.7</td>
<td>51.7 (10.2)</td>
<td>92.0 (19.7)</td>
</tr>
<tr>
<td>Clock hour 3</td>
<td>36.4</td>
<td>34.3 (5.1)</td>
<td>61.4 (16.0)</td>
</tr>
<tr>
<td>Clock hour 4</td>
<td>29.8</td>
<td>40.7 (6.9)</td>
<td>75.3 (17.6)</td>
</tr>
<tr>
<td>Clock hour 5</td>
<td>15.6</td>
<td>60.3 (9.5)</td>
<td>117.7 (25.9)</td>
</tr>
<tr>
<td>Clock hour 6</td>
<td>21.8</td>
<td>79.0 (13.8)</td>
<td>136.5 (23.8)</td>
</tr>
<tr>
<td>Clock hour 7</td>
<td>52.7</td>
<td>78.3 (14.0)</td>
<td>127.6 (20.7)</td>
</tr>
<tr>
<td>Clock hour 8</td>
<td>27.7</td>
<td>40.2 (5.9)</td>
<td>73.8 (17.1)</td>
</tr>
<tr>
<td>Clock hour 9</td>
<td>27.6</td>
<td>32.6 (4.0)</td>
<td>57.7 (14.7)</td>
</tr>
<tr>
<td>Clock hour 10</td>
<td>24.5</td>
<td>46.5 (7.8)</td>
<td>87.5 (20.6)</td>
</tr>
<tr>
<td>Clock hour 11</td>
<td>32.5</td>
<td>80.5 (13.8)</td>
<td>126.3 (19.6)</td>
</tr>
<tr>
<td>Clock hour 12</td>
<td>21.1</td>
<td>73.2 (11.7)</td>
<td>126.3 (22.4)</td>
</tr>
</tbody>
</table>

*Includes all normal eyes of individuals with both eyes not reduced.
†Average RNFL% is out of 712 patients due to 5 patients missing only this measurement. All sectors and clock hours are percentage out of 717 patients.
‡Clock hours are standardized such that left eyes have been flipped to correspond with right eye orientation, that is, 9-o’clock position corresponds to the temporal quadrant and 3-o’clock position corresponds to the nasal quadrant.

RNFL, retinal nerve fiber layer; SD, standard deviation.

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OCT evidence of structural damage to not only the optic nerve but the macula as well at baseline.

The fact that RNFL and macular thinning are linked in this population is not a new idea (8,17,19). However, this study is arguably the largest database of the MS OCT trial data that has undergone strict quality control with a centralized OCT reading center. Additionally, this study detailed which subfields of the macula and quadrants or clock hours of the optic nerve were preferentially affected. They were often affected together, particularly in the inferior region, likely representing inferior peripapillary RNFL from ganglion cells with axons originating in the inferior macula.

Our study also supported the notion that a subset of patients with MS may have structural damage to the macula in the absence of damage to the RNFL. Saidha et al (20) described the preferential macular involvement in 10% of their 450 patients with MS as measured by the spectral domain OCT, who appeared to have worse disease severity scores and more severe macular function by multifocal electoretinography. Our results showed that 7.0% of 712 patients (10.6% of the patients with a normal RNFLT) had reduced TMV in the absence of thin average RNFL. Our data collected with TD-OCT supported the findings of Saidha et al. Reduced central foveal area in 7.8% of our patients also demonstrated that MS can affect the outer retinal layers. This has been observed in patients with long-standing MS using adaptive optics (27,28).

Patients with a history of MS tend to develop peripapillary RNFL thinning in the temporal quadrant, which preferentially affects the papillomacular bundle (29). In our study, the papillomacular bundle region showed great thickness variability. Thinning of the temporal optic nerve quadrant occurred in 246 patients (34.3%). The inner nasal macula was thin in 20.8%, and the outer nasal macula was thin in only 2.5%. The inner macular ring encompasses a thicker ganglion cell layer than that of the outer macular ring (30), which may offer a possible explanation for this disparity because ganglion cells in the inner sector would contribute proportionally more to overall macular thickness.

### TABLE 4. Signal strength differences in reduced and not reduced eyes for macula

<table>
<thead>
<tr>
<th>Macular Subfield</th>
<th>Average Signal Strength of Reduced Eyes (SD)</th>
<th>Average Signal Strength of Not Reduced Eyes (SD)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total macular volume</td>
<td>7.44 (1.53)</td>
<td>7.79 (1.51)</td>
<td>0.01</td>
</tr>
<tr>
<td>Outer superior average thickness</td>
<td>7.30 (1.42)</td>
<td>7.78 (1.53)</td>
<td>0.003</td>
</tr>
<tr>
<td>Outer nasal average thickness</td>
<td>7.09 (1.37)</td>
<td>7.75 (1.53)</td>
<td>0.04</td>
</tr>
<tr>
<td>Outer inferior average thickness</td>
<td>7.40 (1.52)</td>
<td>7.82 (1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outer temporal average thickness</td>
<td>7.43 (1.53)</td>
<td>7.84 (1.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inner superior average thickness</td>
<td>7.61 (1.49)</td>
<td>7.76 (1.52)</td>
<td>0.24</td>
</tr>
<tr>
<td>Inner nasal average thickness</td>
<td>7.61 (1.50)</td>
<td>7.76 (1.53)</td>
<td>0.28</td>
</tr>
<tr>
<td>Inner inferior average thickness</td>
<td>7.59 (1.54)</td>
<td>7.76 (1.50)</td>
<td>0.21</td>
</tr>
<tr>
<td>Inner temporal average thickness</td>
<td>7.68 (1.56)</td>
<td>7.74 (1.51)</td>
<td>0.52</td>
</tr>
<tr>
<td>Central foveal area thickness</td>
<td>7.84 (1.59)</td>
<td>7.72 (1.53)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*Includes all normal eyes of individuals with both eyes not reduced.

### TABLE 5. Distribution of macular thickness by subfield in relapsing–remitting multiple sclerosis patients with at least one eye affected

<table>
<thead>
<tr>
<th>Macular Subfield</th>
<th>Percent of Patients With at Least One Eye &lt;5% Normal, %</th>
<th>Average Value of Reduced Eyes, μm (SD)*</th>
<th>Average Value of Not Reduced Eyes, μm (SD)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMV</td>
<td>25.3‡</td>
<td>5.97 (0.20)</td>
<td>6.83 (0.38)</td>
</tr>
<tr>
<td>Outer superior average thickness</td>
<td>14.1</td>
<td>200.8 (6.9)</td>
<td>234.5 (14.9)</td>
</tr>
<tr>
<td>Outer nasal average thickness</td>
<td>2.5</td>
<td>193.3 (3.8)</td>
<td>245.8 (19.9)</td>
</tr>
<tr>
<td>Outer inferior average thickness</td>
<td>28.4</td>
<td>199.0 (7.7)</td>
<td>230.8 (13.8)</td>
</tr>
<tr>
<td>Outer temporal average thickness</td>
<td>28.3</td>
<td>193.8 (6.8)</td>
<td>221.4 (15.5)</td>
</tr>
<tr>
<td>Inner superior average thickness</td>
<td>23.7</td>
<td>233.5 (9.5)</td>
<td>270.8 (15.1)</td>
</tr>
<tr>
<td>Inner nasal average thickness</td>
<td>20.8</td>
<td>229.2 (10.5)</td>
<td>269.6 (16.9)</td>
</tr>
<tr>
<td>Inner inferior average thickness</td>
<td>34.9</td>
<td>236.0 (12.3)</td>
<td>271.0 (18.0)</td>
</tr>
<tr>
<td>Inner temporal average thickness</td>
<td>37.4</td>
<td>228.9 (9.8)</td>
<td>261.1 (17.1)</td>
</tr>
<tr>
<td>Central foveal area thickness</td>
<td>7.8</td>
<td>159.6 (7.3)</td>
<td>203.6 (21.6)</td>
</tr>
</tbody>
</table>

*Except for TMV, which is measured in cubic millimeters.
†Includes all normal eyes of individuals with both eyes not reduced.
‡TMV% is of 712 patients due to 5 patients missing only this measurement. All sectors are percent of 717 patients.

than other retinal layers. Nevertheless, other macular sectors did not demonstrate such a dramatic difference.

Although the temporal RNFL was the most commonly thinned quadrant, as reported in previous studies (29), the clock hours of greatest thinning were in the inferior quadrant. Since the inferior RNFL is traditionally the thickest quadrant, it is not surprising that the inferior RNFL would show the most thinning since there are more nerve fibers at risk.

A true comparative subfield analysis was limited by predetermined normative database and analysis plots for ETDRS sectors in the macula and RNFL quadrants. These regions may not optimally correspond in anatomical distribution. For example, the superior and inferior RNFL both represent axons from the temporal macula. Also, nominal categories of reduced and not reduced did not allow for continuous variable analysis to determine which patients had values near but not beyond the threshold of 5% (i.e., low-normal, just above 5%), the analysis of which may clarify any linear relationships between RNFL and macular thinning.

The lack of segmentation algorithms in TD-OCT precludes further interpretation of our data set. As technology improves and time domain platforms give way to spectral domain and high-resolution OCT, intraretinal OCT segmentation algorithms and volume mapping are now beginning to detail how much of macular thinning is due to ganglion cell death or RNFL loss vs damage to outer retinal layers (20,27,28,31,32).

In conclusion, our study showed that both the RNFL and macula are commonly thinned in the relapsing-remitting MS population at baseline. We confirmed that when the average RNFL is thin, the macula showed reduced volume at baseline. We also documented a population of patients in whom the macula was preferentially affected, despite normal RNFL as measured by TD-OCT. Future assessment of the longitudinal and clinical data from the MS fingolimod trial should provide insights into the populations at risk of macular pathology and loss of visual function.

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REFERENCES


Primary Spontaneous Cerebrospinal Fluid Leaks and Idiopathic Intracranial Hypertension

Mario A. Pérez, MD, Omer Y. Bialer, MD, Beau B. Bruce, MD, MS, Nancy J. Newman, MD, Valérie Biousse, MD

Introduction: Idiopathic intracranial hypertension (IIH) is increasingly recognized as a cause of spontaneous cerebrospinal fluid (CSF) leak in the otolaryngological and neurosurgical literature. The diagnosis of IIH in patients with spontaneous CSF leaks typically is made a few weeks after surgical repair of the leak when symptoms and signs of elevated intracranial pressure (ICP) appear.

Methods: Case reports and literature review. Two young obese women developed spontaneous CSF rhinorrhea related to an empty sella in one and a cribiform plate encephalocele in the other. Both patients underwent surgical repair of the CSF leak. A few weeks later, they developed chronic headaches and bilateral papilledema. Lumbar punctures showed elevated CSF opening pressures with normal CSF contents, with temporary improvement of headaches. A man with a 3-year history of untreated IIH developed spontaneous CSF rhinorrhea. He experienced improvement of his headaches and papilledema after a CSF shunting procedure, and the rhinorrhea resolved after endoscopic repair of the leak.

Results: These cases and the literature review confirm a definite association between IIH and spontaneous CSF leak based on: 1) similar demographics; 2) increased ICP in some patients with spontaneous CSF leak after leak repair; 3) higher rate of leak recurrence in patients with raised ICP; 4) patients with intracranial hypertension secondary to tumors may develop CSF leak, confirming that raised ICP from other causes than IIH can cause CSF leak.

Conclusions: CSF leak occasionally may keep IIH patients symptom-free; however, classic symptoms and signs of intracranial hypertension may develop after a CSF leak is repaired, exposing these patients to a high risk of recurrence of the leak unless an ICP-lowering intervention is performed.

Cerebrospinal fluid (CSF) leaks traditionally have been classified as traumatic or nontraumatic (1,2). Nontraumatic CSF leaks may be spontaneous in the absence of obvious cause, such as skull base abnormalities or bone erosion related to a mass lesion or hydrocephalus (1–3). Spontaneous CSF leaks sometimes are referred to as high-pressure leaks when increased intracranial pressure (ICP) is a contributing factor (2,3). Idiopathic intracranial hypertension (IIH) is increasingly recognized as a cause of spontaneous CSF leak in the otolaryngological and neurosurgical literature. There are reports suggesting that the so-called primary spontaneous CSF leaks might be due to IIH (2–8). Some of these patients are asymptomatic or only have symptoms attributable to the CSF leak (such as rhinorrhea, CSF hypotension–related headaches, or bacterial meningitis) while the leak is active. The diagnosis of IIH is typically made weeks or months after surgical repair of the leak (9). At times, patients with a known diagnosis of IIH may develop a spontaneous CSF leak, presumably secondary to the chronically raised ICP with skull base erosion and meningoceles (2).

MATERIALS AND METHODS

Medical records and neuroimaging of the illustrative cases were reviewed. PubMed was searched for English-language articles published before January 2013 using the search terms “idiopathic intracranial hypertension,” “encephalocele,” “skull-base defect,” “spontaneous cerebrospinal fluid leak,” “CSF rhinorrhea,” and “CSF otorhrea.” The reference lists of identified articles were searched for further relevant articles.
CASE REPORTS

Case 1
A 49-year-old obese African American woman developed isolated CSF rhinorrhea, which initially was mistaken for sinusitis. One year later, she developed bacterial meningitis, and computed tomography (CT) demonstrated a skull-base defect in the right cribiform area causing meningocele with CSF leak (Fig. 1A). She underwent endoscopic sinus surgery with repair of the leak. Three months later, she complained of headaches and transient visual obscurations and was found to have bilateral papilledema (Fig. 1B). Automated perimetry showed enlarged blind spots and nasal visual field loss (Fig. 1C). Lumbar puncture revealed increased CSF opening pressure (OP) of 37 cm H$_2$O and resulted in temporary resolution of the headaches. She underwent a ventriculoperitoneal shunt with immediate resolution of her symptoms of raised ICP; papilledema resolved within 1 month. The CSF leak did not recur.

Case 2
A 32-year-old obese Caucasian woman was found to have isolated CSF rhinorrhea after presenting with postural headaches. Brain imaging showed an empty sella and intrasellar bone erosion (Fig. 2A, B). She underwent endoscopic surgical repair of the CSF leak, and her headaches resolved after the procedure. A few weeks later, persistent headaches developed, and she experienced transient visual obscurations. She was found to have bilateral optic disc edema (Fig. 2C) with enlarged blind spots on visual field examination. Lumbar puncture showed elevated CSF OP of 42 cm H$_2$O and resulted in temporary resolution of headaches. The patient subsequently underwent a CSF shunting procedure with complete resolution of all symptoms of intracranial hypertension; papilledema had resolved. The CSF leak did not recur.

Case 3
A 43-year-old mildly overweight Caucasian man was followed for 3 years for symptomatic IIH treated intermittently with acetazolamide. He had moderate bilateral papilledema with enlarged blind spots in his visual fields but only mild headaches, and generally did well without treatment. He was reevaluated for worsening headaches, which were occurring daily and associated with tinnitus and transient visual obscurations. Repeat neuro-ophthalmic examination showed persistent, bilateral papilledema (Fig. 3A) and stable visual fields. Repeat lumbar puncture showed elevated CSF OP of 33.5 cm H$_2$O. His headaches improved, but he developed CSF rhinorrhea. Neuroimaging showed a right cribiform plate defect (Figs. 3B & 3C), an empty sella, and bilateral transverse sinus stenoses (Fig 3D). The patient was placed on prophylactic antibiotics and underwent a ventriculoperitoneal shunt. CSF rhinorrhea markedly decreased, and endoscopic repair of the leak was subsequently performed, with immediate resolution of the leak. However, 6 weeks later, the leak recurred in the setting of recurrent increased ICP secondary to proximal shunt obstruction. The shunt was revised, and the CSF leak resolved. One month later, he remained asymptomatic, with improvement of his papilledema.

Review of the Literature
Table 1 presents a summary of reports in the English literature of spontaneous CSF leaks associated with presumed or diagnosed IIH (2–24).

DISCUSSION
IIH is increasingly recognized as a cause of primary spontaneous CSF leaks. Over the past 2 decades, several articles on this topic have been published mostly in the otolaryngological and neurosurgical literature (2–25). These reports highlight the similarities between the demographics of patients with IIH and those with spontaneous CSF leaks suggesting a causal relationship between IIH and the so-called spontaneous CSF leak (Table 1).

Similar to IIH patients, reported cases of spontaneous CSF leak are often young or middle-age obese women, with a mean body mass index (BMI) greater than 30 kg/m$^2$.

FIG. 1. Case 1. A. Coronal computed tomography of the brain without contrast reveals dehiscence of the right cribiform plate with soft tissue in the right olfactory recess (arrow) consistent with a meningocele. B. Following repair of the cerebrospinal fluid leak, the patient developed bilateral papilledema. C. Automated visual fields, performed on the SITA-fast 24-2 program, show an enlarged blind spot and nasal field loss in each eye.
Such demographic overlap also is shared by patients with primary empty sella syndrome, an endocrine entity in which chronically increased ICP may be a contributing factor (26,27). In a retrospective study of 11 patients with β-2 transferrin–proven spontaneous CSF leaks, 72% of patients met the criteria for the diagnosis of IIH (5). Obesity has been suggested as an independent risk factor for the development of spontaneous CSF leaks and spontaneous encephaloceles, and the BMI of these patients is significantly higher than in those of patients developing CSF leaks for other reasons. In 1 study specifically performed to evaluate the role of obesity (BMI ≥ 30 kg/m²) in spontaneous encephaloceles and CSF leak, the mean BMI of the patients with spontaneous encephaloceles was 33.4 kg/m² vs 27.0 kg/m² in the group of nonspontaneous encephaloceles (28).

The presenting symptoms of spontaneous CSF leaks vary greatly depending on multiple factors, including the

**FIG. 2.** Case 2. **A.** Postcontrast sagittal T1 magnetic resonance imaging shows an empty sella (arrow). **B.** Coronal computed tomography reveals intrasellar bone erosion (asterisk). **C.** After repair of the cerebrospinal fluid leak, there is bilateral papilledema. OD, right eye; OS, left eye.

**FIG. 3.** Case 3. **A.** Bilateral papilledema is seen on funduscopic examination. **B.** Noncontrast coronal computed tomography shows dehiscence of the right cribriform plate (arrow) with soft tissue in the right olfactory recess, consistent with meningocele. **C.** Coronal T2 magnetic resonance imaging demonstrates fluid and soft tissue in the right olfactory recess (arrowhead) and distension of the periorbit nerve subarachnoid space (arrows). **D.** Bilateral transverse sinus stenoses (arrows) are present on coronal magnetic resonance venogram.
### TABLE 1. Reports in the English literature of patients with CSF leaks associated with symptoms and signs of presumed idiopathic intracranial hypertension

<table>
<thead>
<tr>
<th>Case Series (Reference)</th>
<th>Number of Cases</th>
<th>% Women</th>
<th>Mean age (Years)</th>
<th>BMI (kg/m²)</th>
<th>CSF OP (cm H₂O)</th>
<th>Clinical Presentation</th>
<th>Site of Leakage (Number of patients)</th>
<th>Treatment</th>
<th>Diagnosis of IIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brisman et al* (10)</td>
<td>1</td>
<td>100</td>
<td>44</td>
<td>?</td>
<td>“Elevated”</td>
<td>Rhinorrhea</td>
<td>Cribiform plate</td>
<td>Surgical (craniotomy + sealing of the cribiform plate with muscle)</td>
<td>Yes</td>
</tr>
<tr>
<td>Applebaum and Desai (11)</td>
<td>1</td>
<td>100</td>
<td>52</td>
<td>?</td>
<td>“Moderately obese”</td>
<td>Rhinorrhea, previous meningitis</td>
<td>Sella turcica</td>
<td>Surgical repair</td>
<td>Maybe</td>
</tr>
<tr>
<td>Eljamel and Foy (12)</td>
<td>2</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>“High”</td>
<td>Rhinorrhea</td>
<td>?</td>
<td>LP shunt in one of the patients, unknown for the other patient</td>
<td>Yes</td>
</tr>
<tr>
<td>Clark et al (2)</td>
<td>4</td>
<td>100</td>
<td>38</td>
<td>?</td>
<td>32</td>
<td>Rhinorrhea</td>
<td>Cribiform plate</td>
<td>Surgical repair/lumbar punctures/diuretics</td>
<td>Yes</td>
</tr>
<tr>
<td>Camras et al (13)</td>
<td>1</td>
<td>100</td>
<td>46</td>
<td>“Obese”</td>
<td>25</td>
<td>Rhinorrhea, headaches</td>
<td>Anterior cranial fossa</td>
<td>Bifrontal craniotomy + fascia lata graft</td>
<td>Yes</td>
</tr>
<tr>
<td>Mokri (9)</td>
<td>4</td>
<td>100</td>
<td>27</td>
<td>?</td>
<td>30.8</td>
<td>Orthostatic headaches—after repair: elevated ICP related-symptoms</td>
<td>Spinal</td>
<td>Surgical repair</td>
<td>Maybe</td>
</tr>
<tr>
<td>Owler et al (14)</td>
<td>1</td>
<td>100</td>
<td>38</td>
<td>?</td>
<td>?</td>
<td>Rhinorrhea, visual disturbances, headaches</td>
<td>Anterior cranial fossa</td>
<td>Craniotomy + LP shunt; transverse sinus stenting</td>
<td>Yes</td>
</tr>
<tr>
<td>Schlosser et al (4)</td>
<td>16</td>
<td>81</td>
<td>49.6</td>
<td>35.9</td>
<td>26.5</td>
<td>Rhinorrhea, symptoms of elevated ICP</td>
<td>Lateral sphenoid recess (8), central sphenoid (4), ethmoid roof (4), cribiform (2), supraorbital/posterior frontal recess (2), frontal sinus (2)</td>
<td>Surgical repair</td>
<td>Yes</td>
</tr>
<tr>
<td>Schlosser and Bolger (15)</td>
<td>16</td>
<td>81</td>
<td>49.6</td>
<td>35.9</td>
<td>28.3</td>
<td>Rhinorrhea, symptoms of elevated ICP</td>
<td>Lateral sphenoid recess (8), central sphenoid (4), ethmoid roof (4), cribiform (2), supraorbital/posterior frontal recess (2), frontal sinus (2)</td>
<td>Surgical repair</td>
<td>Yes</td>
</tr>
<tr>
<td>Case Series (Reference)</td>
<td>Number of Cases</td>
<td>% Women</td>
<td>Mean age (Years)</td>
<td>BMI (kg/m²)</td>
<td>CSF OP (cm H₂O)</td>
<td>Clinical Presentation</td>
<td>Site of Leakage (Number of patients)</td>
<td>Treatment</td>
<td>Diagnosis of IIH</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>-----------------</td>
</tr>
<tr>
<td>Rudnick and Sismanis (8)</td>
<td>1</td>
<td>100</td>
<td>33</td>
<td>48.8</td>
<td>26</td>
<td>Rhinorrhea</td>
<td>Cribiform plate</td>
<td>Gastric bypass (weight loss)</td>
<td>Yes</td>
</tr>
<tr>
<td>Dunn et al (17)</td>
<td>15</td>
<td>93</td>
<td>50</td>
<td>“Obese”</td>
<td>?</td>
<td>Rhinorrhea, symptoms of elevated ICP</td>
<td>Roof of the ethmoid (6), sphenoid (5), cribiform plate (4)</td>
<td>Endoscopic repair</td>
<td>Maybe</td>
</tr>
<tr>
<td>Schlosser et al (5)</td>
<td>16</td>
<td>81</td>
<td>49.6</td>
<td>35.9</td>
<td>31.1</td>
<td>Rhinorrhea, symptoms of elevated ICP</td>
<td>Lateral sphenoid recess (8), central sphenoid (4), ethmoid roof (4), cribiform (2), supraorbital/posterior frontal recess (2), frontal sinus (2)</td>
<td>Surgical repair</td>
<td>Yes</td>
</tr>
<tr>
<td>Prichard et al (18)</td>
<td>8</td>
<td>50</td>
<td>58</td>
<td>34.9</td>
<td>?</td>
<td>Hearing loss, meningitis, otorrhea, rhinorrhea</td>
<td>Posterior fossa</td>
<td>Surgical repair; LP shunt (in 1 patient)</td>
<td>Maybe</td>
</tr>
<tr>
<td>Ransom et al (19)</td>
<td>1</td>
<td>100</td>
<td>53</td>
<td>?</td>
<td>“Elevated”</td>
<td>Postural headaches, rhinorrhea</td>
<td>Roof of the ethmoid sinus</td>
<td>Revision of VP shunt</td>
<td>Maybe</td>
</tr>
<tr>
<td>Suryadevara et al (6)</td>
<td>2</td>
<td>100</td>
<td>47</td>
<td>“Obese”</td>
<td>26</td>
<td>Rhinorrhea, headaches, rhinorrhea, meningitis</td>
<td>Cribiform plate</td>
<td>Surgical repair</td>
<td>Yes</td>
</tr>
<tr>
<td>Woodworth et al (20)</td>
<td>55</td>
<td>78</td>
<td>61</td>
<td>43 patients: &gt;30, only one was &lt;25</td>
<td>27</td>
<td>?</td>
<td>Lateral sphenoid sinus (23), ethmoid roof (17), cribiform plate (12), central sphenoid (7), frontal sinus (7)</td>
<td>Surgical</td>
<td>Maybe</td>
</tr>
<tr>
<td>Stangherlin et al (21)</td>
<td>1</td>
<td>100</td>
<td>45</td>
<td>48</td>
<td>?</td>
<td>Rhinorrhea</td>
<td>Left posterior ethmoidal cell</td>
<td>Gastric banding (weight loss)</td>
<td>Maybe</td>
</tr>
<tr>
<td>Case Series (Reference)</td>
<td>Number of Cases</td>
<td>% Women</td>
<td>Mean age (Years)</td>
<td>BMI (kg/m²)</td>
<td>CSF OP (cm H₂O)</td>
<td>Clinical Presentation</td>
<td>Site of Leakage (Number of patients)</td>
<td>Treatment</td>
<td>Diagnosis of IIH</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------</td>
<td>---------</td>
<td>-----------------</td>
<td>-------------</td>
<td>-----------------</td>
<td>----------------------</td>
<td>--------------------------------------</td>
<td>-----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Seth et al (22)</td>
<td>39</td>
<td>85</td>
<td>57.7</td>
<td>38.5</td>
<td>24</td>
<td>?</td>
<td>Cribiform plate, sphenoid lateral pterygoid recess, ethmoid roof</td>
<td>Surgical repair (+acetazolamide in 9 patients) (+CSF shunting in 6 patients)</td>
<td>Maybe</td>
</tr>
<tr>
<td>Reh et al (23)</td>
<td>12</td>
<td>92</td>
<td>?</td>
<td>40</td>
<td>Monitoring: &gt;25 (at least 4% of the time)</td>
<td>Rhinorrhea, headaches, tinnitus</td>
<td>Sphenoid, ethmoid, cribiform</td>
<td>Endoscopic repair + lumbar drain with continuous CSF pressure monitoring</td>
<td>Maybe</td>
</tr>
<tr>
<td>Yang et al (3)</td>
<td>21</td>
<td>86</td>
<td>53</td>
<td>31.2</td>
<td>25.5</td>
<td>Rhinorrhea</td>
<td>Ethmoid sinus (13), lateral sphenoid sinus (?), frontal sinus (1)</td>
<td>Surgical repair + oral diuretics (in some cases)</td>
<td>Yes</td>
</tr>
<tr>
<td>Brainard et al (7)</td>
<td>9</td>
<td>89</td>
<td>57</td>
<td>41</td>
<td>24.5</td>
<td>Otorrhea</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Rosenfeld et al (24)</td>
<td>4</td>
<td>100</td>
<td>42</td>
<td>34.7</td>
<td>30.6</td>
<td>Rhinorrhea, otorrhea</td>
<td>Cribiform plate, middle ear</td>
<td>Surgical repair in 2 patients and CSF shunting in 2 patients</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*This study also reports 4 additional women with spontaneous CSF leaks and empty sella, but no diagnosis of IIH.

BMI, body mass index; CSF OP, cerebrospinal fluid opening pressure; ICP, intracranial pressure; IIH, idiopathic intracranial hypertension; LP, lumboperitoneal; VP, ventriculoperitoneal; ?, not known/undetermined.
location and activity of the leak, and the presence of concurrent signs of raised ICP. If the leak is active, symptoms and signs of intracranial hypotension (e.g., orthostatic headaches, neck stiffness) may occur (9). Depending on the location of the leak, CSF otorrhea and conductive hypoacusia may be a presenting sign in patients with bone defects in the posterior fossa (24), whereas CSF rhinorrhea usually develops in patients with defects of the cribriform plate (6,8,29). Bacterial meningitis may be the initial presentation leading to the discovery of the CSF leak. Some patients may have symptoms of increased ICP even when the leak is active (including headache, tinnitus, visual disturbances, and papilledema) (2), but most often, patients develop symptoms and signs of intracranial hypertension only after the CSF leak has been repaired (9,30).

The factors predisposing some IIH patients to develop spontaneous CSF leaks remain unclear, although it is likely that chronically elevated ICP is necessary, as demonstrated by our third patient. Some patients with increased ICP secondary to intracranial tumors (distant from the skull base) or hydrocephalus may also develop CSF leak, confirming that raised ICP in itself can cause CSF leaks, possibly through remodeling of the skull base and resultant encephaloceles (1,2,31,32).

CT and MRI of the brain are required to identify skull base defects. Often, these studies show imaging findings associated with increased ICP (32). A retrospective study showed that 100% of patients with spontaneous CSF leaks had a completely or partially empty sella compared with 11% of patients with nons spontaneous CSF leaks and 5%–6% of the general population (15). Tortuosity of the optic nerves, increased CSF around the optic nerves, arachnoid pits and dural ectasias are other radiological findings often observed in patients with both IIH and spontaneous CSF leaks (31). The most frequent site of skull basal defects includes the ethmoid sinuses and lateral wall of the sphenoid sinus (3). In addition, there are reports that spinal CSF leak might be associated with increased ICP (9). Given the overlapping clinical and neuroimaging profiles, it has been proposed that patients with primary spontaneous CSF leaks may have a variant of IIH (5).

Spontaneous CSF leak patients may develop raised ICP once the leak is repaired (9,25), as did 2 of our patients. In a small prospective study measuring ICP through lumbar catheters after surgical repair of spontaneous CSF leaks, elevated ICP was observed in 7 of 8 patients and in none of 3 patients with traumatic CSF leaks (30). Although spontaneous resolution of spontaneous CSF leak may occur after treatment of increased ICP, the high risk of bacterial meningitis usually requires endoscopic surgical repair of the skull base defect (33). Interestingly, following skull base surgical repair in patients with spontaneous CSF leak, the leak recurrence rate is high, ranging from 25% to 87% (2,3,20). This high rate of recurrence likely reflects excessive elevation of ICP that occurs after leak repair in those patients with presumed IIH (30). Obesity (common in IIH) is also associated with the failure of the CSF leak repair (21).

Appropriate ICP-lowering management usually is the first step in managing patients with CSF leak. Reh et al (23) proposed monitoring of CSF pressure through a lumbar drain to assess response to a therapeutic trial of acetazolamide before surgical intervention. Once there is appropriate control of ICP, the rate of success of the spontaneous CSF leak repair approaches 95% and is similar to that of repair of CSF leaks due to other causes (2). It has been proposed that interventions to lower the ICP including medical therapy (weight loss, acetazolamide) or a CSF diversion procedure be performed before or at the time of surgical repair of the skull base (20, 25). Our patients underwent CSF shunting procedures as the first-line treatment due to concern that medical management alone might not result in an immediate and dramatic decrease in ICP, necessary to prevent visual loss from papilledema. Indeed, recurrence of the leak occurred in the patient who had shown malfunction soon after surgery.

Because elevated BMI is a risk factor for patients with primary spontaneous CSF leaks, weight loss likely should be recommended. However, there are only case reports of resolution of spontaneous CSF leaks after bariatric surgery (22,25), so further study is needed to assess the effectiveness of weight loss in the treatment of spontaneous CSF leaks (22,25).

Our cases illustrate the association between IIH and spontaneous CSF leaks and support systematic screening for symptoms and signs of increased ICP within weeks after surgical repair of a spontaneous CSF leak. Identification of these patients is warranted to prevent failure of the CSF leak repair and to prevent potential visual loss from papilledema. Additionally, IIH patients with chronically raised ICP require close follow-up for the development of a CSF leak.

REFERENCES


Bilateral Nonarteritic Anterior Ischemic Optic Neuropathy: Comparison of Visual Outcome in the Two Eyes

Sohan Singh Hayreh, MD, PhD, DSc, FRCS, FRCOphth (Hon), M. Bridget Zimmerman, PhD

Background: In patients with bilateral sequential nonarteritic anterior ischemic optic neuropathy (NA-AION), previous studies have reported conflicting results on whether or not the visual outcome is similar in the 2 eyes. The authors investigated this issue in 174 consecutive patients with bilateral NA-AION.

Methods: At the first visit, all patients had a detailed ophthalmic and medical history and comprehensive ophthalmic evaluation. Visual evaluation was performed by recording Snellen visual acuity and visual fields with kinetic perimetry. The same ophthalmic evaluation was performed at each follow-up visit. The data on the difference in visual acuity, which was converted to logarithm of the minimum angle of resolution (logMAR) form, and visual field defects between the first eye and the second eye of each patient at the initial visit and at the final follow-up were analyzed. A similar subgroup analysis was performed on patients treated with systemic corticosteroids.

Results: At presentation, both initial visual acuity and visual field defects were significantly better in the second eye than in the first eye ($P < 0.0001$). As a predictor of initial visual acuity in the second eye, the initial logMAR of the first eye only explained 7.0% ($R^2$) of the total variation in the initial logMAR of the second eye. Intraclass correlation (ICC) between the paired eyes was 0.19 (95% confidence interval [CI], 0.04–0.33), indicating poor agreement. The absolute difference in initial visual field grade between the 2 eyes was 0.5 or greater in 78%. The weighted kappa statistic for agreement between visual field defects of the 2 eyes was 0.27 (95% CI, 0.19–0.36), indicating poor agreement. At the final follow-up, a difference in logMAR of at least 0.3 between the paired eyes was found in 38% of the steroid-treated group and 45% of the untreated group. For visual field grade, there was a difference of at least 0.5 in 70% of those who were treated with steroid and in 76% of those not treated. The ICC for logMAR and weighted kappa for visual field grade for the paired eyes was below 0.60 for both the groups. The findings indicated poor agreement between the 2 eyes.

Conclusion: The results show that in patients with bilateral sequential NA-AION, there are large differences between the visual acuity and visual field findings of paired eyes at initial and final visit, whether or not treated with steroids. It is not possible to predict the visual acuity and visual field grade in the second eye based solely on the first eye.

METHODS

We compared visual acuity and visual field defects in the 2 eyes of patients with bilateral sequential NA-AION who were seen in our clinic from 1973 to 2000, as a part of prospective studies on various aspects of NA-AION. The data were compiled from 174 consecutive bilateral NA-AION patients who fulfilled our inclusion and exclusion criteria, and the study was approved by our institutional review board. Inclusion criteria were: 1) a history of sudden visual loss, usually...
discovered in the morning; 2) presence of optic disc edema (ODE) at onset; 3) presence of optic disc–related visual field defects; 4) no neurological, systemic, or ocular disorder, which could be responsible for ODE and visual impairment; 5) patients seen within 3 months of onset of NA-AION; and 6) only patients with follow-up of at least 6 months, this is because studies (10–12) on NA-AION have shown that visual functions become stable 6 months after the onset. Exclusion criteria were: 1) patients who had any retinal or optic nerve disorder or any other factor (e.g., cataract), which might affect vision; 2) patients with unreliable visual fields; and 3) patients with incipient NA-AION (13) who had no demonstrable visual dysfunction.

Studies Performed
A detailed ophthalmic and medical history was obtained at the patient’s first visit to our clinic (by S.S.H.). A comprehensive ophthalmic evaluation was performed at that time (by S.S.H.). When giant cell arteritis was suspected, based on systemic symptoms, elevated erythrocyte sedimentation rate, and/or C-reactive protein or suspicion of arteritic AION, a temporal artery biopsy was performed to rule out giant cell arteritis.

Follow-up Protocol for all Patients
Patients were followed initially every 2–4 weeks as long as there was ODE, which lasted 7.9 weeks (range, 5.8–11.4 weeks) (14). After that, they were followed at 3 months, 6 months, and then yearly.

Visual Acuity
This was measured with Snellen visual acuity chart and under identical testing conditions and converted to logarithm of the minimum angle of resolution (logMAR) for statistical analysis.

Visual Fields
Throughout this study, we used kinetic perimetry. Automated perimetry did not exist when we started the study in 1973; moreover, the changing face of automated perimetry would make such long-term studies difficult. Visual field testing was attempted in all patients with a visual acuity of hand motion or better at all visits, with a kinetic perimeter using I-2e, I-4e, and V-4e targets regularly.

Evaluations of Visual Acuity and Visual Field Defects
Each was evaluated separately in a masked fashion, that is, changes in visual acuity and visual fields were evaluated independent of each other, so that the severity of one did not influence the evaluation of the other. Also, in eyes that developed recurrence of NA-AION, only the data from ophthalmic examination collected up to the last follow-up visit of the first episode were used, that is, before the onset of recurrence.

### Table 1. Literature summary of comparison of visual acuity in the 2 eyes of bilateral sequential NA-AION

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study Type</th>
<th>Number of Patients</th>
<th>Number (%) ≥0.3 LogMAR Difference Between Eyes</th>
<th>Pearson Correlation Between Eyes (r)</th>
<th>Authors’ Conclusion VA in 2 Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgiadès et al (1)</td>
<td>1966</td>
<td>Retrospective</td>
<td>6</td>
<td>4 (67%)* first visit</td>
<td>0.26* first</td>
<td>Different</td>
</tr>
<tr>
<td>Boghen and Glaser (2)</td>
<td>1975</td>
<td>Retrospective</td>
<td>14</td>
<td>6 (100%)* last visit</td>
<td>−0.30* last</td>
<td>Different</td>
</tr>
<tr>
<td>Kupersmith et al (3)</td>
<td>1997</td>
<td>Retrospective</td>
<td>33</td>
<td>22 (67%)</td>
<td>0.28</td>
<td>Different</td>
</tr>
<tr>
<td>WuDunn et al (4)</td>
<td>1997</td>
<td>Retrospective</td>
<td>31</td>
<td>22 (71%)*</td>
<td>0.29*</td>
<td>Different</td>
</tr>
<tr>
<td>Newman et al (5)</td>
<td>2002</td>
<td>Prospective</td>
<td>128 (80/48)</td>
<td>53/80† (66%)</td>
<td>0.51† first</td>
<td>Different</td>
</tr>
<tr>
<td>Kurz (6)</td>
<td>1969</td>
<td>Retrospective</td>
<td>7</td>
<td>22/48† (46%)</td>
<td>0.29† first</td>
<td>Similar (no test performed)</td>
</tr>
<tr>
<td>Moro et al (7)</td>
<td>1989</td>
<td>Retrospective</td>
<td>26</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Similar (only tested for pairwise difference, NS)</td>
</tr>
<tr>
<td>Boone et al (8)</td>
<td>1996</td>
<td>Retrospective</td>
<td>16</td>
<td>7 (44%)*</td>
<td>0.52*</td>
<td>Similar</td>
</tr>
<tr>
<td>Mercado et al (9)</td>
<td>2012</td>
<td>Retrospective</td>
<td>86</td>
<td>Not reported</td>
<td>0.28 Spearman</td>
<td>Similar</td>
</tr>
</tbody>
</table>

*Calculated from table listing the data for visual acuity for each subject in the study.
†Counts obtained from figure provided in the study for last visit.
‡Reported separately for those with 80 existing NA-AION in fellow eye and 48 with new NA-AION in fellow eye.

logMAR, logarithm of the minimum angle of resolution; NA-AION, nonarteritic anterior ischemic optic neuropathy; NS, nonsignificant; VA, visual acuity.
Visual Acuity Evaluation
A change of at least 3 lines in the Snellen visual acuity chart was considered a significant change, which is equivalent to a logMAR change of at least 0.30.

Visual Field Evaluation
The entire visual field was graded in 4 levels—from 0 (normal) to 4 (severe loss) in steps of 0.5 (and occasionally 0.25 when the differences were subtle). The method of grading visual fields is discussed at length elsewhere (11). The findings were then condensed for descriptive purposes into minimal (grade 0.5), mild (grades >0.5–1.0), moderate (grades 1.5–2.0), marked (grades 2.5–3.0), and severe (grades 3.5–4.0) loss (10–12). As shown by our previous study (11), a change of 0.5 or more in visual field grade is significant.

Statistical Methods
Descriptive statistics (median, interquartile range, and percentages) were calculated for visual acuity (logMAR) and visual field grade for the first eye and the second eye and for the difference between the paired eyes at the initial visit and at the final follow-up. Wilcoxon signed-rank test was used to test for the difference in visual acuity and visual field grade between the first eye and the second eye of the same patient. Weighted kappa statistics was used to assess the agreement in visual field grade between the first eye and the second eye of the same patient.

For assessing final visual acuity and visual field grade, patients were classified into 3 groups based on the treatment received (both eyes with steroid treatment; both eyes with no treatment; and one eye treated and the other not treated). Initial visual acuity and visual field of the first eye and the second eye, and the difference between eyes were compared among the 3 groups using the Kruskal–Wallis exact test.

In addition, parametric methods for measuring agreement in logMAR were also used. This required the data to have a normal distribution, which was not seen in our logMAR data. To satisfy the normality assumption, the natural log transformation was applied to the logMAR values to normalize the data distribution. Because there were negative and 0 logMAR values (corresponding to 20/15 and 20/20, respectively), the natural log transformation was applied to the logMAR value plus a constant, that is, in (logMAR + c), with c determined as the value that resulted in the largest Shapiro–Wilk normality test statistic. Statistical analysis performed on the transformed logMAR included: 1) Pearson correlation between the first eye and the second eye of the same patient, 2) variance component analysis, and 3) intraclass correlation (ICC). Variance component analysis and ICCs were computed as described by Shrout and Fleiss (15). For interpreting ICC and weighted kappa, agreement >0.8 is almost perfect, >0.6–0.8 substantial, >0.4–0.6 moderate, >0.2–0.4 fair, and ≤0.2 poor (16).

RESULTS
Of the 174 patients, the eye that was first diagnosed with NA-AION was the right eye in 45%, left eye in 47%, and 8% with bilateral involvement.

Initial visual acuity and visual field defect in the first eye and the second eye are presented in Table 2. Initial visual acuity at presentation showed significantly better initial visual acuity in the second eye compared with the first eye (P < 0.0001). The plot of initial logMAR between the first eye and the second eye is presented in Figure 1A. In 59% of the cases, there was at least a 0.3 logMAR difference, which is considered clinically significant.

| TABLE 2. Initial visual acuity and visual field in the first and second eye |
|-------------------------------------------------|---------|---------|--------------------|
| Visual acuity, logMAR                          | First Eye | Second Eye | Difference/Agreement |
| Median (IQR)                                    | 0.4 (0.1–1.0) | 0.1 (0.0–0.4) | −0.1 (−0.8 to 0) |
| Range                                           | −0.1 to 5.3 | −0.1 to 3.3 | −4.3 to 3.2 |
| Distribution                                    | Absolute difference |
| ≤0.1 (20/25 or better)                          | 61 (35%) | 91 (52%) | <0.3: 72 (41%) |
| >0.1 to ≤0.3                                    | 24 (14%) | 30 (17%) | 0.3–1.0: 58 (33%) |
| >0.3 to ≤0.5                                    | 19 (11%) | 15 (9%) | >1.0: 44 (25%) |
| >0.5 to ≤0.6                                    | 12 (7%) | 8 (5%) | Pearson correlation (95% CI) |
| >0.6 to ≤1.3                                    | 19 (11%) | 19 (11%) | 0.26 (0.12–0.40), R² = 7% |
| >1.3 (CF or worse)                              | 32 (18%) | 11 (6%) | Intraclass correlation (95% CI) |
| Visual field defect                             | Absolute difference |
| None–Minimal (0–0.5)                            | 21 (12%) | 51 (29%) | <0.5: 38 (22%) |
| Mild (>0.5–1.0)                                 | 17 (10%) | 20 (11%) | 0.5–1.0: 79 (45%) |
| Moderate (1.5–2.0)                              | 52 (30%) | 43 (25%) | >1.0: 57 (33%) |
| Marked (2.5–3.0)                                | 56 (32%) | 44 (25%) | Weighted kappa (95% CI) |
| Severe (3.5–4.0)                                | 28 (16%) | 16 (9%) | 0.27 (0.19–0.36) |

IQR, interquartile range; logMAR, logarithm of the minimum angle of resolution.
Pearson correlation between the 2 eyes was 0.26. Although this correlation was statistically significant, this level of agreement was low, with the initial logMAR of the first eye only explaining 7.0% ($R^2$) of the total variation in the initial logMAR of the second eye, indicating that it is not adequate to predict the visual acuity in the second eye based solely on the first eye. Partitioning the variance components of initial logMAR resulted in a much greater within-patient (eyes from same patient) variance component than between-patient (eye from different patients) variance component resulting in a low ICC of 0.19, indicating poor agreement between the paired eyes. For initial visual field defect, the weighted kappa statistic for agreement between the 2 eyes was 0.27, with 95% lower limit of 0.19, indicating fair to poor agreement.

The 174 paired cases were classified into 3 groups based on the treatment received. There were 75 patients (43%) who received steroid therapy for both eyes, 42 (24%) with neither eye treated with steroids, and 57 (33%) with one eye treated with steroids but not the other. These groups did not differ significantly in initial logMAR of the first eye ($P = 0.243$), second eye ($P = 0.347$), and in the initial logMAR difference of paired eyes ($P = 0.329$). There was also no significant difference among the groups in initial visual field defect severity of the first eye ($P = 0.354$), second eye ($P = 0.384$), and in the initial visual field grade difference of paired eyes ($P = 0.296$).

Assessing agreement in final visual acuity and visual field defect in the paired eyes was performed separately for the 2 groups: 1) where both eyes were treated with steroid therapy and 2) where both eyes had no treatment. Those with only one eye treated with steroids and the other not treated were not included in the analysis of final visual acuity and visual fields. For the remaining 2 groups, only paired cases, where both eyes were followed for at least 6 months, $n = 60$ of the 75 with both eyes treated with steroids and $n = 29$ of the 42 with both eyes with no steroid treatment, were used in the assessment of agreement of final visual findings in paired eyes.

Final visual acuity and visual field in the first eye and the second eye by treatment group are presented in Table 3. Comparison of final visual acuity between the first eye and the second eye in those with steroid treatment showed significantly better visual acuity in the second eye ($P = 0.030$). For these patients, there were 38% with logMAR difference of 0.3 or greater between the 2 eyes. For those not treated with steroids, although the median difference in logMAR between the first eye and the second eye was not significantly different from zero ($P = 0.539$), the range of the logMAR differences was wide, from −2.1 to +3.9, with 21% having $>1$ logMAR difference. There were 45% that had 0.3 or greater logMAR difference between the 2 eyes (Table 3).

The plots of final logMAR between the first eye and the second eye are shown in Figure 1B for those with steroid treatment and in Figure 1C for those without steroids. As predictor of the second eye’s final logMAR, the total variation in the second eye that was explained by the first eye final logMAR was 14% in steroid-treated eyes and 27% in
those without steroid treatment. The ICC for both groups was <0.60 with the 95% confidence interval (CI) lower limit of <0.25 (Table 3).

Comparison of the final visual field defect between the first eye and the second eye in the steroid-treated group showed less degree of visual field defect in the second eye ($P = 0.004$). For those not treated, although median difference in final visual field grade between the first eye and the second eye was not significantly different from zero ($P = 0.78$), the visual field grade differed by as much as 3 points, with 21% having a difference of at least 1 (Table 3). The absolute difference in visual field grade at the final follow-up between the first eye and the second eye was at least 0.5 in 70% of those who were treated with steroids and in 76% of those with no steroids. Weighted kappa statistic was <0.5, and 95% CI lower limit was at the level of fair to poor agreement.

### DISCUSSION

Table 1 summarizes the findings of previous studies (1–9) of visual acuity in the first eye and the second eye of patients experiencing bilateral sequential NA-AION. In general, 0.3 logMAR is a clinically significant difference between 2 visual acuities. Using that criterion, of the 9 studies that presented findings on bilateral NA-AION, 3 provided either the percentage of subjects with a difference of at least 0.3 logMAR between eyes or a correlation coefficient for visual acuity between eyes and 3 studies gave a listing of the visual acuity for each pair of eyes for which the difference and the correlation between eyes was calculated. By applying meta-analysis under the random-effects model (17) on the findings from these 6 studies and our study (102/174 with at least 0.3 logMAR difference and correlation of $r = 0.26$ between eyes), a combined estimate for each of these 2

### TABLE 3. Final visual acuity and visual field in the first and second eye by treatment group

<table>
<thead>
<tr>
<th>With steroid treatment</th>
<th>First Eye</th>
<th>Second Eye</th>
<th>Difference/Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual acuity, logMAR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.2 (0.1–0.7)</td>
<td>0.1 (0.0–0.4)</td>
<td>0.0 (–0.3 to 0)</td>
</tr>
<tr>
<td>Range</td>
<td>−0.1 to 3.3</td>
<td>−0.1 to 3.3</td>
<td>−2.9 to 1.1</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Absolute difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0.1 (20/25 or better)</td>
<td>26 (43%)</td>
<td>31 (52%)</td>
<td>&lt;0.3: 37 (62%)</td>
</tr>
<tr>
<td>&gt;0.1 to ≤0.3</td>
<td>10 (17%)</td>
<td>11 (18%)</td>
<td>0.3–1.0: 15 (25%)</td>
</tr>
<tr>
<td>&gt;0.3 to ≤0.5</td>
<td>7 (12%)</td>
<td>12 (20%)</td>
<td>&gt;1.0: 8 (13%)</td>
</tr>
<tr>
<td>&gt;0.5 to ≤0.6</td>
<td>1 (2%)</td>
<td>2 (3%)</td>
<td>Pearson correlation (95% CI)</td>
</tr>
<tr>
<td>&gt;0.6 to ≤1.3</td>
<td>12 (20%)</td>
<td>7 (12%)</td>
<td>0.37 (0.13–0.57), $R^2 = 14$%</td>
</tr>
<tr>
<td>&gt;1.3 (CF or worse)</td>
<td>4 (7%)</td>
<td>2 (3%)</td>
<td>Intracl class correlation (95% CI) 0.46 (0.24–0.64)</td>
</tr>
<tr>
<td><strong>Visual field defect</strong></td>
<td>Absolute difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None–minimal (0–0.5)</td>
<td>11 (18%)</td>
<td>21 (35%)</td>
<td>&lt;0.5: 18 (30%)</td>
</tr>
<tr>
<td>Mild (&gt;0.5–1.0)</td>
<td>6 (10%)</td>
<td>5 (8%)</td>
<td>0.5–1.0: 26 (43%)</td>
</tr>
<tr>
<td>Moderate (1.5–2.0)</td>
<td>17 (28%)</td>
<td>13 (22%)</td>
<td>&gt;1.0: 16 (27%)</td>
</tr>
<tr>
<td>Marked (2.5–3.0)</td>
<td>16 (27%)</td>
<td>18 (30%)</td>
<td>Weighted kappa (95% CI) 0.32 (0.16–0.48)</td>
</tr>
<tr>
<td>Severe (3.5–4.0)</td>
<td>10 (17%)</td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>No treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visual acuity, logMAR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.1 (0.0–0.4)</td>
<td>0.2 (0.0–0.5)</td>
<td>0.0 (–0.1 to 0.1)</td>
</tr>
<tr>
<td>Range</td>
<td>−0.1 to 4.3</td>
<td>−0.1 to 4.3</td>
<td>−2.1 to 3.9</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Absolute difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0.1 (20/25 or better)</td>
<td>16 (55%)</td>
<td>14 (48%)</td>
<td>&lt;0.3: 16 (55%)</td>
</tr>
<tr>
<td>&gt;0.1 to ≤0.3</td>
<td>3 (10%)</td>
<td>5 (17%)</td>
<td>0.3–1.0: 7 (24%)</td>
</tr>
<tr>
<td>&gt;0.3 to ≤0.5</td>
<td>4 (14%)</td>
<td>3 (10%)</td>
<td>&gt;1.0: 6 (21%)</td>
</tr>
<tr>
<td>&gt;0.5 to ≤0.6</td>
<td>2 (7%)</td>
<td>1 (3%)</td>
<td>Pearson correlation (95% CI) 0.52 (0.19–0.74), $R^2 = 27$%</td>
</tr>
<tr>
<td>&gt;0.6 to ≤1.3</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>Intracl class correlation (95% CI) 0.54 (0.22–0.75)</td>
</tr>
<tr>
<td>&gt;1.3 (CF or worse)</td>
<td>3 (10%)</td>
<td>5 (17%)</td>
<td></td>
</tr>
<tr>
<td><strong>Visual field defect</strong></td>
<td>Absolute difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None–minimal (0–0.5)</td>
<td>4 (14%)</td>
<td>8 (28%)</td>
<td>&lt;0.5: 7 (24%)</td>
</tr>
<tr>
<td>Mild (&gt;0.5–1.0)</td>
<td>4 (14%)</td>
<td>2 (7%)</td>
<td>0.5–1.0: 16 (55%)</td>
</tr>
<tr>
<td>Moderate (1.5–2.0)</td>
<td>11 (38%)</td>
<td>5 (17%)</td>
<td>&gt;1.0: 6 (21%)</td>
</tr>
<tr>
<td>Marked (2.5–3.0)</td>
<td>5 (17%)</td>
<td>7 (24%)</td>
<td>Weighted kappa (95% CI) 0.42 (0.21–0.63)</td>
</tr>
<tr>
<td>Severe (3.5–4.0)</td>
<td>5 (17%)</td>
<td>7 (24%)</td>
<td></td>
</tr>
</tbody>
</table>

CF, counting fingers; IQR, interquartile range; logMAR, logarithm of the minimum angle of resolution.
statistics was computed. Overall, 60% (95% CI, 53%–66%) of patients with bilateral NA-AION had a difference of at least 0.3 logMAR between the first eye and the second eye. The correlation of initial visual acuity between the first eye and the second eye was 0.32 (95% CI, 0.24–0.40) or an R² of 10.5% (95% CI, 5.7%–16.4%). This indicates that 89.5% of the variation in the visual acuity in the second eye was not explained by its relation to the visual acuity in the first eye.

The most recent study on the predictability of visual outcome in 86 patients with sequential episodes of NA-AION was by Mercado et al (9). Their conclusions differed from ours, as they reported, “Visual function between fellow eyes showed a fair to moderate correlation that was statistically significant.” This conclusion focused primarily on the P value being <0.05 instead of the size of the correlation. Although this correlation was statistically significant, converting this to R², using the logMAR of the first eye as a predictor of logMAR of the second eye explained only 7.0% of the total variation in the initial visual acuity in the second eye. Their study design also differed from ours with a smaller patient cohort and different method to quantify visual field loss. For example, for evaluating visual field loss, they used the method described by Esterman (18), which we found did not provide satisfactory information about quantitative and qualitative changes in visual fields in a study of 101 eyes (11). In addition, pre-existing medical treatment (e.g., aspirin, corticosteroids, pentoxifylline, or brimonidine tartrate) was not an exclusionary criterion.

Moro et al (7) reported that visual acuity in the second eye of bilateral NA-AION cases was slightly better than that in the first eye. In our study, comparison of both initial and final visual acuity between the first eye and the second eye also showed significantly better visual acuity in the second eye (P < 0.0001 for initial and P = 0.030 for final visual acuity). Comparison of the final visual field defect between the first eye and the second eye showed less degree of visual field defect in the second eye (P = 0.004). The reasons for this observation remain unclear.

In conclusion, in patients with bilateral sequential NA-AION, there are large differences between visual acuity and visual field findings of paired eyes at both the initial and final visits, with 60% having at least 0.3 logMAR difference between eyes. Regression of the logMAR of the second eye with the logMAR of the first eye explained only 10% of the variation in the logMAR of the second eye. Therefore, it is not possible to predict the visual outcome in the second eye based only on the first eye.

REFERENCES
Evaluation of Fixation Pattern and Reading Ability in Patients With Leber Hereditary Optic Neuropathy

Elke K. Altpeter, MD, Björn R. Blanke, MD, Beate Leo-Kottler, MD, Xuan N. Nguyen, MD, Susanne Trauzettel-Klosinski, MD

Background: Leber hereditary optic neuropathy (LHON) is characterized by progressive loss of central vision leading to impaired reading ability. The aim of this study was to evaluate sensory adaptation and reading ability in LHON patients.

Methods: This prospective pilot study included 12 male patients with a clinical diagnosis and a positive genetic analysis of LHON, who matched the inclusion criteria of a central scotoma on visual field testing and the use of magnifying aids to read. Examination included best-corrected visual acuity, magnification need, reading speed, and evaluation of fixation by corneal reflexes and by Rodenstock scanning laser ophthalmoscope (SLO). Central scotoma was assessed by conventional perimetry (Tübingen Automated Perimeter) and microperimetry (NIDEK MP1).

Results: Mean magnification need was 13.2 ± 7.3-fold (range: 2- to 25-fold). Mean reading speed was 53 ± 18 words per minute (WPM) (range: 24–85 WPM). With automated perimetry, all patients showed central scotomas with a mean radius of 13° ± 7° (range: 1°–30°) in the better eye. Microperimetry in all patients showed fenestrated central scotomas. Eccentric fixation with a preferred retinal locus (PRL) was detected with SLO examination and microperimetry correlated well in 11 of 12 patients. The SLO results showed no systematic pattern in the placement of the PRL; however, 7 of 12 patients (58%) placed their PRL in an unfavorable location left or below the fovea. In 8 of 12 patients, fixation was unstable. Between reading speed and central scotoma size, there was a statistically significant negative correlation (P = 0.021, r = –0.65).

Conclusions: The percentage of unfavorable PRL locations was extremely high compared with other disorders with central scotomas. Unstable fixation and fenestrated central scotomas led to difficulties in reading. Early rehabilitation and, if necessary, eccentric viewing training should be considered in LHON patients.

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Leber hereditary optic neuropathy (LHON) leads to profound vision loss with a prevalence of 1:31,000 to 1:50,000 (1,2). Mitochondrial point mutations at positions np11778G>A, np3460G>A, and np14484T>C account for most cases (3–5).

Despite intense research, no proven therapy for LHON is available. The central visual field loss leads to reading disability at an early stage (6–8), with profound impact on quality of life and independent living (9). Visual rehabilitation with magnifying aids is very important for these patients to continue their education and their ability to work (10).

The aim of this pilot study was to evaluate the sensory adaptation of LHON patients to their acquired central visual field loss in regard to reading performance.

METHODS

Patients
Thirty-one LHON patients with perimetrically verifiable central scotomas and reading with magnifying aids (optical or electronic) were identified, of whom 12 agreed to participate in our prospective study. All had been using individually optimized low vision aids. The Ethics Committee of the Medical Faculty, University of Tübingen, Germany, approved this study. Informed consent was obtained from all patients. All procedures complied with the tenets of the Declaration of Helsinki.

Clinical Examination
All patients underwent an ophthalmological examination testing, including best-corrected distance visual acuity (Early
Treatment Diabetic Retinopathy Study chart), magnification need (assessed as critical print size by the Zeiss chart at 25 cm), and reading speed (IReST cards = International Reading Speed Texts) (11) with the individual magnifying aid (the magnifying aid was provided according magnification need of critical print size).

We performed conventional perimetry (Tübingen Automated Perimeter 30°) and microperimetry with the NIDEK MP1 (Nidek, Padua, Italy). The MP1 provides automated full-threshold perimetry with fundus tracking to correct for eye movements.

Microperimetry and examination by scanning laser ophthalmoscope (SLO) fixation behavior were always assessed monocularly. To assess fixation behavior binocularly, the location of corneal reflexes was measured by an orthoptic examination, the “Hirschberg” test (12). One millimeter decentration of the corneal reflex equated to 7° deviation of gaze.

**Examination by Scanning Laser Ophthalmoscope and Preferred Retinal Locus**

Patients with an absolute central scotoma fixate eccentrically. This eccentric area is called “preferred retinal locus” (PRL) (13) and becomes the new sensory and oculomotor “center” (14). The same PRL may be used for reading but can also be located elsewhere depending on the reading visual field (15). The location of the PRL was identified by SLO (SLO 101; Rodenstock Instruments, Munich, Germany). From the PRL in the SLO image of the retina, we determined the equivalent location of the PRL in the visual field. For example, fixation above the fovea detected with the SLO corresponds to a fixation locus (FL) below the scotoma in the visual field.

Using the SLO, patients fixated on a central cross (36 arc minutes in diameter) with the better eye were recorded on videotape. The better eye was defined as the eye with the lower magnification need. Fixation stability was assessed semiquantitatively by tracking a retinal blood vessel on the SLO image for 15 seconds on an overhead transparency by a text marker. The quality of the SLO images was not sufficient for a quantitative analysis at the time of this study. The size of the fixation area was measured semiquantitatively in relation to the size of the optic disc.

**Statistical Analysis**

We calculated the means, standard deviations, and ranges from the individual values. Correlations between reading speed and scotoma size were calculated using Pearson correlation coefficient. P-values < 0.05 were regarded as indicators of statistical significance. Statistical analysis was performed using “R,” an open source programming language for statistical computing, version 2.15.1 (http://www.revolutionanalytics.com/).

**RESULTS**

Mean age of our patient cohort at the time of examination was 41 years (range: 20–70 years). Mean duration since onset of disease was 18 years (range: 2–44 years). Seven patients had the mutation np17778G>A, 4 patients np3460G>A, and 1 patient np14484T>C. Mean best-corrected distance visual acuity with the better eye was 1.38 logarithm of the minimum angle of resolution (range: 0.5–2.0 logarithm of the minimum angle of resolution; range in Snellen range: 20/40 to 20/200). Mean magnification required by our patients was 13.2-fold (range: 2 - to 25-fold). Mean reading speed was 53 ± 18 words per minute (WPM) (range: 24–85 WPM). Ten patients used an electronic magnifying device, and 2 patients used magnifying spectacles. In testing binocular ocular alignment by corneal reflexes, 4 patients showed fixation of 5° to 15° upgaze, 6 patients had near central fixation, and 2 patients fixated in 5° to 15° downgaze.

Clinical findings are summarized in Table 1 and an illustrative case is presented in Figure 1.

**Evaluation of Central Scotomas**

Using automated perimetry, all patients showed absolute central scotomas. In the better eye, mean radius of the central

<p>| Table 1. Summary of clinical findings in patients with Leber hereditary optic neuropathy |
|---------------------------------|-------------|--------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Visual Acuity (LogMAR)</th>
<th>Magnification Need</th>
<th>Magnifying Aid</th>
<th>Reading Speed (WPM)</th>
<th>Scotoma Radius (TAP30°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.7</td>
<td>12.5</td>
<td>em</td>
<td>56</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>16.0</td>
<td>em</td>
<td>85</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>25.0</td>
<td>em</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>6.25</td>
<td>em</td>
<td>46</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>6.25</td>
<td>em</td>
<td>56</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>8.0</td>
<td>em</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>20.0</td>
<td>em</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>1.7</td>
<td>20.0</td>
<td>em</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>1.4</td>
<td>16.0</td>
<td>em</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>1.6</td>
<td>20.0</td>
<td>em</td>
<td>46</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>0.5</td>
<td>2.0</td>
<td>ms</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>1.0</td>
<td>6.25</td>
<td>ms</td>
<td>63</td>
<td>10</td>
</tr>
</tbody>
</table>

em, electronic magnifier; logMAR, logarithm of the minimum angle of resolution; ms, magnifying spectacles; TAP, Tübingen Automated Perimeter; WPM, words per minute.

scotoma was 13° ± 7° (range: 1°–30°). All microperimetry results with the NIDEK MP1 showed a fenestrated central scotoma, that is the central scotoma was not completely dense, but there were tiny “holes” or “isles” in the scotoma with better retinal function (16, 17).

**Fixation Behavior Analyzed by SLO and MP1 Microperimetry**

**Fixation Locus**

During fixation of a central cross with the better eye, the SLO showed the PRL above or diagonally above the fovea in 4 eyes (i.e., fixation was below the central scotoma in the visual field), and in right of the fovea in 1 eye. A PRL right of the scotoma is less favorable than left because it is not in the direction of reading. In 4 eyes, the PRL was left of the fovea/central scotoma, and in 3 eyes, the PRLs lay below or diagonally below the fovea (i.e., above the central scotoma in the visual field). The remaining 7 eyes (58%) showed an unfavorable PRL for reading located below and left of the fovea.

Eleven patients showed correspondence between the FL in MP1 microperimetry and in the SLO. The PRL in the SLO was different from the PRL in microperimetry in only Patient 8. In 7 of 12 patients, the monocular fixation behavior in the better eye using the SLO matched the fixation behavior detected with the binocular orthoptic examination. It did not match for patients 3, 7, 8, 10, and 12.

**Fixation Stability**

In 8 of 12 patients, fixation was very unstable with large fixation areas (Fig. 2).
Reading Speed

There was a statistically significant negative correlation (Pearson product-moment) between reading speed and the size of the central scotoma determined with automated perimetry, that is, the larger the scotoma, the lower the reading speed (correlation coefficient $r = -0.65$, df = 10, $P = 0.021$). Patients with a reading speed below 50 WPM showed an unfavorable PRL and/or high magnification requirements.

DISCUSSION

This is the first systematic study examining fixation behavior and reading speed in patients with LHON. Our finding of fenestrated scotomas in patients with LHON is consistent with previous reports (16,17). In all 12 patients, we demonstrated that the PRL was located within the scotoma. The fenestrations were too small for reading, not meeting the minimum size of 2° to the left and right of fixation (10,18,19). Additionally, the size of the central scotoma in our patients was quite large with a mean radius of 13° ± 7°. Therefore, our patients had very high magnification needs and very poor reading speed. This resulted in a negative correlation between scotoma size and reading speed.

In our LHON patients, our findings of an average magnification need of 13.2-fold and an average reading speed of 53 WPM are comparable with patients with large central scotomas due to advanced age-related macular degeneration. In a study of 298 patients with advanced...
AMD, if magnification need was more than 6-fold, their reading speed using standardized texts (IReST) was poor at 46 ± 20 WPM (20).

We used both SLO and microperimetry to examine each patient’s PRL. We found good correlation of these 2 methods, which is in agreement with other studies (21,22).

Some patients choose a PRL location that is favorable for orientation and reading and some choose an unfavorable one. Besides the topography of the central scotoma, additional factors play a role, including focal sustained attention (23). A variety of reports have examined PRL distribution in different locations in patients with central scotomas. These scotomas arise from a variety of causes, including AMD and macular dystrophies. In most cases (39%-76%), the central scotoma is located above the FL, that is, the scotoma is shifted upward, optimal for daily tasks of living, especially reading. In 16% to 34% of cases, fixation was left of the fovea, that is, the central scotoma is on the right side of the FL (i.e., the scotoma is shifted to the right, in the reading direction); in 5% to 19.9% of cases, it was shifted to the left, and in 2.5% to 7.5% of cases, it was shifted downwards (24-27). A scotoma below the FL will lead to difficulties with walking and reading. Fixation left of the fovea means shifting the scotoma in the reading direction (i.e., left to right). Our LHON patients often chose an unfavorable PRL location: 3 below the fovea and 4 left of the fovea. The unfavorable location of the PRL coupled with unstable fixation and fenestrated central scotomas all contributed to difficulty reading.

Limitations of our study include small sample size and use of Zeiss charts to determine critical print size. These charts have yet to be validated for establishing critical print size. Another limitation is long duration of vision impairment in most of our patients, which likely resulted in long established PRLs. Possibly early intervention with low vision services combined with eccentric reading training in LHON patients will lead to improvement in both reading speed and quality of life.

REFERENCES


First Cases of Dominant Optic Atrophy in Saudi Arabia: Report of Two Novel OPA1 Mutations

Alberto Galvez-Ruiz, PhD, Christine Neuhaus, PhD, Carsten Bergmann, PhD, Hanno Bolz, PhD

Background: Fifty to 60% of patients with dominant optic atrophy (DOA) have mutations of the OPA1 gene, which encodes dynamin-related GTPase, a protein of the internal mitochondrial membrane. To date, more than 200 OPA1 mutations in the OPA1 gene have been described. However, DOA is genetically heterogeneous with certain families linked to other chromosomal loci, that is, OPA3, OPA4, OPA5, and OPA7.

Methods: This study describes a clinical series of 40 patients from Saudi Arabia with a positive DOA phenotype (i.e., decreased visual acuity during the first 2 decades of life, temporal or global optic disc pallor, and absence of other neurological or ophthalmological diseases that could explain the optic neuropathy) who underwent molecular genetic testing for OPA1 (and, in some cases, for OPA3).

Results: This study describes for the first time 4 OPA1 mutations in DOA patients from Saudi Arabia, including 2 novel OPA1 mutations in 2 different patients.

Conclusion: The question remains whether certain patients in Saudi Arabia with a clearly defined DOA phenotype may be due to mutations in chromosomal loci other than OPA1 and OPA3. It is likely that genetic alterations associated with different loci will be discovered in the future.

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The hereditary optic neuropathies most frequently described in the scientific literature are Leber hereditary optic neuropathy (LHON) and dominant optic atrophy (DOA), both resulting from mitochondrial disorders (1). Mitochondrial diseases may be caused either by mutations of the mitochondrial DNA (mtDNA), as in LHON, or by mutations of nuclear genes encoding proteins of the mitochondrion. For example, the major DOA gene, OPA1, is part of the nuclear genome, and OPA1-related DOA is inherited in a Mendelian fashion, as an autosomal dominant trait (1–3).

The majority of OPA1 mutations (up to 50%) are truncated, predicting either shortened OPA1 protein or haploinsufficiency because of nonsense-mediated decay of the mutant transcript. However, missense mutations preserving OPA1 protein have been described (1,3). These mutations affect the stability of mitochondria and the function of the mitochondrial respiratory chain (4,5).

Clinically, DOA manifests as a progressive loss of visual acuity (VA) that begins in the first 2 decades of life with temporal pallor of the optic discs and cecocentral scotomas on visual field testing. The extent of VA deterioration does not tend to be as pronounced as in LHON patients; however, there is a significant phenotypic overlap between DOA and LHON (1,6–8).

In addition, a “DOA plus” phenotype has been reported, which includes deafness, ataxia, myopathy, and peripheral neuropathy (1,9). This suggests that clinical expressivity of OPA1 mutations is variable and other cell groups may be affected.

In this study, we report the results of clinical and molecular evaluation in a series of 40 DOA patients from Saudi Arabia.

MATERIALS AND METHODS

Patients

Forty patients from different regions of Saudi Arabia were referred to a tertiary care center (King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia) between 2010 and 2012 evaluation of optic neuropathy present in the first 2 decades of life. Inclusion criteria were as follows: VA decrease in the first 2 decades of life, temporal or diffuse pallor of the optic disc, and absence of other neurological
and ophthalmological diseases that could explain the optic neuropathy (e.g., demyelinating disease, perinatal hypoxia, previous trauma). Patients with nystagmus and strabismus were included. Although the autosomal dominant inheritance of OPA1-related DOA often implies a multigenerational pedigree, patients with DOA phenotype, but without family history of VA loss, also were enrolled. Medical and family history was recorded for all patients; however, in some patients, these data could not be reliably obtained.

All patients were evaluated in the Division of Neuro-Ophthalmology by the same neuro-ophthalmologist (A.G.-R.) with the following tests: VA, color vision (Ishihara color plates), kinetic visual fields (KVF), (if the patient’s age allowed for adequate cooperation). In addition, patients underwent neurological examination and magnetic resonance imaging (MRI) of the brain and orbits. The research protocol had been approved by the locally appointed ethics committee (King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia) and informed consent was obtained from subjects (or their guardians).

Genetic Analysis

A blood sample from all 40 patients was used for genetic testing for OPA1, whereas OPA3 was analyzed in 23 patients. The 30 coding exons and the exon–intron boundaries of OPA1 on chromosome 3q28-29 (OMIM 605290) were amplified by polymerase chain reaction (PCR) and sequenced directly. The resulting sequence data were compared with the reference sequence NM_130837.2.

We also conducted a deletion analysis of OPA1 (OMIM 605290) with the material obtained by multiplex ligation-dependent probe amplification (MLPA); kit: SALSA MLPA P229-B1 OPA1 (10). All coding exons of OPA1 and the adjacent regions were screened for deletions/duplications.

To identify OPA3 mutations, the 2 coding exons and the exon–intron boundaries of the OPA3 gene on chromosome 19q13.32 (OMIM 606580) were amplified by PCR and sequenced directly. The resulting sequence data were compared with the reference sequence NM_025136.3.

Additionally, given the clinical overlap between patients with DOA and LHON, the 3 most frequent genetic LHON mutations at mtDNA positions 11,778, 3460, and 14,484 were excluded in all patients. For these analyses, mtDNA was obtained from peripheral blood leukocytes. Portions of the ND-4, ND-1, and ND-6 genes were amplified using the PCR-based amplification-refractory mutation system.

RESULTS

Our case series consisted of 40 patients, 27 men (67.5%) and 13 women (32.5%), with a mean age of 22.35 years (range, 7–55 years). Sixteen patients (40%) had a positive family history of optic nerve disease and 25 (62.5%) had consanguineous parents.

VA ranged from 20/20 to 20/400 (mean: 20/160). Using Ishihara color plates, color vision ranged from 0/15 to 15/15 plates read correctly (mean: 6/15). Twenty-seven patients had temporal optic disc pallor and 13 (32.5%) had diffuse pallor. On KVF testing, most patients exhibited cecocentral scotomas (50%) followed by arcuate defects (12.5%) and generalized decreased sensitivity (12.5%), and 10% had normal visual fields.

Nine patients (22.5%) presented with strabismus and/or nystagmus. The range of eye movements was normal in all these patients, and nystagmus was horizontal and pendular.

Six patients (15%) had hearing loss or unsteady gait (DOA plus syndrome), and 38 patients (95%) showed no disease progression during the 2 years of follow-up.

Genetic tests for OPA1 and LHON were conducted for all patients while OPA3 was analyzed in 23 patients. No LHON or OPA3 mutations were identified. Four patients (10%) were identified with mutations in OPA1.

Case Reports

Case 1

A 12-year-old girl was referred to neuro-ophthalmology because of mild, bilateral optic disc pallor. The patient was asymptomatic and family history was unremarkable. Her parents were distantly related (no first-degree consanguinity). VA was 20/30, right eye, and 20/25, left eye and the patient was able to identify 12 of 15 color plates with the right eye and 11 of 15 with the left eye. Minimal temporal pallor of the optic discs was detected on funduscopy (Fig. 1). KVF and brain MRI were within normal limits.

An OPA1 gene sequence analysis was performed that revealed the heterozygous mutation c.852T>A, substituting the codon for tyrosine by a stop codon at position 284 (p.Tyr284X). This nonsense mutation either results in messenger RNA degradation (nonsense-mediated decay) or in a truncation of the OPA1 protein.

Case 2

A 17-year-old adolescent boy had a history of bilateral progressive VA loss since early childhood. There was no family history of ophthalmic or neurologic disease. VA was 20/80, right eye, and 20/60 left eye, and the patient could identify 9 of 15 color plates with each eye. There was temporal pallor of both optic nerves (Fig. 1). KVF and brain and orbital MRI were unremarkable.

OPA1 gene sequencing revealed the heterozygous mutation c.1099C>T, substituting the codon for arginine by a stop codon at position 367 (p.Arg367X). This nonsense mutation results in nonsense-mediate decay or in a truncation of the OPA1 protein and can be regarded pathogenic.

Case 3

A 13-year-old boy presented with a history of bilateral visual loss beginning early in life. There was no significant family history of eye disease, but there was consanguinity between his parents, although not of first degree. VA was 20/100 bilaterally and he was able to see 1 of 15 color plates with the right eye and 4 of 15 with the left eye. The patient had a comitant esotropia of 10 prism diopters and full extraocular...
FIG. 1. The optic discs show temporal pallor in the 4 Saudi patients found to have OPA1 gene mutations.
movements. Funduscopy revealed temporal pallor of both optic nerves (Fig. 1). KVF testing showed a cecocentral scotoma in both eyes and an increase in the blind spot in the left eye. Brain and orbital MRI were normal.

OPA1 sequencing detected a heterozygous A to T substitution at position c.949-2A>T (IVS9-2A>T) in intron 9 of the OPA1 gene, affecting the invariant acceptor splice site consensus of exon 10. The novel splice site was subjected to different splice site prediction tools. The wild-type acceptor site was not recognized in NNSplice and Netgene2, which is not unusual especially for acceptor sites. However, the wild-type sequence obtained a score of 7.92 in MaxEnt (reference PMID: 15285897), whereas the mutant sequence was not recognized, supporting the assumption that the mutation should impair splicing.

Case 4 A 35-year-old woman reported progressive visual loss over the past 10 years. She had a sister with decreased vision. There was no consanguinity between her parents. VA was 20/125, right eye, and 20/100, left eye. On the Ishihara test, she was able to distinguish 7 of 15 plates with the right eye and 5 of 15 plates with the left eye. Funduscopy revealed mild temporal pallor of both optic nerves (Fig. 1). KVF examination showed global loss of sensitivity in both eyes, and MRI evaluation was unremarkable.

Analysis of OPA1 revealed the heterozygous mutation c.1313A>T, which results in a substitution of asparagine by valine at position 438 (p.Asp438Val). This missense mutation has been described previously (11) and likely results in functional null alleles.

In none of the patients was a deletion or duplication in the OPA1 gene found. To the best of our knowledge, c.882T>A (Case 1) and C.949-2A>T (IVS9-2A>T) (Case 3) mutations of the OPA1 gene have not been reported previously.

DISCUSSION

To the best of our knowledge, this study presents the first DOA cases with OPA1 mutations in Saudi Arabia. Two patients had a nonsense mutation (1 of them with a novel mutation), 1 a missense mutation, and 1 had a novel splice site mutation.

LHON testing was negative in all our patients, and none who were analyzed for alterations in OPA1 carried a mutation in this gene. It seems that OPA3 mutations are a rare cause of DOA. But we are cautious about this conclusion because MLPA analysis was not carried out and large-scale OPA3 gene rearrangements cannot be fully excluded.

Our study is not the first attempt to identify OPA1 mutations in Saudi patients. In 2008, Bosley et al (12) published a report of patients from Saudi Arabia with sporadic bilateral optic neuropathy in infancy. The authors enrolled 21 patients and 159 control subjects and evaluated the evidence for mitochondrial disease, including direct sequencing tests for OPA1 and OPA3. Their inclusion criteria consisted of bilateral decrease in VA since infancy, a lack of family history (i.e., only sporadic cases), and lack of clinical or any underlying etiologies that could explain optic atrophy. They failed to detect any cases with OPA1 or OPA3 genes. The authors found 1 patient who tested positive for LHON (11,778) and 3 additional patients with mutations that could be pathological for LHON.

In contrast, we included 11 patients with a family history of optic nerve disease. However, of the 4 patients with a positive OPA1 test, all except 1 were sporadic. Therefore, it is unlikely that the lack of OPA1 mutations in the report by Bosley et al (12) was because of the inclusion of only sporadic patients.

A study by Yu-Wai-Man et al (13) highlighted that having a family history increased the positivity of the OPA1/OPA3 test. In their series of 188 patients, the overall detection of OPA1 was 14.4%, but detection of OPA1 gene mutations was up to 50% among patients with a positive family history.

Considering the high rates of consanguinity in Saudi Arabia, the low proportion of patients with a family history (27.5%) is surprising. We propose 3 possible explanations. First, given the high rate of consanguinity, a large proportion of patients with inherited optic nerve disease, especially the sporadic cases, were due to autosomal recessive transmission. Second, it was often difficult to establish the presence or lack of a family history. Many individuals were from remote regions of the country and were poorly informed about the causes of reduced vision in family members. Third, our hospital is a referral center for the entire country and some patients had to travel great distances. This made it difficult to examine and conduct genetic studies in family members.

Regarding the presence of the DOA plus phenotype in our series, we found only 5 patients with hypoacusis and gait instability, and all of them had negative results for OPA1. This group represents 12.5% of patients with DOA in our series and is lower than in multicenter studies that have reported a prevalence of 20% (13,14). This may be due to our small sample size or that the clinical manifestations of OPA1 mutations in Saudi Arabia differ from those detected elsewhere.

Currently, several genetic screening or sequencing methods, such as polymerase chain reaction and or single-strand conformational polymorphism analyses, are available (3,13). In addition, methods are available that can detect large-scale rearrangements, such as comparative genomic hybridization microarray technology and MLPA. One drawback of screening methods is that they overlook large-scale rearrangements that could cause up to 20% of all OPA1 cases (3,13,15). In the study by Yu-Wai-Man et al (13), the application of methods for detecting both point mutations and large-scale rearrangements in a large series of probands with possible DOA did not increase the detection rate. The authors concluded that given the high cost of rearrangement detection techniques, these assays should be reserved for patients with a positive family history. Yu-Wai-Man et al (13) recognized that false negatives cannot be completely excluded even when using rearrangement detection techniques.

DOA has great genetic heterogeneity. To date, it has been associated with 5 chromosomal loci (OPA1, OPA3,
OPA4, OPA5, and OPA7), yet the causative genes have only been found for OPA1 and OPA3. It is likely that genetic alterations associated with different loci will be discovered in the future, including in the Saudi population.

Not only is there extensive genetic heterogeneity of DOA but also large variability of its clinical expression (16–18). As genetic tests for OPA1 become more affordable, the reports of disease mechanisms and therapeutic strategies. The neuro-ophtalmology of mitochondrial disease, Surv Ophthalmol. 2010;55:299–334.

References

Subretinal Abscess Causing Restricted Diffusion on Magnetic Resonance Imaging

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Background: Restricted diffusion of water molecules on diffusion-weighted magnetic resonance imaging most commonly associated with acute stroke, has also been described in brain abscess. It has been reported in only one case of sub-retinal abscess.

Methods: Review of two cases.

Results: Two cases of visual loss from subretinal abscess had restricted diffusion in the region of the abscess. In the first case, DWI revealed restricted diffusion in a white mass visible in the posterior retina. In the second case, restricted diffusion was present in an anterior retinal mass invisible by ophthalmoscopy and ultrasound. In combination of restricted diffusion in the cerebrum consistent with septic emboli, these imaging abnormalities allowed earlier treatment that either preserved vision or prevented enucleation.

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Diffusion-weighted imaging (DWI) is a magnetic resonance imaging (MRI) pulse sequence based on the movement of water molecules within brain parenchyma. DWI assigns an apparent diffusion coefficient (ADC) to biological tissues (1). When the extracellular diffusion of water via Brownian motion is impeded by edema, restricted diffusion is seen on DWI (2–8).

Most commonly found in acute ischemic infarction, restricted diffusion also has been noted in intracranial neoplastic conditions (lymphoma, meningioma, epidermoid) (1,2) and inflammatory disorders (abscess, empyema, acute demyelinating plaques) (3). In head and neck cancer, DWI has been applied to differentiate benign from malignant tumors, discriminate between recurrent tumors and post-therapeutic changes, and detect lymph node metastasis for staging purposes (4). In spine and spinal cord disease, DWI aids in distinction of acute demyelination from infarction and trauma, and helps to identify extradural osseous lesions (5). In orbital disease, DWI has been used to demonstrate ischemic and infiltrating optic neuropathies (6), endophthalmitis (7), and thrombosis of the superior ophthalmic vein (8).

Only 1 case of restricted diffusion has been reported in a case of subretinal abscess (9). We describe 2 additional cases to emphasize the diagnostic value of DWI in this unusual setting.

CASE REPORTS

Case 1
A 16-year-old boy presented with pain and blurred vision in the right eye of 1-day’s duration. For the previous 10 days, he had experienced fever, generalized weakness, cough, joint pain, and headaches that were attributed to mononucleosis based on a positive Monospot test. He had received nebulizer treatment, ketorolac, and intravenous fluids.

Examination disclosed that visual acuity was hand movements in the right eye and 20/20 in the left eye. There were no ocular adnexal abnormalities or tenderness to palpation. The right pupil measured 4 mm and the left pupil measured 2 mm in dim illumination, and there was a right relative afferent pupillary defect. Ocular ductions were full and the eyes were aligned. The visual field was unobtainable in the right eye due to poor visual acuity and full to finger counting in the left eye. Slit-lamp biomicroscopy and intraocular pressures were normal in both eyes. In the right eye, ophthalmoscopy revealed a large (3 disc diameters horizontally by 4 disc diameters vertically), yellow-white, round subretinal lesion with indistinct margins. In the left eye, there was a smaller (1/2 disc diameter) subretinal fluid collection nasal to the optic disc. Fundus photography was not performed at that time.
MRI of the brain and orbits was performed on a 1.5 T magnet (Siemens Medical Systems, Enlargen, Germany) using an 8-channel head coil. Diffusion imaging data were obtained using an echo-planar single-shot technique with the shortest TR, 89 ms TE, and a 90° flip angle, and with a b value of 1,000 seconds/mm². The data were recorded on a 128×128 matrix and were zero filled for a final resolution of 128×256. Axial slices with 5-mm slice thickness and a 0.5-mm interslice gap were obtained.

Diffusion-weighted imaging (DWI) revealed a small nodular abnormality in the posterior aspect of the right globe that exhibited restricted diffusion (Fig. 1). In addition, multiple foci of restricted diffusion were visualized in both cerebral and cerebellar hemispheres in cortical, subcortical, and periventricular locations (Fig. 2A). Most of these foci exhibited dark signal on the corresponding ADC maps, confirming that the DWI signal reflected true areas of restricted diffusion without any T2 effect (Fig. 2B). Susceptibility sequences demonstrated punctate hemorrhagic components within some of the brain lesions. After contrast administration, many of the lesions demonstrated peripheral enhancement (Fig. 2C). The brain findings were interpreted as septic infarctions and the retinal abnormality as an abscess.

Transesophageal echocardiography revealed a small thrombus in a right pulmonary vein at its junction with the left atrium. Additional imaging showed numerous embolic foci involving the lungs, liver, kidneys, and left hip. Methicillin-sensitive Staphylococcus aureus (MSSA) was cultured from the blood, left hip joint, right hand skin lesion, and pericardial fluid.

The patient was treated with intravenous rifampin, nafcillin, and gentamicin for MSSA bacteremia. On hospital day 4, the subretinal abscess appeared to extend beyond the plane of the retina into the vitreous cavity (Fig. 3), so the patient underwent a vitreous aspiration for culture, followed by intravitreal injection of vancomycin and ceftazidime. Culture of vitreous fluid revealed no growth of microorganisms.

**FIG. 1.** Case 1. Subretinal abscess attributed to methicillin-sensitive Staphylococcus aureus. A. T2 axial magnetic resonance imaging (MRI) shows an area of low signal (arrow) in the right posterior subretinal space. B. Diffusion-weighted MRI shows a corresponding area of high signal (arrow). C. Apparent diffusion coefficient MRI shows corresponding dark signal (arrow), indicating restricted diffusion.

**FIG. 2.** Case 1. Septic brain infarctions. A. Diffusion-weighted magnetic resonance imaging (MRI) shows areas of restricted diffusion in both cerebral hemispheres. B. Apparent diffusion coefficient MRI shows corresponding areas of dark signal, indicating restricted diffusion. C. Postcontrast T1 axial magnetic resonance imaging demonstrates ring enhancement of the cerebral lesions.
On hospital day 7, the patient underwent open heart surgery for removal of a right pulmonary vein vegetation. Mild noncompaction of the left ventricular apex in the setting of heavily trabeculated endocardium was cited as the likely etiology of thrombus formation. Blood cultures remained negative for MSSA following thrombectomy. The size and elevation of the right fundus lesion began to decrease following a second vitreous injection of vancomycin in the right eye on hospital day 9.

One month following presentation, the patient’s visual acuity had improved to 20/200 in the right eye and remained 20/20 in the left eye. There was a persistent right relative afferent pupillary defect but no anisocoria. Ocular ductions and alignment remained normal. Visual field testing showed a supronasal defect to finger counting on the right eye and remained full on the left eye. Ophthalmoscopy of the right eye showed gliosis and retinal pigment epithelial atrophy, and the lesion in the left eye also appeared atrophic with resolution of subretinal fluid.

Case 2
A 62-year-old woman with necrotizing pancreatitis complicated by multiple enterocutaneous fistulas presented with headache, altered mental status, and abdominal pain. She had awakened the previous night with a severe frontal headache and fever. Brain computed tomography (CT) suggested multifocal abscesses in the right cerebral hemisphere.

Ophthalmologic consultation was requested to evaluate chemosis and periorbital swelling of the right eye. Complicated by depressed mental status, examination disclosed visual acuity of finger counting in both eyes. There was swelling of the right upper and lower eyelids with minimal erythema. The right pupil measured 3 mm and the left pupil measured 5 mm in dim illumination, and there was a right relative afferent pupillary defect. Ocular ductions and visual field testing were unobtainable given the patient’s mental status. Slit-lamp biomicroscopy revealed chemosis temporally in the right eye and was normal in the left eye. Intraocular pressures were normal in both eyes. In the right eye, ophthalmoscopy revealed dense vitritis with no view to the posterior pole. In the left eye, ophthalmoscopy was normal. B-scan ultrasonography of the right eye showed dense vitreous membranes.

Brain MRI revealed a prominent area of restricted diffusion in the region of the far anterior retina of the right eye.
eye (Fig. 4). In addition, at least 3 lesions were identified in the right cerebral hemisphere with a peripheral rim of restricted diffusion (Fig. 5A). These foci exhibited dark signal on the corresponding ADC maps (Fig. 5B), confirming that the DWI high signal reflected restricted diffusion. The brain findings were interpreted as septic emboli and the retinal abnormality as an abscess. Vitreous aspiration for culture was negative. A Bacillus species (not anthraxis or cereus) was cultured from the patient’s blood. She was treated with intravenous vancomycin, cefepime, and metronidazole, intravitreal vancomycin and ceftazidime, and topical moxifloxacin, prednisolone acetate, and atropine.

A transesophageal echocardiogram was negative for valvular vegetations, and imaging of the abdomen showed no evidence of an abscess as the source of the patient’s bacteremia. The enterocutaneous fistulas were considered the probable source of the retinal and cerebral abscesses.

Despite treatment, repeat MRI of the brain and orbits on hospital day 4 revealed interval enlargement of the areas of restricted diffusion in the brain and subretinal abscesses. Intravenous voriconazole and levofloxacin were added to the treatment regimen. A repeat vitreal injection was performed with vancomycin and voriconazole.

The patient underwent stereotactic biopsy and drainage of the most anterior brain abscess, which revealed purulent material but demonstrated no growth on culture.

One month following admission, the patient’s visual acuity remained hand motions in the right eye. A view of the posterior pole continued to be obstructed by fibrin, although repeat B-scan ultrasonography showed interval clearing of the vitreous space. At this point, she was deemed neurologically stable and discharged to a long-term care facility for ongoing antibiotic treatment.


DISCUSSION

We report the finding of restricted diffusion on DWI in 2 cases of subretinal abscess. The only previously reported case concerned a 41-year-old woman in whom DWI showed restricted diffusion in the subretinal space, and Gram stain of purulent subretinal fluid from the enucleated globe revealed filamentous gram-positive bacteria consistent with Nocardia (9).

Our cases differ from the previously reported case in that the restricted diffusion in the subretinal space was apparent on DWI at an earlier stage in the disease process. Based on a correlation of the ophthalmoscopic and imaging findings in the retina and brain, a presumptive diagnosis of abscess could be made promptly. In the first case, intensive treatment allowed preservation of useful vision, as has been described in subretinal abscess caused by S. aureus (10) and Aspergillus (11). Early diagnosis is critical, as subretinal abscess caused by other organisms such as Nocardia asteroides (12) tends to respond poorly to antibiotics. In our second case, DWI identified an anteriorly located abscess that could not be visualized on ophthalmoscopy or B-scan ultrasonography. Although the visual outcome in the second patient was poor, prompt treatment spared the patient loss of the eye.

Subretinal abscess is a rare presentation of endogenous endophthalmitis, with Nocardia species being the most commonly reported organism (11). Risk factors include endocarditis or structural cardiac abnormality, immunosuppression, and intravenous drug use (10). Differentiating between bacterial or fungal infection and a sterile or viral uveitis may be complicated by the low sensitivity of vitreous culture and an often poor view to the fundus in the setting of vitritis. As our patients lacked typical features of endophthalmitis (hypopyon, vitritis), the imaging findings were particularly helpful.
REFERENCES


Post-traumatic Amaurosis Secondary to Paraophthalmic Internal Carotid Artery Pseudoaneurysm Treated With Pipeline Embolization Device

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Abstract: During evaluation for monocular visual loss, a 48-year-old woman was found to have a posttraumatic paraophthalmic internal carotid artery (ICA) pseudoaneurysm. She underwent reconstruction of the ophthalmic segment of the right ICA with a Pipeline embolization device but her vision did not return.

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A 48-year-old African American woman with a history of hypertension and a 15 pack-year smoking history experienced an acute onset of visual loss in the right eye and retrobulbar pain 20 minutes after striking her right temple against a bed post. Review of systems was otherwise negative. She drove herself to an emergency room where computed tomography (CT) of the brain was normal and magnetic resonance imaging demonstrated mild induration of the intraconal fat and subtle enhancement of the optic nerve. She was instructed to see a neurologist as an outpatient, and 2 days later, her vision spontaneously returned to baseline.

Two weeks later, the patient again acutely lost vision in her right eye and was admitted to a hospital where a temporal artery biopsy was negative. She was transferred to our facility and neurological examination was normal except for loss of vision in the right eye. Visual acuity was light perception, right eye, and 20/30, left eye. Pupillary examination revealed a right relative afferent pupillary defect. Intraocular pressure was normal in both eyes as was the left visual field. The right fundus revealed splinter hemorrhages, segmental arteriolar narrowing, optic disc pallor, and macular ischemia with a prominent cherry red spot in the macula (Fig. 1). The left fundus was unremarkable. Fluorescein angiography demonstrated delayed choroidal and optic disc perfusion in the right eye (Fig. 2). The constellation of clinical findings were consistent with a right ophthalmic artery occlusion. Within a few days, vision in the right eye was no light perception.
Laboratory workup yielded normal results for erythrocyte sedimentation rate, anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, and cytoplasmic antinuclear cytoplasmic antibody, vitamin B12 and folate, rapid plasma reagin, thyroid function, lipid profile, liver function studies, and hypercoaguable panel. Transthoracic echocardiogram, electrocardiogram, and carotid Doppler failed to reveal a source of thromboemboli. Magnetic resonance angiogram (MRA) and magnetic resonance venogram were normal as was cerebrospinal fluid analysis. Cerebral angiography demonstrated nonvisualization of the origin of the right ophthalmic artery from the right internal carotid artery (ICA) with distal refilling of the ophthalmic artery via flow from the meningolacrimal branch of the right middle meningeal artery. In addition, there was a 1.73 × 1.75 mm irregular dilation of the ophthalmic segment of the right ICA associated with distal narrowing of the right supraclinoid ICA, consistent with dissecting pseudoaneurysm (Fig. 3).

A Pipeline embolization device (PED; Covidien Vascular Therapies, Mansfield, MA) was positioned within the supraclinoid ICA from the level of the anterior choroidal artery extending into the anterior genu of the cavernous ICA. Angiography performed following embolization demonstrated complete obliteration of the pseudoaneurysm (Fig. 4). The patient’s vision in the right eye remained unchanged 12 months later.

Ophthalmic artery occlusion is uncommon and compromises blood flow to the retinal and choroidal circulations. It is usually due to embolic phenomena related to atherosclerotic disease, myxoma, mural thrombus, or vasculitis (1).

Our patient’s vision returned to baseline 2 days after the initial presentation and was subsequently lost a second time. This may be explained by the hypothesis of Duker and Brown (2) that ophthalmic artery occlusion often causes hypoperfusion of choroidal and retinal vessels, thus compromising retinal cell function without necessarily causing cell death. It is likely that retinal perfusion recovered because of resolution of the initial thromboembolic occlusion but a second thromboembolic event resulted in permanent loss of vision. A less likely explanation is that visual loss may have resolved and recurred because of ophthalmic artery vasospasm, which is known to occur in the setting of trauma.

Traumatic intracranial aneurysms are rare (3–5) and result from shearing of intracranial vessels due to rapid deceleration forces (5). Arteries arising nearby may become occluded because of local thromboembolism, hemodynamic compromise, and changes in vessel morphology brought about by aneurysmal expansion and dissection (6). Mortality secondary to rupture of traumatic intracranial aneurysms approaches 50% in the first 3 weeks (7–9), necessitating prompt treatment. These aneurysms are less amenable to surgical intervention or endovascular coil embolization because of their thin walls, wide necks, and propensity for intraoperative rupture (10,11).

The PED is an implantable, platinum-based mesh conduit designed to divert arterial flow away from the aneurysm, resulting in intra-aneurysmal hemostasis and thrombosis. Parent vessel reconstruction with the PED was decided upon in our patient for its ability to treat the pseudoaneurysm without the need for aneurysmal catheterization and without risk of coil migration.

Computed tomography angiography (CTA) and MRA are favored over conventional angiography as an initial screening method for intracranial vascular pathology because of their increased availability and lower frequency of complications. However, traumatic intracranial aneurysms often are small in size (3,8,12,13), and CTA and MRA have a sensitivity of 30%–60% for aneurysms <5 mm in size (14). Therefore, patients suspected of post-traumatic pseudoaneurysm may require cerebral catheter angiography for both diagnosis and treatment.
FIG. 3. Top panel: Digital subtraction angiography (DSA). Bottom panel: Three-dimensional reconstructed images of DSA. A broad-based ophthalmic segment aneurysm is present with irregular contour (A, arrowhead) and mild narrowing of the distal supraclinoid internal carotid artery (ICA) (arrow) (B, arrow). The origin of the right ophthalmic artery from the right ICA is not visualized. Townes view (C) and lateral images (D) following right internal maxillary artery injection reveals the right ophthalmic artery filling distally from the meningolacrimal branch of the right middle meningeal artery (arrow). Anteroposterior superior (E, F), lateral (G), and anteroposterior caudal (H) reconstructed images of right ICA injection demonstrates a broad-based 1.73 x 1.75 mm dilation of the ophthalmic segment of the right ICP (arrowheads) with irregular contour and broad-based neck with mild narrowing of the distal supraclinoid ICA (arrows). The origin of the right ophthalmic artery from the right ICA is not visualized.

FIG. 4. Six months after Pipeline device embolization. Top panel: Digital subtraction angiography (DSA). Bottom panel: Three-dimensional reconstructed images of DSA. Anteroposterior (A) and lateral (B) DSA images show that the dissecting pseudoaneurysm has been completely obliterated and the distal ICA stenosis has resolved (arrows). Lateral skull radiograph (C) shows the Pipeline embolization device in position within the ophthalmic segment of the right internal carotid artery (ICA; arrow). Townes view of DSA following a right external carotid injection (D) shows that the right ophthalmic artery continues to be filled distally by the meningolacrimal branch of the right middle meningeal artery (arrow). Anteroposterior superior (E, F) and lateral (G) and anteroposterior caudal (H) reconstructed images following right ICA injection. The dissecting pseudoaneurysm has been obliterated, and the distal ICA stenosis has resolved (arrows). The origin of the right ophthalmic artery from the right ICA still is not visualized.
REFERENCES


Paraneoplastic Dermatomyositis Related to a Chondrosarcoma Involving the Cavernous Sinus

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Abstract: Approximately one third of all cases of dermatomyositis may be associated with malignancy. We describe a patient with unexplained rash, joint pain, and muscle weakness, who subsequently developed a cavernous sinus syndrome due to a central nervous system chondrosarcoma. Discovery of this tumor and further dermatologic evaluation, including skin biopsy, resulted in diagnosis of paraneoplastic dermatomyositis due to cavernous sinus chondrosarcoma.

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A 51-year-old woman with a history of asthma presented with 1 month of painful, red skin eruptions of the face and buttocks and the dorsal and palmar surfaces of both hands (Fig. 1). A skin biopsy from a lesion on the left elbow was nondiagnostic, showing dermal fibrosis and minimal inflammation. She was treated with topical clobetasol and

FIG. 1. Skin lesions characterized by red papules involving both hands, including the palmar surface and preferentially located in the interphalangeal areas.
oral fluconazole and valacyclovir, without improvement. Four weeks later, she noted joint pain and swelling in the hands, wrists, hips, and shoulders, as well as weakness of her upper legs. An echocardiogram was negative for endocarditis. Laboratory studies included hemoglobin of 12.5 g/dL (normal: 12.0–16 g/dL), hematocrit of 35.9% (normal: 36%–46%), erythrocyte sedimentation rate of 100 mm/h, C-reactive protein of 21.7 mg/L (normal: <8.0 mg/L), ferritin level of 1,177 ng/mL (normal: 10–200 ng/mL), aspartate aminotransaminase of 7 U/L (normal: 9–32 U/L), alanine aminotransferase of 87 U/L (normal: 7–30 U/L), aldolase of 10.9 U/L (normal: <7.7 U/L), angiotensin-converting enzyme of 59 U/L (normal: <53 U/L), and antinuclear antibody positive at 1:40 (speckled). Other tests were normal, including rheumatoid factor, anti-nuclear cytoplasmic antibody, immunoglobulin and complement levels, hepatitis markers, Lyme, and parvovirus. Electromyography of the right thigh showed active denervation in the right iliopsoas muscle without evidence of a peripheral neuropathy or myopathy. Treatment with 10 mg of prednisone lessened her joint pain, skin discontent, and proximal leg weakness.

Six weeks later, the patient reported intermittent vertical diplopia. Neuro-ophthalmic examination revealed visual acuities of 20/20 in each eye with an intact afferent visual system, including funduscopy. Pupils were equal in size and reacted normally. There was 2 mm of right ptosis. Ocular motility testing revealed limited supraduction and abduction of the right eye, and there was decreased sensation of the trigeminal and maxillary division of the right trigeminal nerve.

Magnetic resonance imaging of the brain showed an enhancing mass (5.5 × 4.8 × 5.5 cm³) in the right petroclival
fissure involving the right cavernous sinus (Fig. 2). A second skin biopsy from the dorsum of the left hand demonstrated a combination of vacuolar interface dermatitis and dermal mucinosis consistent with dermatomyositis, lupus, or paraneoplastic dermatomyositis (Fig. 3).

Given the presence of a large central nervous system tumor, paraneoplastic dermatomyositis was thought to be the most likely diagnosis. Computed tomography of the chest, abdomen, and pelvis failed to disclose any other source of malignancy. A craniotomy for partial debulking and biopsy of the tumor was performed, revealing a myxoid chondrosarcoma, Grade II (Fig. 4A, B). Consistent with this diagnosis, immunostaining was positive for S100 (Fig. 4C) and negative for epithelial marker antigen and pancytokeratin.

The patient’s prednisone dose was increased to 20 mg/day, and 6 weeks later, her diplopia resolved in primary gaze, with 1 mm of right ptosis and only mild limitation of abduction of the right eye. She also reported further improvement in her joint pain but still had persistent skin lesions and was transitioned from steroids to mycophenolate mofetil. She began adjuvant radiation therapy for her chondrosarcoma 4 months later. Her diplopia did not recur during a follow-up of 1 year.

Thirty percent of dermatomyositis cases are due to an underlying malignancy, but the majority of these are pulmonary or gynecological in origin (1,2). To our knowledge, there are no previous reports of a cavernous sinus tumor initially presenting with paraneoplastic dermatomyositis. Moreover, there is only 1 previous report of dermatomyositis secondary to chondrosarcoma that involved the tibia (3).

Dermatomyositis is a cutaneous disease with a myriad of skin findings, most classically Gottron papules of the interphalangeal areas of the fingers, or a heliotropic rash of the eyelids and cheeks. Proximal muscle weakness often is present (4). Laboratory findings for typically include elevated transaminases, aldolase, and creatinine kinase and the presence of anti-Mi-2 or anti-Jo antibodies (4). Normal creatinine kinase (5) and absence of anti-Mi2 or anti-Jo antibodies (6) may be more typical of paraneoplastic dermatomyositis and should prompt systemic workup for malignancy. Testing for additional antibodies, such as CA125, for ovarian tumors may be considered. An antibody that seems to be specific for cancer-associated dermatomyositis ("anti-155/140") has been reported (7) but is not yet commercially available.

Our patient presented with skin eruptions, joint pain, and proximal muscle weakness. The cause of her signs and symptoms was not detected for 6 weeks until she underwent imaging for a right cavernous sinus syndrome, which revealed her malignancy. Laboratory tests for anti-Mi-2 and anti-Jo were negative, consistent with paraneoplastic dermatomyositis. Despite successful partial resection of her tumor, portions of her chondrosarcoma remained unresectable. This may explain the persistence of her skin lesions following surgery.

REFERENCES


The Blind Photographer. Observations on the Bewildering Nature of Feigned Vision Loss

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Abstract: The diagnosis of feigned vision loss in adults taxes the doctor–patient relationship because the relationship should be based on trust, honesty, and the mutual desire to improve the medical condition. Even under ideal circumstances, physicians rarely have a complete understanding of the factors that lead patients to simulate disease they do not have. We describe the historical figure of John Howard Griffin (1920–1980) who likely perpetuated feigned vision loss for a decade. His writings provide a unique perspective on motivation (or inspiration) behind factitious disease.

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Nonorganic vision loss in adults is one of the most common isolated manifestations of simulated disease and a condition that most ophthalmologists and neurologists are trained to recognize (1–5). As a broad diagnostic category, this form of visual loss provides no information as to etiology, but for practical purposes necessitates a decision as to causation: is the visual loss intentionally feigned or an unconscious somatoform disorder? (1,5). The importance of making this distinction is in the divergent strategies for managing culpable malingering and involuntary hysteria.

In terms of deliberately faking disability, the question of motivation naturally arises. J. M. Charcot, the famous 19th century neurologist, saw the purposeful simulation of neurological illness as a diagnostic challenge (6). He fully appreciated the difficulty of separating nonorganic from organic disease, yet when confronted by feigned illness he preferred not to speculate on motivation.

There is a facet of feigned vision loss in adults that has gone largely unrecognized because perpetrators have limited interest in medically legitimizing their visual impairment through physicians, preferring instead to live as sightless individuals in the public domain. We describe the case of John Howard Griffin (1920–1980), author and historical figure associated with the civil rights movement, as an example of the wide-ranging motives behind factitious vision loss.

CASE REPORT

This history is extracted from John Howard Griffin’s autobiography Scattered Shadows. A Memoir of Blindness and Vision, which details his 10-year experience of total blindness and recovery (7). Griffin grew up in Texas and traveled to France before World War II where he was a premedical student. He interrupted his studies in 1941, at the age of 21 years, to join the United States Navy, serving in the Pacific theater until the end of the war. When stationed on the island of Morotai in 1944, he sustained a concussive injury that left him unconscious for 2 days (7) (p. 32). After waking in a rudimentary medical facility, he remembered overhearing his doctors say “damage to the sub-arachnoid area of the brain” (7) (p. 37). No focal neurological deficit was ever described. At discharge from the Navy that December, his vision was 20/200. Having never worn glasses, this screening test was the first indication that his vision might not be normal.

Griffin returned home to Fort Worth, telling his family about his concussion and discharge examination. He was seen by an eye specialist who offered no explanation for his impairment but sent him to a neurosurgeon for another opinion. After tests and an examination, the neurosurgeon advised Griffin to abandon the idea of studying medicine (7) (p. 39). Given the normal appearance of his eyes, the neurosurgeon explained “there’s still a great deal about the brain that we don’t yet know” (7) (p. 39).

Griffin returned to France in the summer of 1946, describing his solitary journey back to Europe in this context: ‘I felt that losing my sight was a thing I had to do
alone” (7) (p. 40). In Tours, he met a blind man, who demonstrated by example how to cope with blindness on a daily basis. By the spring of 1947, Griffin was totally blind. On his voyage back to America, he reported not being able to see sunlight, appreciating only its warmth on his face (7) (p. 109).

After rejoining his family in Texas, he learned Braille, took up farming, became a rancher, and tried writing. He married, became involved in community affairs, and appeared to enjoy the challenge of blindness. Griffin wrote: “I was so immersed in discovery that I never stopped to dwell on my condition as tragic. I felt that I was simply living in a new and different way that fascinated me” (7) (p. 117). Although he associated the concussive injury during the war with his blindness, Griffin never applied for any disability benefits he was entitled to, claiming it was a matter of principle (7) (p. 123). His success as a blind writer attracted considerable attention. In 1952, LOOK Magazine devoted an article to his accomplishments (Fig. 1) (8).

Almost 10 years to the day after losing vision, his sight returned over a span of days. On January 13, 1957, Griffin was walking to the barn when he suddenly saw the “door, cut in portions, dancing at crazy angles” (7) (p. 213). His eyes were filled with “triangles of color [that] faded and swirled.” By January 15, he could appreciate the serene beauty of Vermeer’s paintings while thumbing through an art book. When Senate majority whip Lyndon B. Johnson heard of the news, he sent a telegram to his fellow Texan congratulating him on the miracle (7) (p. 216). Twelve days later, Griffin was playing ping-pong and billiards and began to read again. He was driving his car months later.

Having fully regained his vision, Griffin was able to reassemble the many activities that interested him before the war, particularly photography, which he described in a collection of essays published under the title Available Light (9). In that publication, Griffin attributes his appreciation of visual detail to his decade of blindness.

DISCUSSION

Despite the lack of objective medical documentation about John Howard Griffin’s ophthalmic condition, it is improbable that any disease adequately explains the full recovery of vision after a decade of absolute blindness. Griffin was propelled onto the national stage several years later when he altered his skin color to simulate that of an African American. In 1959, during the turbulent civil rights movement, he traveled throughout the South disguised as a Black man so he could better understand the personal injustice of racial segregation. This curious experiment, and unflattering portrait of the South, was recounted in his book Black Like Me (10). It made Griffin a celebrity and an unwelcomed member of his local community.

It is difficult to ignore the parallels between faking racial identity to better understand the challenges of being Black in the segregated South and feigning vision loss to better understand the challenges of living in a world designed for the sighted. Having the will and determination to actually implement such experiments in public for any length of time is indeed quite remarkable.

Griffin would not be the first public figure to voluntarily deny himself sight for the sake of curiosity. Charles Fletcher Lummis, an Indian rights advocate, author, editor, and friend of Theodore Roosevelt, made a highly public display of his blindness in 1911, from which he totally recovered a year later (11). Like Griffin, Lummis was energized by the daily test of blindness but was unable to adequately simulate total vision loss without the use of a bandana to cover his eyes, a maneuver that smacked of theatrics. John Muir, a close friend, doubted whether Lummis was truly blind and suggested in a personal letter that too much work might have been a contributing factor (11).

There are other noteworthy similarities between the behaviors of Griffin and Lummis. In the 1890s, Lummis suffered a devastating paralytic stroke that left him without function of his left arm. Although details of the anatomical and physiological inconsistencies of his stroke-mimicking condition are described elsewhere (11), for 3 years and 7 months, he delighted in learning to shoot a rifle with 1 arm, role cigarettes with 1 hand, and break wild broncos with 1 arm tied to his side. Several years after his paralysis suddenly (literally instantaneously) disappeared, Lummis wrote a book titled My Friend Will, in the same inspirational genre as Scattered Shadows (12). Both Lummis and Griffin minimized their contact with doctors, despite the devastating nature of their disabilities.
Historically, the medical profession has had a limited role as gatekeeper in judging disability. For instance, requiring a medically validated diagnosis for visual impairment is a 20th century prerequisite for disability compensation, income tax benefits, and workers’ compensation. Unfortunately, the administrative process is vulnerable to abuse and often entangles physicians to function as a safeguard against misuse (13) (p. 54). Before social safety nets existed, feigned blindness for monetary gain was a public affair. A typical example is depicted by Harry Bernstein in his autobiographic account of immigrating to America during the Great Depression (14). After coming to the United States as a young teenager, Bernstein accidentally discovered his grandfather posing as a blind man selling pencils on the streets of New York City (14). Having injured his back in a fall as a roofer, Bernstein’s grandfather had no means of support. He was compelled by his circumstances to simulate another disability in order to beg successfully in public.

The psychosocial factors that contribute to factitious vision loss are complex and associated with unflattering connotations that almost reflexively discourage inquiry into the murky territory of motivation. The memoir of John Howard Griffin provides some insight into the machinations of an abstruse man whose inspiration to feign blindness remains difficult to comprehend.

REFERENCES
Fingolimod Therapy and Macular Hemorrhage

M. Tariq Bhatti, MD, S. Mitchell Freedman, MD, Tamer H. Mahmoud, MD, PhD

Abstract: A 54-year-old woman with relapsing-remitting multiple sclerosis (MS) developed visual loss in her left eye due to a macular hemorrhage 11 months after starting fingolimod. Visual acuity was 20/80 in the left eye, with a dense retinal hemorrhage involving the fovea with adjacent hard exudate and macular thickening confirmed by spectral domain optical coherence tomography. Three months after stopping fingolimod, vision in the left eye improved to 20/30 with resolution of the macular hemorrhage and exudates. Fingolimod has been associated with macular edema, but prior to this report, the authors are unaware of it causing a macular hemorrhage in a MS patient. The authors speculate that the macular hemorrhage may be due to a disruption of cellular adhesions between vascular endothelial cells that maintain the inner blood-retinal barrier.

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Fingolimod (Gilenya; Novartis Pharma AG, Stein, Switzerland), a structural analog of sphingosine-1-phosphate (S1P), is a S1P receptor (S1PR) agonist that irreversibly binds to 4 of the 5 S1P (1,3–5), known subtypes of S1PR. Its primary mechanism of action for the treatment of multiple sclerosis (MS) is believed to be its effect on the immune system through the sequestration of circulating lymphocytes into lymphatic tissue (1). S1P and S1PR have also been shown to be important in the regulation and maintenance of vascular integrity by contributing to the intercellular adhesion of endothelial cells (2). Macular edema may develop in a small percentage (0.4%) of patients treated with fingolimod (3). However, we are not aware of any reported cases of macular hemorrhage in the setting of fingolimod therapy.

CASE REPORT

A 54-year-old Caucasian woman reported a 3-day history of seeing a gray opaque spot in the central visual field of her left eye. She had no eye or head pain nor visual complaints regarding her right eye. Her medical history was only notable for relapsing-remitting MS diagnosed 14 years previously. She had no history of hypertension, diabetes mellitus, rheumatological disease, or hematological disease. The patient had experienced only 2 MS exacerbations since diagnosis while being treated with interferon β-1b, but she was switched to 0.5 mg/day of fingolimod 11 months before her visual complaints because of injection fatigue. Four months after starting fingolimod, her ophthalmologic examination was stable. Her ocular history was notable for narrow angles, for which she underwent laser peripheral iridectomy, refractive surgery in both eyes, and mild amblyopia in the left eye.

When we initially evaluated the patient, visual acuity was 20/20 in the right eye and 20/80 in the left eye. Color vision and pupillary testing were normal. Slit-lamp examination revealed mild corneal scarring bilaterally from previous refractive surgery, and the intraocular pressure was 13 mm Hg in each eye. Funduscopic examination of the right eye was unremarkable. In the left eye, there was a retinal hemorrhage involving the fovea with adjacent hard exudate (Fig. 1A). Spectral domain optical coherence tomography (SD-OCT) showed a hyperdense opacity encroaching on the center of the fovea and extending from the inner retina to involve the outer retinal layers (Fig. 1B). Intravenous fluorescein angiography of the right eye was normal, but in the left eye, there was fluorescein blockage.

Departments of Ophthalmology (MTB, THM) and Medicine (Division of Neurology) (MTB), Duke Eye Center and Duke University Medical Center, Durham, North Carolina; and Raleigh Neurology Associates, PA (SMF), Raleigh, North Carolina.

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from the hemorrhage with adjacent hyperfluorescence corresponding to the hard exudate (Fig. 1C). After discussion with her neurologist, the fingolimod was immediately discontinued. The patient was found to have normal blood pressure with no clinical or laboratory evidence of diabetes mellitus.

After consulting her neurologist, fingolimod was discontinued. One month later, visual acuity was 20/40 in the left eye. Funduscopy showed complete resolution of the macular hemorrhage with small amounts of residual hard exudates (Fig. 2A). SD-OCT revealed near complete resolution of the hyperdense opacity in the macula (Fig. 2B), and intravenous fluorescein angiography of the left eye showed resolution of the blocked fluorescence and faint hard exude hyperfluorescence (Fig. 2C). Three months after cessation of fingolimod, visual acuity improved further returning to a baseline level of 20/30, and SD-OCT was normal.

**DISCUSSION**

Unlike the brain in which there is a single blood–brain barrier, the eye has 2 blood–ocular barriers: anterior (blood–aqueous) and posterior (blood–retinal). The blood–retinal barrier can be further divided into inner (intraretinal vasculature) and outer (retinal pigment epithelium) barriers (4). Disruption of the blood–retinal barrier from a wide variety of ocular and systemic pathologies can result in the accumulation of fluid within the retina.

In patients treated with fingolimod, reports of macular edema (3), branch retinal vein occlusion (5), arterial vaso- spasm (6), hemorrhagic encephalitis (7), and posterior reversible encephalopathy syndrome (8) have suggested a connection between fingolimod and an alteration in retinal and cerebral vasculature. Substantial evidence has confirmed a vital role of S1P and S1PR in endothelial cell-to-cell and cell-to-matrix adhesions. Coupled to G-protein receptors,
S1P signals a complex chain of events to the cytoskeleton system to regulate and maintain vascular impermeability between endothelial cells by way of tight junctions, adherens junctions, and focal adhesions (2). In animal models, disruption of this system with the application of S1P antagonists results in pulmonary edema (9). Although the precise pathomechanism of fingolimod-associated macular edema is not known, it is believed to be the result of the dysfunction of the S1PR in regulating retinal vascular integrity. A subset of MS patients particularly appear to be sensitive to fingolimod and development of macular edema, including those with uveitis. Therefore, inflammation may be a contributing factor. Recently, a small percentage of untreated MS patients were found to have microcystic macular edema suggesting underlying retinal inflammation or blood-retinal barrier disruption as part of the MS disease process (10).

Two aspects of our patient’s clinical course deserve comment. First, the macular hemorrhage occurred in only 1 eye. Of interest is that almost 75% of fingolimod-associated macular edema cases in 2 phase III MS clinical trials were unilateral (11). Second, although our patient developed a macular hemorrhage after 11 months of fingolimod therapy, approximately 25% of patients with fingolimod-associated macular edema presented 6 months after initiating treatment (11). After discontinuation of fingolimod, 85% of patients had complete resolution of their macular edema as occurred with our patient’s macular hemorrhage.

It is difficult to state with absolute certainty that the macular hemorrhage in our patient was related to fingolimod therapy. However, we believe this to be the case, given the temporal relationship of the clinical findings, the initiation and discontinuation of the medication, and the known effect of fingolimod on vascular integrity. We were unable to identify any systemic or ocular abnormality to account for the hemorrhage. We caution clinicians that patients receiving fingolimod require careful funduscopic examination if they note a change in vision while on treatment.

REFERENCES
Pipeline Embolization Device: A New Source for Embolic Retinal Vascular Occlusion

Adam B. Sise, MD, James M. Osher, MD, Martin P. Kolsky, MD, Andrew Stemer, MD, William O. Bank, MD, Richard A. Garfinkel, MD

Abstract: A 57-year-old woman underwent treatment of a left internal carotid artery aneurysm with a Pipeline embolization device. She subsequently experienced multiple branch retinal artery occlusions in her left eye. Although rare, ophthalmic complications may follow this new technique in the treatment of intracranial aneurysms.

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The Pipeline embolization device (PED; ev3/Covidien, Irvine, CA) has emerged as a novel endovascular treatment for intracranial aneurysms. It is a cylindrical braided wire mesh implant that creates a pathway to bypass aneurysmal cavities. By diverting blood flow through the implant, blood in the aneurysmal cavity is left to stagnate leading to thrombosis, thus walling it off from the parent vessel. Approved by the Food and Drug Administration in 2011, it has shown success in treating intracranial aneurysms, especially those with challenging anatomic subtypes (1–4). Although there have been rare reports of vision loss related to the device, we describe a patient who presented with multiple branch retinal artery occlusions (BRAOs) following PED placement for treatment of an intracranial aneurysm of the internal carotid artery.

CASE REPORT

A 57-year-old woman was evaluated for left-sided headache, neck pain, and excess lacrimation from the left eye. Her medical history was significant for hypertension, and she had a brother who died 4 years previously from complications related to a subarachnoid hemorrhage. Magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and computed tomography angiography revealed a 6.8 × 6.4 × 6.8-mm³ aneurysm at the anterior genu of the left internal carotid artery, opposite to the origin of the left
ophthalmic artery (Fig. 1). The patient was treated with 2 Pipeline devices telescoped from the origin of the left posterior communicating artery to the vertical segment of the petrous portion of the left internal carotid artery covering the entire length of the aneurysm (Fig. 2). There were no reported intraoperative or immediate postoperative complications, and postprocedure angiography of the parent and branching vessels appeared normal (Fig. 3A). The patient was discharged on clopidogrel and aspirin.

Three weeks after the procedure, she presented to the emergency department with sudden, painless vision loss in her left eye. Emergent computed tomography, MRI, and MRA of the head and neck revealed no acute abnormalities, expected artifact from the Pipeline device, and no evidence of aneurysmal filling (Fig. 4). The patient refused cerebral angiography. Neuro-ophthalmic examination disclosed visual acuity of 20/25, right eye, and 20/40, left eye. Color vision was impaired in the left eye, and there was a left relative afferent pupillary defect. Eyelids, slit-lamp examination, and extraocular movements were normal. The right fundus was unremarkable while the left showed area of retinal whitening along the superotemporal and inferotemporal arcades, which contained plaque material. Cotton wool spots were seen temporal and superonasal to the optic disc (Fig. 5). Fluorescein angiography revealed delayed filling of the superotemporal arteriole with eventual retrograde perfusion (Fig. 6).

Platelet inhibition at the time of the patient’s vision loss was measured using the VerifyNow point-of-care system (Accumetrics, San Diego, CA). P2Y12 and aspirin reaction units were within normal limits. The patient was diagnosed with multiple BRAOs and instructed to continue her aspirin and clopidogrel.

Cerebral angiography performed during routine 6-month follow-up showed patent flow through the Pipeline devices and complete obliteration of the aneurysm, with some narrowing of the proximal Pipeline device at its proximal and distal ends (Fig. 3B). The left ophthalmic artery filled through the walls of the Pipeline devices, and there was an intact choroidal blush of the left eye. The patient’s visual acuity stabilized at 20/20 bilaterally, with a dense visual field defect in the right eye.

**DISCUSSION**

The PED represents a significant improvement in the treatment of intracranial aneurysms compared with conventional microsurgical techniques in both aneurysmal occlusion rates and patient outcomes (4,5). The PED is placed within the parent artery and, because of this, carries a risk of thromboembolic complications until endothelialization is complete. Most Pipeline procedures are performed with double antiplatelet therapy to decrease these risks because aneurysmal occlusion occurs over many months (5,6).

The Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial was the major clinical study that led to Food and Drug Administration approval and included safety and efficacy data.
on 108 patients (1). Although our patient’s aneurysm was smaller than the criteria used in the PUFS study, a PED was used in our patient because of the wide neck of the aneurysm. The PUFS report included 5 cases of amaurosis fugax, none of which occurred in direct relationship to the procedure. The other 4 occurred after Day 90 and there was no evidence of retinal arteriole occlusion. There was 1 case of cilioretinal artery occlusion that occurred on the day of the procedure (1). Several subsequent large studies failed to report permanent visual loss due to embolic arteriole occlusion (4–11).

In our patient, it is presumed that the narrowing of the second Pipeline device may have caused a disruption of flow into the ophthalmic artery, or thrombus, that embolized distally into the retinal arterioles. The cause of the narrowing is unclear, and although the use of angioplasty to widen the areas of stenosis was considered, ultimately this was dismissed because of the patient’s stable clinical course.

Long-term data are still needed to fully evaluate the risk of delayed events related to Pipeline device placement, and patients should be appropriately counseled regarding the risk of vision loss both during and in the months after the procedure.

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Optic Nerve Cupping and the Neuro-Ophthalmologist

Clare L. Fraser, MBBS, MMed, FRANZCO, Andrew J. R. White, MBBS, PhD, FRANZCO, Gordon T. Plant, MD, FRCP, FRCOphth, Keith R. Martin, DM, MRCP, FRCOphth

Background: While glaucoma is the most common cause of optic disc cupping, it can also be seen in a number of congenital and acquired optic neuropathies. It behooves both glaucoma and neuro-ophthalmic specialists to be able to differentiate glaucoma from neurological conditions, which give a similar ophthalmoscopic appearance to the optic disc.

Evidence Acquisition: This review is a combination of the authors’ clinical experience from tertiary glaucoma and neuro-ophthalmology referral centers, combined with a literature review using PubMed.

Results: Even for experienced observers, differentiation between glaucomatous and nonglaucomatous cupping can be difficult. In the majority of cases, this distinction can be made following a careful clinical examination combined with a variety of imaging techniques. Possible mechanisms, which lead to changes in optic disc morphology, are reviewed.

Conclusions: Differentiating glaucomatous from nonglaucomatous optic disc cupping can be a formidable challenge for the clinician. Examination of the patient combined with imaging of the retinal nerve fiber layer and optic disc topography provides a basis to resolve this clinical conundrum.

OPTIC DISC CUPPING

The ONH consists of 3 layers (3). The first is a continuation of the retinal nerve fiber layer (RNFL) (Fig. 1A). The second is the prelaminar layer, with loose trabecular glial tissue containing capillaries and retinal nerve fibers. Progressive loss of prelaminar neural tissues results in increased optic cup depth and width, classified as “prelaminar cupping” (Fig. 1B). The third layer lies within the lamina cribrosa: Axon bundles pass through a meshwork of connective tissue covered in astrocytes and containing capillaries (4). The short posterior ciliary arteries are the sole vascular supply via a capillary network and the peripapillary choroid. The lamina extracellular matrix provides structural support and allows passage of nutritional support for the axons (5). Loss of support of deeper structures leads to posterior displacement of the lamina cribrosa and excavation beneath the anterior scleral canal (4). This has been designated “laminar cupping” (Fig. 1C). Therefore, cupping is the result not only of axonal loss but also of supportive glial tissue. Extensive axonal loss with preservation of glial structures results in a pale optic disc without cupping.

Normal Reference Values

Normal reference ranges for optic disc morphological parameters have been established in different ethnic groups (6). On clinical examination and using optical coherence tomography (OCT), the horizontal disc diameter and the disc area are significantly smaller in Caucasians and Hispanics compared to populations from South Asia, Southeast Asia, and Africa (7,8). South Asian and Hispanic participants have the thickest global RNFL measurements. Statistically significant differences have been demonstrated among racial groups for all OCT ONH and RNFL parameters except rim area (9).
The mean horizontal cup-to-disc ratio (CDR) in the Caucasian North American population is 0.25–0.49, compared to 0.35–0.66 in African-Americans (10,11). In a predominantly Caucasian European population, mean vertical CDR was 0.49 and horizontal CDR was 0.4 (12). Asymmetry of the optic disc cup diameter is 0.1 in 92% of a normal North American population (13).

**CLINICAL ASSESSMENT**

**Congenital Optic Disc Cupping**
There are a variety of optic disc anomalies that are characterized by significant cupping. They are summarized in Table 1 and Figure 2.

**Acquired Optic Disc Cupping**
While glaucoma is the most frequent cause of acquired optic disc cupping, a variety of ischemic, toxic, compressive, and genetic causes can lead to optic disc excavation. Differentiating glaucomatous optic neuropathy (GON) and nonglaucomatous cupping (NGC) requires careful clinical examination and use of various imaging techniques.

**Visual Acuity and Color Vision**
Loss of visual acuity and color vision will occur in advanced glaucoma but usually occur early in other optic neuropathies. However, both acuity and color vision can be affected at any stage in GON if the patient develops a temporal RNFL bundle defect with a corresponding macular arcuate scotoma splitting fixation across the

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**FIG. 1.** Anatomical changes of optic disc cupping. *Dashed line* indicates original location of internal limiting membrane (ILM). *Solid black line* indicates altered location of ILM. *Orange area* indicates prelaminar neural and vascular tissue. *Blue line* indicates anterior laminar surface. *Green lines* indicate Bruch’s membrane opening. **A.** Normal optic nerve head. **B.** Prelaminar or shallow cupping. *Black arrows* indicate the movement towards the altered position of the ILM. **C.** Laminar or deep cupping. *White arrows* indicate posterior movement of anterior laminate surface. Note there is also prelaminar cupping (*black arrows*). Modified from Burgoyne and Downs (3).
horizontal meridian (14). The Amsler grid and automated visual fields of the central 10° can help detect macular involvement. A particularly confusing situation for the clinician is preserved acuity with poor performance on Ishihara plates in early glaucoma. Such patients are often referred to neuro-ophthalmology. With a preserved central island of visual field, visual acuity is retained, but the paramacular field required to read Ishihara plates is lost as a result of macular arcuate defects.

Decreased visual acuity in NGC is caused by a scotoma centered on the fovea or splitting the central visual field vertically. Anterior ischemic optic neuropathy (AION) can split fixation horizontally. The altitudinal visual field defect (VFD) in AION typically involves a number of RNFL bundles subserving more than an isolated arcuate area (15). Loss of acuity out of proportion to disc cupping has been reported in NGC (16), with a reduction in acuity <20/40 having a 77% sensitivity for NGC (17).

Color vision loss in optic neuropathy classically causes a red-green deficiency, as described by Kollner in 1912 (18). Performance on Ishihara plates is a useful screening test in discriminating early glaucoma from other causes of optic neuropathy. However, if visual acuity is preserved, as is often the case in glaucoma, the color vision defect is predominantly blue yellow (18,19). Deficiencies in color vision testing (pseudoisochromatic plates, Hardy-Rand-Rittler, Farnsworth-Munsell) greater than expected from acuity or visual field loss should lead to suspicion of NGC (Table 2).

Macular and cone dystrophies can present with color vision deficits and temporal optic disc pallor and are best diagnosed with a full-field, multifocal, and pattern electroretinography (20).

**Pupillary Findings**

Estimates of the presence of a relative afferent pupillary defect (RAPD) in GON range between 9% and 82% (21). The magnitude of a RAPD is proportionate to the difference in visual field loss between the 2 eyes (22). A RAPD is detectable when RNFL thickness is decreased to 83% of

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<th>Name</th>
<th>Cause</th>
<th>Appearance</th>
<th>Associations</th>
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<tbody>
<tr>
<td>Morning glory (Fig. 2A)</td>
<td>Abnormal closure of embryonic fissure</td>
<td>Funnel-shaped excavation</td>
<td>Mid face anomalies</td>
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<td></td>
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<td>Elevated pigment epithelium</td>
<td>Basal encephalocele</td>
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<tr>
<td>Coloboma (Fig. 2B)</td>
<td>Failure of closure of embryonic fissure</td>
<td>Can resemble deep cupping</td>
<td>CHARGE syndrome: coloboma, heart defects, choanal atresia, mental retardation, genitourinary and ear abnormalities</td>
</tr>
<tr>
<td>Tilted optic disc (Fig. 2C)</td>
<td>Oblique insertion of optic nerve through scleral canal</td>
<td>Elevated superior pole, with posterior displacement of inferonasal disc</td>
<td>Myopia</td>
</tr>
<tr>
<td>Megalopapilla (Fig. 2D)</td>
<td>Unknown</td>
<td>Abnormally large optic disc diameter with increased cup-to-disc ratio</td>
<td>Optic nerve glioma</td>
</tr>
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<td>Optic nerve hypoplasia (Fig. 2E)</td>
<td>First trimester insult</td>
<td>Disc is pale and small with a surrounding scleral crescent “double ring sign”</td>
<td>Absent septum pellucidum</td>
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<td>Abnormal vascular pattern or tortuosity</td>
<td>Agensis of corpus calosum</td>
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**TABLE 1. Congenital causes of optic nerve cupping and associated features**

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that in the fellow eye (23). Discovery of a RAPD has been shown to be highly specific (>90%) for detecting glaucoma within a normal population (21). Although a RAPD cannot differentiate among optic neuropathies, the degree of RAPD may be important. The simple rule is that optic neuropathies that tend to be symmetrical will not show a RAPD; these are principally glaucoma, papilledema, nutritional, toxic, and genetically determined optic neuropathies. Neuroimaging should be considered if a large RAPD is present, unless there is highly asymmetric field loss, which is clearly glaucomatous (Table 2).

**Glucomatous Optic Disc Assessment**

Focal loss of the neuroretinal rim (NRR) is reported to be 87% specific for glaucoma (1,24) and is associated with progressive disease (25,26). Other GON characteristics include normal color of the remaining NRR, vertical cup elongation, splinter hemorrhages (27), and positional changes of the optic disc vasculature (Fig. 3).

A greater proportion of glucomatous optic disc cupping is classified as “deep” compared to NGC (2). Conformational changes within the neural canal and posterior bowing of the lamina cribrosa explain this appearance of deep cups (28) (Fig. 1C).

In an ocular hypertensive cohort, the strongest predictors of glucomatous visual field loss were vertical CDR corrected for disc size, total NRR area, rim-to-disc area ratio, and CDR corrected for disc size (29). Tatham et al (30) showed a nonlinear relationship between estimates of retinal ganglion cell (RGC) number and CDR. Therefore, in glaucoma patients with a physiologically large CDR, even a relatively small change in CDR may be associated with a large loss of RGCs.

Peripapillary atrophy (PPA) is divided into a central (beta) zone with sclera and large choroidal vessels visible on ophthalmoscopy, and a peripheral (alpha) zone with irregular pigmentation. The size, shape, and frequency of alpha and beta PPA do not differ significantly between normal

### TABLE 2. When to consider neuroimaging of a patient with a cupped optic disc

<table>
<thead>
<tr>
<th>Definite Indications</th>
<th>Potential Indications</th>
</tr>
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<tbody>
<tr>
<td>Vertically aligned field defects</td>
<td>Relative afferent pupillary defect</td>
</tr>
<tr>
<td>Pallor of the neuroretinal rim</td>
<td>&lt;50 years old</td>
</tr>
<tr>
<td>Hypothalamic pituitary dysfunction</td>
<td>Asymmetrical loss of color vision</td>
</tr>
<tr>
<td>Other neurological abnormalities</td>
<td>Visual acuity &lt; 20/40</td>
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</table>

eyes and those with optic atrophy (31). However, in glaucoma, PPA is thought to be caused by ischemia (32), as the posterior ciliary arteries supply the optic disc and this region as well. While beta zone atrophy is often enlarged in glaucoma (33–35) and predictive of progression (36,37), it is not thought as essential in establishing the diagnosis of GON. However, on recent histological studies in cadaveric eyes, it was found that a more rigidly defined beta zone was strongly correlated with glaucoma (38). Progressive enlargement of beta zone atrophy is not seen in NGC (39). The PPA seen in myopia, tilted discs, and optic disc hypoplasia does not have a region of choroid interposed between the retina and the sclera, as in GON (40).

Features that do not help distinguish GON from NGC are the intraocular pressure (IOP), presence of laminar dots, and thinning of the NRR without complete obliteration (1).

**Nonglaucomatous Optic Disc Assessment**

Indicators and specificity (shown in brackets) of NGC reported in the literature are reduction in acuity <20/40 (77%), pallor of remaining rim (94%), patients presenting age <50 years (93%), and visual fields obeying vertical meridian (81%) (1,17). Other features typical of NGC include visual field loss with minimal cupping and retinal vasculature changes (41) (Fig. 3). In addition, a normal disc in the fellow eye with an abnormal visual field should raise concerns of chiasmal or retrochiasmal pathology. NGC has been reported in a variety of optic neuropathies including compressive (16,42–44), ischemic (45), inflammatory, and traumatic (46) neuropathies.

Compressive lesions include meningioma (42), pituitary adenoma (47), craniopharyngioma (48), and internal carotid artery aneurysm (48). Compression of the intracranial portions of the optic nerves by the supraclinoid internal carotid artery has also been reported to cause NGC (49). In compressive NGC, the median CDR asymmetry in patients was only 0.13 but significantly higher than controls who had 0.04 asymmetry (48).

Optic disc cupping may be the result of arteritic anterior ischemic optic neuropathy (A-AION) secondary to giant cell arteritis (45,50). NRR thinning and enlargement of the CDR in A-AION is similar to glaucoma, supporting the vascular theory of GON (50–53). However, other reports in patients with GON have demonstrated more marked posterior excavation and large cups with less rim volume than in those with AION (both A-AION and nonarteritic AION [NA-AION]), after adjusting for the amount of RGC loss (15).

Methanol poisoning produces profound RGC loss leading to blindness with pale, cupped optic discs (54) (Fig. 4). Loss of NRR and ONH excavation have been...
described in long-standing autosomal dominant optic atrophy (ADOA) (55) and Leber hereditary optic neuropathy (LHON) (2,56). Cases have been misdiagnosed as glaucoma (57). In one study, 48%–89% of ADOA patients were found to have significant NRR thinning and CDR >0.5 (58), but another found all to have NRR pallor, either temporally (52%) or globally (48%) (59). Clinical features, which should lead to genetic testing, are outlined in Table 3.

ANCILLARY TESTING

Visual Fields

Glaucomatous VFDs follow 4 major patterns: an isolated scotoma, an arcuate scotoma, nasal step (if there are both superior and inferior arcuate defects), and generalized depression (60). VFDs of NGC are more often central. Progressive glaucomatous field loss will be reflected in the changes seen at the ONH and RNFL measurements. The anatomical correlation between visual fields, RNFL trajectory, and position on the optic disc has been well described (61–63). Several groups have mapped OCT optic disc sectors with VFDs on standard automated perimetry (SAP) (64,65). There is a simple linear relationship between RNFL in superior and inferior disc sectors and corresponding arcuate SAP function (decibel units) in GON, as there is in AION (61).

Glucoma patients are almost always tested on SAP 24-2 protocols, with central test points spaced 6° apart, thereby underestimating any macular arcuate changes. In patients with normal-tension glaucoma, VFDs often are more localized, closer to fixation, and in the superior hemifield (inferior macula) (66). The optic disc region, the most vulnerable to glaucoma damage, is the border between

| TABLE 3. When to consider ordering genetic tests for patients with optic disc cupping |
|---------------------------------------------|---------------------------------------------|
| Leber hereditary optic neuropathy | Sudden loss of central vision |
| Bilateral or sequential profound vision loss |
| Maternal family history of vision loss |
| Relative preservation of pupil responses |
| Autosomal dominant optic atrophy | Very slowly progressive visual loss over decades despite normal intraocular pressures |
| Family history of poor vision |
| Color vision deficit |
| Pallor of the remaining neuroretinal rim |
| Disc changes seen in younger family members |
the temporal and inferior quadrants (67), producing macular field defects that are typically described as an arcuate “comma” or a “pistol barrel scotoma” (67,68).

The least vulnerable macular region to GON is the papillomacular bundle between the nasal fovea and the temporal optic disc (69). In contrast, the papillomacular bundle is particularly susceptible in other optic neuropathies, although the explanation for this vulnerability is unknown. Therefore, the involvement of the “central isle” of the visual field on Amsler, 10-2 SAP, or kinetic perimetry should raise the suspicion of a neurological process.

VFDs that respect the vertical meridian should be considered neurological until proven otherwise. Bitemporal visual field changes place the pathology at the optic chiasm. Homonymous defects (complete, incomplete, incongruous, and sectoral defects) are all seen with retrochiasmal pathology. An algorithm has been proposed to discriminate vertical neurological visual field abnormalities from horizontal glaucoma defects (70). However, SAP protocols can give the false appearance of VFDs respecting a vertical (or horizontal) meridian because of the sparsity of the points tested. Common mimics are temporal wedge defects extending from the blind spot as seen in optic nerve hypoplasia and acute zonal occult outer retinopathy. Kinetic visual fields are essential to more accurately assess the relationship to the horizontal and vertical meridians and to show the peripheral extent of a scotoma. SAP protocols for central fields have an extension nasally to facilitate the identification of a nasal step, but coverage temporal to the blind spot is minimal.

Retinal Nerve Fiber Layer Imaging
The confocal scanning laser ophthalmoscope (Heidelberg Retinal Tomograph [HRT]; Heidelberg Engineering, Heidelberg, Germany) provides quantitative measures of optic disc topography with reconstruction of a 3-dimensional image of the optic disc. OCT provides cross-sectional measures of RNFL thickness with the use of interferometry, using time-domain (TD-OCT) or spectral-domain (SD-OCT) methodology. Scanning laser polarimetry technology (GDx; Carl Zeiss Meditec, Dublin, CA) also provides a quantitative measure of the RNFL thickness. Using these instruments, there is a substantial overlap in structural measurements of the normal optic disc and the optic disc in GON and in NGC. This limits their diagnostic capability.

Glucoma
Optic nerve and RNFL imaging have allowed earlier detection of glaucoma (71). When a sloping cup is present, OCT can quantify the disc changes better than clinical observation alone. This is particularly true for comprehensive ophthalmologists; however, optic disc assessment by a glaucoma specialist is still more reliable than either (72). Neither OCT nor GDx is useful in distinguishing GON from NGC in highly myopic individuals (73). Thinning of the lamina cribrosa is present in myopic eyes with no other pathology, and refractive error leads to high artifact levels in image acquisition.

Enhanced depth imaging OCT can be used to evaluate the types of PPA to help differentiate GON and NGC. The beta-zone atrophy, located next to the optic disc, is associated with GON (74). However, gamma-zone atrophy, defined as the region between the temporal disc margin to the beginning of Bruch’s membrane, was not associated with GON and more likely a sign of NGC.

Nonglaucomatous Optic Disc Cupping
Gupta et al (75) used OCT to evaluate GON vs NGC (optic neuritis and NA-AION). In cases matched for CDR or average RNFL thickness, it was found that patients with NGC had a lower mean RNFL in the nasal and temporal quadrants (76). The pattern of RNFL thinning in ischemic optic neuropathy and ONH drusen is more likely to mimic the pattern of glaucomatous change caused by the predilection for the superior and inferior quadrants (77).

Using HRT, glaucoma patients have been shown to have less disc rim tissue, a greater cup volume, and a deeper optic cup than AION (arteritic and nonarteritic) (15). However, only in glaucoma were the lamina and connective tissues damaged, resulting in retroplacement of the cup. These findings were confirmed on OCT (78) with glaucoma patients having greater RNFL thinning overall. However, in the affected hemifields, RNFL thickness was not significantly different.

With HRT, 73% of LHON patients were misclassified as having glaucoma (79). In the acute phase of LHON, RNFL thickness initially increases in the temporal and inferior quadrants, progressing to involve superior and nasal quadrants within 3 months (80). By 9 months, there is a significant reduction in RNFL thickness in all but the nasal quadrants. These changes were of greater magnitude in patients with the 11,778 mutations than the 14,484 mutations (81).

Ninety percent of a group of ADOA patients had a statistically significant reduction in temporal RNFL thickness (82). Other studies showed a reduction in all quadrants with preferential involvement of temporal and inferior sectors (76) and relative sparing of the nasal region (83). Patients with a severe disease OPA1 variant mutation, having additional symptoms such as deafness, ataxia, and myopathy, had more pronounced RNFL thinning. Other causes of NGC also have a predilection for temporal RNFL loss, including ethambutol (84,85), syphilis (86), and toxic optic neuropathies (87). Eyes affected by demyelinating optic neuritis also have a reduction in RNFL thickness predominantly in the temporal quadrant involving the papillomacular bundle (88). These changes become evident 3–6 months after the acute episode (89). In nervemelitidis optica, the superior and inferior quadrants typically are more severely affected (90).
Caution is needed when diagnosing GON on OCT in patients following cerebral infarction or other damage to the postchiasmal visual pathways. This causes RNFL thinning in a “band” pattern in the eye with the temporal hemianopia and thinning of the superior and inferior arcuate bundles in the eye with the nasal hemianopia (91). The degree of change depends on the time since stroke, location of the damage (e.g., optic tract involvement will give greater loss), and the extent of the VFD (92).

Macular Imaging
Since a large portion of macular thickness is composed of RGCs and the inner plexiform layer, the macula also loses volume as glaucomatous damage progresses. Previous studies concluded that macular segmentation to measure these layers was less accurate than RNFL thickness measured by TD-OCT (93,94). However, with newer algorithms (67), macular analysis may become more important in diagnostic decisions.

Using frequency-domain OCT to examine the macular RGC layer plus the inner plexiform layer (RGC+), GON can be differentiated from nonglaucomatous changes (67). In GON, there is arcuate thinning of the inferior retina associated with a narrow region of RNFL thinning at the border of temporal and inferior disc quadrants. Normal tension glaucoma (NTG) patients are the more likely to be referred to neuro-ophthalmology with central VFDs than those with elevated IOP, making these macular scans invaluable (95). In patients with A-AION who have outer retinal ischemia secondary to occlusion of posterior ciliary arteries, there is disruption of the inner-outert photoreceptor segment line on SD-OCT (96).

Multifocal Visual Evoked Potentials
Although multifocal visual evoked potential (mfVEP) testing has been described for many years (97,98), it is not commonly used in clinical practice. Cappirolli et al (95) described the use of mfVEP to demonstrate objective VFDs in patients with disc changes but no abnormalities on SAP. In addition, the mfVEP was able to confirm central arcuate scotoma in normotensive glaucoma patients in 44% of eyes with normal SAP. This finding is because of the mfVEP protocols having greater representation of the central field than the 24-2 SAP.

The mfVEP can give additional information about visual pathways, with latency analysis showing abnormalities in compressive and inflammatory optic neuropathies (99,100). In comparison, relatively few glaucomatous eyes have latency delays (101). The domination of the “full-field” visual evoked potential by the macula severely limits its use in the diagnosis of glaucoma.

Magnetic Resonance Imaging
Magnetic resonance imaging (MRI) studies have shown morphological changes in the visual pathways of glaucoma patients, including loss of chiasmal height and reduced optic nerve cross-sectional area, which correlate with OCT RNFL thickness and VFDs (102–104). However, MRI optic nerve changes are seen with increasing age and are not specific for glaucoma (104). Glaucoma-related changes are seen in the lateral geniculate nucleus, visual cortex, and optic radiations (105,106). By analyzing the diffusion tensor imaging (DTI) features of the optic radiation, distinction between primary open angle glaucoma, NTG and controls, can be made with >90% accuracy (107). Optic nerve DTI measures correlate with changes in RNFL on HRT and glaucoma staging (108). However, reduced optic nerve volume and anisotropy on DTI also have been reported in patients with optic neuritis (109) and LHON (110). Whether MRI is more suitable diagnostically than OCT or SAP in some patients and whether these techniques can distinguish between different causes of ONH cupping remain to be seen. In NTG, diffuse cerebral ischemic changes are detectable on MRI, indicating that GON may be a manifestation of more widespread cerebrovascular disease (111,112).

Using standard MRI protocols, the optic nerve usually has a normal appearance in the acute phase of ischemic optic neuropathy. However, there are increasing reports of the detection of optic nerve ischemia with diffusion-weighted imaging (113). In comparison to optic neuritis, only 16% of NA-AION had abnormal MRIs, with increased short T1 inversion recovery or T2 signal and nerve enhancement (114). The acute T2 changes with increased intensity within the optic nerve are the result of the breakdown of the blood-brain barrier in optic neuritis. The chronic T2 hyperintensity in the affected portion of the anterior visual pathway occurs in all forms of optic neuropathy with Walleran degeneration (optic neuritis, LHON, and AION) (115). These T2 changes have not been reported in GON, which may be because the axonal loss in GON is gradual and incremental.

In ADOA, there is significant thinning of the optic nerves on MRI (116). However, even in ADOA patients with extraocular neurological features, no evidence of demyelination or structural abnormalities has been documented on MRI (117). In contrast, white matter changes with a multiple-sclerosis-like phenotype are seen in some cases of LHON (118,119).

Potential Common Pathophysiological Mechanisms of Optic Disc Cupping
Anatomical and experimental research regarding the basis of optic disc cupping is primarily found in the glaucoma literature. These theories involve a pathophysiological mechanism at the level of the lamina cribrosa.

Mechanical
The biomechanical paradigm of glaucomatous ONH damage provides an explanation as to how the pressure-related stress of increased IOP and the local deforming strain within the load-bearing tissues of ONH influence the physiology of all
tissues within the ONH. This theory assumes that the ONH astrocytes and glia support both the lamina cribrosa extracellular matrix and RGC axons (4).

How the ONH connective tissues respond to biomechanical stress is determined by posterior scleral compliance and rigidity (120). However, it is difficult to separate the mechanical forces leading to laminar deformation from other ONH effects caused by IOP-related stress (4). Differences in collagen genes alter the mechanical behavior of the sclera, reducing the RGC loss following chronic IOP elevation experimentally (121). However, regional differences in peripapillary fiber anisotropy seen between nonglaucoma and glaucoma eyes may represent either adaptive change in response to elevated IOP or baseline structural properties associated with predisposition to GON (122).

Vascular

The vascular theory (123) emphasizes the potential importance of IOP elevation on blood flow at the ONH (124). Autoregulation is a process whereby blood flow is kept relatively constant, despite changes in the ocular perfusion pressure. However, induced levels of high IOP affect autoregulation mechanisms in the choroid (125). Whether this also is true for ONH blood flow remains controversial. There is evidence that glaucoma patients show abnormal autoregulation, although the reasons for this remain largely unknown (126). A reduction in IOP may improve the regulatory capacity of the optic disc vasculature, thereby reducing the likelihood of ischemic periods and progressive GON (125).

Cerebrospinal Fluid Pressure Gradient

The intraocular to intracranial pressure (ICP) gradient may cause changes in ONH structure and function (127). Cerebrospinal fluid (CSF) surrounds the optic nerve to the level of the lamina cribrosa, thereby directly influencing the translaminar pressure difference and laminar position. The average posterior force from IOP on the lamina is 1 mm Hg per 100 μm (assuming a mean IOP of 16 mm Hg, mean ICP of 12 mm Hg, and a lamina cribrosa thickness of 450 μm) (128). As the lamina becomes increasingly weakened and thinned with glaucoma, this posterior force is spread across a smaller tissue volume, and this may explain why continued optic nerve damage occurs even with IOP at “normal” levels (129).

Mean lumbar CSF opening pressure in NTG is 3–4 mm Hg lower than in controls (130–132). Interestingly, in large population studies, the difference between IOP measurement in controls and progressive primary open angle glaucoma is 4 mm Hg higher. In both situations, the difference in translaminar pressure gradient between the normal and glaucoma patients is the same. Even this small difference in CSF pressure may be significant in the pathogenesis of GON. In addition, Ren et al (133) found a statistically significant difference in CSF pressure in 17 ocular hypertensive patients (16.0 ± 2.5 mm Hg) compared to 71 control subjects (12.9 ± 1.9 mm Hg). The authors speculate that this finding might explain why ocular hypertension patients do not develop progressive optic disc changes.

A COMMON METABOLIC PATHWAY: MITOCHONDRIAL DYSFUNCTION AND OPTIC NEUROPATHIES

RGCs are particularly sensitive to mitochondrial dysfunction, which is recognized as the underlying cause of optic neuropathy in LHON and ADOA (134). LHON is caused by mitochondrial DNA mutations (135), and increasingly, mitochondrial changes are thought to contribute primary open angle glaucoma pathogenesis. This could explain the morphological similarities in the optic discs of LHON and GON (2).

ADOA is the most common inherited nonglaucomatous optic neuropathy (59) and has been linked to the OPA1 gene on chromosome 3q (136). This gene encodes a mitochondrial dynamin-related protein and plays a role in the maintenance of mitochondrial cristae (134). Interestingly, OPA1 polymorphisms have been found in patients with NTG (137). Although results are controversial, a recent meta-analysis showed that some OPA1 variants may affect individual susceptibility (138). Data suggest that OPA1 deficiency impairs oxidative phosphorylation efficiency, but compensation through increases in the distal complexes of the respiratory chain may preserve mitochondrial adenosine triphosphate (ATP) production in patients who maintain normal vision (139). This raises the possibility that NTG is also an inherited optic neuropathy with similar mitochondrial dysfunction to ADOA but a different phenotypic expression (137,140).

An increase in free radical production is an early event related to increased IOP in experimental models of glaucoma (141,142). Generation of reactive oxygen species appears to be a NADPH related event that can be modulated to reduce cell death in experimental models of glaucoma (143,144).

Further analysis of mitochondrial dysfunction in glaucoma patients compared to controls has confirmed a specific reduction in ATP synthesis from mitochondrial oxidative phosphorylation (145). The RGCs are particularly vulnerable to stressors (i.e., elevated IOP) because of the very high bioenergetic demand created propagating action potentials and driving axoplasmic flow within unmyelinated axons found in the retina.

Superoxide generation is associated with axonal injury in other experimental models of optic neuropathy and can likewise be modulated (146–148). Recent attempts at neuroprotective therapies for glaucoma have, at least in part, focused on altering mitochondrial oxidative phosphorylation with some success in vitro (142,149).

CONCLUSIONS

In evaluating a patient with optic disc cupping, neuroophthalmic pathology should be considered when: 1) color...
vision loss is disproportionate to reduction in visual acuity and cannot be explained by the presence of macular arcuates; 2) VFDs do not correlate with optic disc changes; 3) vertically aligned VFDs are present; 4) there is a marked RAPD; and 5) the surviving neural rim of the optic disc shows pallor. Fundus imaging techniques can provide additional information in making the clinical decision between glaucomatous cupping and NGC, while neuro-imaging provides information regarding the cerebral changes seen with GON and other optic neuropathies.

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Acute Monocular Visual Loss in an Elderly Woman: A Neuro-Ophthalmologic Emergency

Michael S. Vaphiades, DO, Jennifer Doyle, MD, Patricia A. Hudgins, MD, Daniel J. Brat, MD

Drs. Vaphiades and Doyle:

An 84-year-old woman complained of a 2-week history of frontal headache and a 1-day history of sudden visual loss in the left eye. Her medical history included hypertension and hyperlipidemia. She denied jaw claudication, scalp tenderness, weight loss, fever, and chills. Her examination revealed normal blood pressure and heart rate. Visual acuity was 20/30, right eye, and no light perception, left eye. Color vision was reduced in the right eye. Pupils were isocoric, and the left pupil was amaurotic. The visual field of the right eye was full to confrontation and funduscoppy was normal bilaterally.

Suspected of having giant cell arteritis, the patient was treated with 80 mg/d of prednisone and 100 mg of doxycycline twice a day. Laboratory studies were obtained that showed a white blood cell count of 15,500/μL (normal, 4000–10,500/μL), platelets of 445,000/μL (normal, 140,000–415,000/μL), C-reactive protein of 12.1 mg/dL (normal, 0–4.9 mg/dL), and erythrocyte sedimentation rate of 62 mm/h. A left temporal artery biopsy was performed.

Dr. Brat:

Numerous cross sections of the temporal artery show slightly thickened smooth muscular walls and focal calcification but no acute or chronic inflammatory infiltrates (Fig. 1A). An elastic Van Gieson stain reveals an intact internal elastic lamina (Fig. 1B). There is no evidence of arteritis.

Drs. Vaphiades and Doyle:

In view of the negative temporal artery biopsy, plans were made to perform a contralateral biopsy, and urgent brain magnetic resonance imaging (MRI) was performed.

Dr. Hudgins:

MRI demonstrates opacification of the left sphenoid sinus (Fig. 2). In addition, the left anterior clinoid process is pneumatized, and the pneumatized area also is opacified. Because of the pneumatization, the sinus essentially surrounds the canalicular portion of the left optic nerve.

Drs. Vaphiades and Doyle:

In view of the MRI findings, the patient was admitted to hospital directly from the MRI facility. To clarify the relationship of the lesion with the surrounding bone and soft tissue, we elected to obtain an emergent computed tomography (CT) of the paranasal sinuses.

Dr. Hudgins:

The noncontrast axial CT of the brain demonstrates left sphenoid sinus opacification and focal dehiscence of the optic canal (Fig. 3).

Drs. Vaphiades and Doyle:

The patient was taken to the operating room where she underwent endoscopic sinus surgery that revealed pus surrounding the left optic nerve and destruction of the optic canal. Marsupialization of the left sphenoid sinus was performed, and tissue was removed from around the optic nerve and from the optico-carotid recess and sent for pathological examination. At the conclusion of the operation, gentamycin-soaked sinus foam was placed into the operative bed.

Dr. Brat:

Histopathologic evaluation of the sphenoid sinus contents shows respiratory mucosa and submucosa with marked acute and chronic inflammation. The chronic inflammatory infiltrate is mostly lymphoplasmacytic and associated with...
prominent myxoid change and edema in the submucosa (Fig. 4A, B). In other regions, the inflammatory process was more acute, with necrobiotic material associated with tissue destruction and bone erosion (Fig. 4C).

**Drs. Vaphiades and Doyle:**

Cultures of material removed at the time of surgery grew methicillin-resistant *Staphylococcus aureus* (MRSA). The patient was treated with intravenous clindamycin and oral sulfamethoxazole/trimethoprim as well as high-dose intravenous corticosteroids. On postoperative day 2, visual acuity in the left eye had improved from no light perception to 20/20. Twenty days later, the patient was off all antibiotics and steroids, and her vision remained stable.

**Final Diagnosis**

Acute left optic neuropathy from a sphenoid sinus mucopyocele.

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**Fig. 1.** Cross sections of temporal artery biopsy specimen show no evidence of inflammation and the internal elastic lamina is intact (A, hematoxylin and eosin, ×100; B, elastic Van Gieson, ×100).

**Fig. 2.** Contrast-enhanced T1 axial (A) and coronal (B) magnetic resonance imaging with fat suppression demonstrates opacification of the left sphenoid sinus with a pneumatized but opacified anterior clinoid process (arrows).

**Drs. Vaphiades and Doyle:**

Mucocles are cyst-like lesions lined with respiratory epithelium that contain mucoid secretions that lead to thinning and erosion of the bony walls of the affected paranasal sinus (1,2). When the lesion contains pus, it is termed a mucopyocele. More than half of these lesions are located in the frontal sinuses, with most of the remainder being in the ethmoid sinuses. Sphenoid sinus mucocles are relatively rare, representing 1% of all paranasal sinus mucocles (3,4). They usually start unilaterally, but by the time of presentation, the entire sphenoid sinus complex may be opacified and expanded with deossification and thinning of the bony walls.

Mucocles and mucopyoceles most often develop after long-standing sinus ostial obstruction in the setting of sinusitis, allergy, or trauma. On MRI, these lesions show variable intensity depending on protein concentration and viscosity but commonly demonstrate high signal on both T1 and T2 images. There is peripheral enhancement in the...
edematous and inflamed mucoperiosteum, but no central enhancement, a useful pattern to help distinguish a mucocele from sinus neoplasm. CT is helpful in demonstrating the relationship of the lesion with surrounding bone and soft tissue, showing an isodense smooth mass with an enhancing rim, usually associated with bowing and thinning of the bony margins of the affected sinus (5).

Cranial neuropathies are a feature in as many as 50% of mucoceles and mucopyoceles (4). Compression of the cavernous sinus may cause proptosis and periorbital pain (2,3,6–8). The cavernous sinus expands anteriorly at the level of the anterior clinoid process in close proximity to the third nerve (9). The third nerve is most commonly affected (9), with sparing of pupillary function mimicking a vasculopathic process in 46.6% of cases (7). Patients may present with periorbital pain and a third nerve palsy with pupillary involvement, suggesting aneurysmal compression (9). In some cases, the third nerve palsy may wax and wane (2). Frontal sinus mucoceles can cause downward displacement of the globe and limitation of elevation by erosion into the orbit from above (10,11).

Optic neuropathy from sphenoid sinus mucocele, as occurred in our patient, is rare and may be caused by direct compression of the nerve or its blood supply by the expanding mucocele or by spread of inflammation or infection (12). Mild elevation of the optic chiasm usually does not cause visual loss. However, involvement of the optic canal often is associated with an optic neuropathy, where the optic nerve is particularly susceptible to vascular compromise (12–14). The rapid improvement in visual function from no light perception to 20/20 in the left eye in our patient suggests that in our case, visual loss was related to direct compression of the canalicular portion of the optic nerve by the mucocele.

With respect to the causative organism of mucopyocele, MRSA has been isolated in up to 20.7% of patients with both acute and chronic rhinosinusitis (15). Indeed, S. aureus was the most common etiologic agent associated with acute and chronic sinusitis in a review of bacterial causes of sphenoid sinus inflammation (16). However, no specific organism has been found to be associated with mucopyoceles (17–20). One review of maxillary sinus mucopyoceles found coagulase-negative S. aureus to be the most frequently encountered organism (17), whereas another found alpha-hemolytic Streptococcus to be the most common pathogen (18). A chart review of patients with cystic fibrosis presenting for lung transplantation found asymptomatic frontal sinus

FIG. 3. Noncontrast axial computed tomography of the orbits demonstrates left sphenoid sinus opacification and a focal dehiscence in the medial and superior aspect of the left optic canal (arrow).

FIG. 4. Histopathology of the sphenoid sinus contents. The sphenoid sinus mucosa and submucosa show marked chronic inflammation with myxoid change and edema (A) and a dense lymphoplasmacytic infiltrate (B). Other regions showed acute inflammation and necrobiosis material along with fragments of eroded bone (C) (hematoxylin and eosin: A, ×40; B, ×400; C, ×40).
mucoceles in 3 patients; endoscopic surgery was performed and intraoperative culture results showed *Pseudomonas aeruginosa* from all 3 patients (20). This was not surprising as patients with cystic fibrosis frequently are colonized with *P. aeruginosa*; however, 3 other isolates were found in these cases, 1 of which was MRSA (20). Another study reviewed isolated sphenoid sinus disease in 29 patients with 4 different diagnoses: sinusitis, noninvasive fungus balls, neo-plasms, and mucoceles (19). Mucoceles were the least common source for sphenoid disease with a prevalence of 12%. Although MRSA was isolated from 8 of 11 cultures in this study, the authors did not indicate the specific source of the organism (i.e., mucocele vs sinusitis). A case report of bilateral sphenoid sinus disease with visual impairment due to *S. aureus* has been reported, although the causative organism was not specifically identified as MRSA (21).

Treatment of both mucoceles and mucopyoceles consists of relieving the sinus ostial obstruction, marsupialization of the lesion followed by antibiotics. This usually results in rapid regression of ophthalmic and other manifestations (19,22). In our case, recognition of the lesion with MRI and CT as a sphenoid sinus mucocele or mucopyocoele lead to urgent surgery and resultant visual recovery. However, delay in treatment may result in permanent blindness (22).

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Diagnosing Giant Cell Arteritis: Is Ultrasound Enough?

Klara Landau, MD, Peter J. Savino, MD, Philipp Gruber, MD

Establishing the diagnosis of giant cell arteritis (GCA) remains challenging. Although a positive temporal artery biopsy (TAB) is the only gold standard for the diagnosis of GCA, it is sometimes negative, and many clinicians choose not to always obtain a TAB in patients with suspected GCA (1,2). A number of alternative methods for the diagnosis of GCA have been suggested, including diagnostic algorithms, and noninvasive vascular imaging, such as color Doppler ultrasound (CDU) (1). This point-counter point reviews the evidence regarding the use of CDU for the diagnosis of GCA.

Point: Color Doppler Ultrasound is a Suitable Examination Method in the Management of Patients With Suspected Giant Cell Arteritis: Klara Landau, MD, and Philipp Gruber, MD

Since the seminal work of Schmidt et al in 1997 (3), many studies have examined the role of CDU in patients with suspected GCA. Controversy still exists on this topic. Here, we support the view that in most clinical scenarios, CDU is a sufficient and effective method in establishing or ruling out the diagnosis with important advantages over TAB.

Need for the correct diagnosis of GCA

GCA is a chronic systemic immune-mediated vasculitis with frequent involvement of the temporal arteries and other cranial arteries, including the vertebral, ophthalmic, and short posterior ciliary arteries. The disease most commonly affects Caucasians older than 60 years and its incidence is rising (4). Prompt diagnosis and initiation of treatment are crucial since otherwise the dreaded complication of irreversible visual loss may occur. Up to 50% of patients present with ocular symptoms. Although vision loss is the most common, other manifestations include transient visual loss and diplopia (5). If untreated, permanent visual impairment usually develops in the fellow eye within days to weeks, possibly leading to complete blindness (6,7).

Immediate and long-term use of systemic corticosteroids represents the only treatment modality that can effectively suppress the inflammatory disease process albeit side effects are inevitable. These include depression, diabetes mellitus, osteoporosis, infection, arterial hypertension, and gastrointestinal hemorrhage. Up to 90% of patients on corticosteroids will develop clinically significant side effects within 10 years of treatment (8,9).

According to the American College of Rheumatology (ACR), diagnosis of GCA can be made in a patient older than 50 years with newly acquired acute headache, painful and pulseless temporal artery, erythrocyte sedimentation rate more than 50 mm/h, and positive TAB. The diagnosis is established when 3 or more of these 5 criteria are present with a sensitivity of 93.5% and specificity of 91.2% (10). It needs to be pointed out that from neuro-ophthalmological point of view, the current ACR criteria may provide suitable inclusion criteria for clinical trials but not for managing individual patients with suspected GCA (2,11).

Although the diagnosis of GCA primarily is based on clinical criteria, TAB generally is performed to firmly establish the diagnosis and is still considered the diagnostic gold standard with a specificity of 87%–90%. It was Hall et al (12) who showed in the early 1980s that TAB is diagnostically useful. Despite the relative safety of TAB, complications include hematoma, wound dehiscence, brow ptosis (13), and facial nerve paresis (14). While the risk of more serious complications such as blindness has been discussed (15), no instance of visual loss has ever been recorded following TAB.

TAB may appear histologically normal even with obvious clinical signs (16). A frequently cited cause is the segmental involvement of the artery, referred to as "skip areas" (17). Techniques, such as contralateral biopsy, bilateral biopsy, or biopsy guided by ultrasound, have not improved the diagnostic yield of this procedure (18–21). Thus, there is a need for a diagnostic technique with a higher sensitivity than TAB and good specificity that will quickly and reliably diagnose or rule out GCA.

CDU as a diagnostic tool in patients with suspected GCA

CDU is a noninvasive method both to create images of the vessel wall and its lumen and to determine the flow characteristics within the vessel. By means of the B-mode and suitable linear array transducer of 10–15 MHz, high

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resolution of anatomic structure and a good delineation of blood vessels can be achieved. Combined with pulsed-wave Doppler, it is efficient in assessing the blood flow (22).

The classic sign that indicates the presence of GCA using ultrasound is termed the “halo sign,” a distinct hypoechogenic perivascular structure, with a diameter of 0.32 mm (Fig. 1). It was first described by Schmidt et al in 1995 (23). This appearance may represent perifocal arterial wall edema possibly due to increased vascular permeability caused by inflammation. Ultrasound detects the vascular wall swelling, whereas the histological findings represent inflammatory cell infiltration and granuloma formation (1). In addition, further ultrasonographic diagnostic criteria have been defined, such as stenosis and complete occlusion of the small arterial branches (3). Although this occurs in only 30% of patients, it seems to be very specific (24). Moreover, CDU allows examination of the entire length of the temporal artery and can be performed bilaterally, whereas biopsy is used to sample only one segment of the vessel.

Almost 20 years ago, Puechal et al (25,26) showed that the use of Doppler ultrasound in temporal, facial and ophthalmic arteries has a sensitivity of 77% and a specificity of 80% for the detection of GCA. In the ground-breaking study of Schmidt et al (3) in 1997, it was shown that CDU can be used as an effective technique to establish the diagnosis of GCA using the halo sign. In their prospective, controlled study of 30 patients with GCA, 37 patients with polymyalgia rheumatica, 15 patients with other disorders and 30 control subjects, Schmidt et al (3) obtained a sensitivity of 73% and specificity of 100% compared with the clinical presentation and a sensitivity of 76% and specificity of 92% compared with TAB. Other vascular features such as stenosis or occlusion of temporal arterial branches showed similar sensitivity and specificity. Combining all ultrasound features (halo sign, stenosis, and occlusion) improved the sensitivity markedly (73% to 93% vs clinical presentation; 76% to 95% vs TAB) while only mildly decreasing the specificity (100% to 93% vs clinical presentation; 92% to 85% vs TAB) (3).

Subsequent reports have yielded similar results. The prospective study of Romera-Villegas et al (27) included 68 patients and established a sensitivity of 95.4% and specificity of 91.3% (27). In a smaller study of 26 patients, Murgatroyd et al (28) found a sensitivity of 86% and a specificity of 68% compared with TAB. Another prospective study of 86 patients revealed a sensitivity of only 40% and a specificity of 79% compared with biopsy (29). LeSar et al (30) found in a prospective study of 32 patients, a sensitivity of 85.7% and a specificity of 92.0% compared with histological findings. A retrospective study of 85 patients, which compared CDU with histopathology, showed a sensitivity of 44.4% with a specificity of 90% (31). Habib et al (32) compared the diagnostic accuracy of the halo sign with clinical findings and TAB and calculated a sensitivity of 81% and specificity of 88%. Karahaliou et al (33) used CDU as the sole diagnostic method in suspected cases of GCA and showed that a bilateral presence of the halo sign increases the specificity to 100%. They concluded when the halo sign is bilaterally present, TAB is not necessary.

CDU-guided TAB increased the diagnostic yield compared with TAB alone. Alberts and Mosen (34) conducted a retrospective study of 290 patients suspected of having GCA. Comparing medical decision and outcome after CDU-negative vs TAB-negative results, they concluded that bilateral CDU is comparable with TAB and TAB should only be reserved for cases in which CDU results were equivocal. Pfenninger et al (31) published a retrospective study of 85 patients with suspected GCA and also concluded that given the high positive predictive value of CDU, temporal artery biopsy should be performed in CDU-negative cases. In a prospective study of 182 patients with potential GCA, Stammler et al (35) studied the value of CDU in relation to clinical pretest probability. In the group with high clinical pretest probability, the halo sign was found in 83% of patients. They concluded that in patients with high positive clinical pretest probability and negative halo sign, temporal artery biopsy is not needed. In only 33% of their patients was a biopsy performed to establish or exclude the diagnosis. In a prospective study by Nesher et al (36) of 69 patients suspected of having GCA, sensitivity of 86% and specificity of 78% was found for CDU compared with clinical findings. A high negative predictive value was established, whereas the positive predictive value was low. They concluded that TAB could be omitted only in patients with negative CDU results.

Meta-analyses of studies on the value of CDU in GCA

The first-ever meta-analysis involving 2,036 patients from 23 studies concluded that ultrasound with the halo sign is an accurate diagnostic test for GCA with an overall sensitivity of 69% and overall specificity of 82% compared with TAB (37). Two recently conducted meta-analyses found similar results. One of them included 17 studies with a total of 998 patients and documented an overall sensitivity of 73% and a specificity...
of 83% (38). The other, comprised 8 studies with a total of 575 patients, found a sensitivity of 75% and a specificity of 98% (39). This study confirmed that with a positive halo sign bilaterally, the specificity rose to 100%.

**Further advantages of CDU**

Beyond its use as a diagnostic tool, CDU can also be used to monitor treatment. Schmidt et al (3) demonstrated that the halo sign remained in the same location on follow-up examination and resolved after 10 to 16 days of corticosteroid administration. The range for this to occur was 7–56 days. Similar observations were made in later studies in which the halo sign disappeared with steroid therapy in 2–4 weeks, correlating with clinical and laboratory findings (32). A retrospective study, comparing the sensitivity of magnetic resonance imaging (MRI) and CDU in GCA patients on corticosteroids, demonstrated that the sensitivity, both of the halo sign and the specific MRI findings, drops significantly within days of treatment (40). In single case reports, when corticosteroid therapy was tapered and the patient experienced a relapse of GCA, the halo sign was shown to reappear (33,40).

The halo sign also can be found in other cranial arteries that are affected by GCA. A prospective study of 78 patients that compared the halo sign with clinical presentation and with biopsy in occipital arteries revealed a sensitivity of 65% and specificity of 100% compared with the histological findings (mostly taken from the temporal artery) (41). The halo sign was also described by Garcia-Garcia et al (42) in vertebral arteries. Their prospective study included 1,237 patients with stroke and demonstrated that the halo sign in vertebral arteries assisted in the diagnosis of GCA as a cause of stroke.

The possibility of examining several different arteries in a single session represents another major advantage of CDU over temporal artery biopsy. Moreover, the result of a CDU examination is available immediately without a need to wait for several days until a histological diagnosis is provided by the pathologist.

**Note of caution**

Admittedly, CDU is a sensitive and very specific test, but it remains highly examiner dependent. This was addressed by Maldini et al (43) in a retrospective study of 77 patients seen over 7 years in a single institution in which a sensitivity of 17% was found, whereas specificity was comparable with previous studies. The low sensitivity was probably due to interoperator variability because the detection of the crucial halo sign is dependent on the experience of the examiner.

To make CDU more operator independent, Aschwan-den et al (44) introduced the "compression sign," which should be methodologically more robust than the halo sign. A positive compression sign was defined as visibility of the temporal artery upon transducer-imposed compression of the artery. In their study of 80 patients, the compression sign proved to have the same sensitivity of 79% and specificity of 100% in comparison with the halo sign (44). Further studies are required to validate this observation.

**Conclusion**

In the setting of a typical clinical presentation and in the hands of a skilled examiner, CDU is a noninvasive, sensitive, and highly specific examination technique that helps to confirm the diagnosis of GCA and may assist in monitoring the effect of treatment. Several arteries can be examined in the same session and an immediate result is provided to the clinician to help guide the patient’s management. In patients with a low pretest probability of having GCA, normal CDU examination helps to rule out the disease and renders TAB unnecessary. We advocate that CDU should be increasingly implemented as a diagnostic and monitoring technique when caring for patients with suspected GCA.

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**Counter Point: All Patients With Presumed Giant Cell Arteritis Should Have a Temporal Artery Biopsy: Peter J. Savino, MD**

I agree that accurately making the diagnosis of giant cell arteritis (GCA) is critical. Failing to make the diagnosis in a patient who has GCA can result in bilateral, untreatable, permanent blindness. On the other hand, making the diagnosis of GCA in a patient who does not have the disease, results in an elderly patient being subjected to high dose, long-term toxic corticosteroid therapy. Therefore, it behooves us to utilize the tests for GCA that have the highest sensitivity and specificity.

**Diagnosis of GCA**

A positive temporal artery biopsy (TAB) is near 100% specific for GCA. There are rare conditions where other conditions (herpes zoster ophthalmicus) might be confused with GCA but a positive TAB is diagnostic of GCA. The sensitivity of a TAB is a more difficult to state unequivocally. The best study regarding this question, I believe, is a mathematical evaluation of the sensitivity of TAB by Niederkohr and Levin (45). They found that the highest sensitivity for accurately diagnosing GCA was using TAB (sensitivity 98.7%).

Therefore, the question must be posed: if the TAB is negative for GCA, how does one make the diagnosis of “biopsy negative GCA”? In fact, does this entity exist? Various strategies have been advocated to substitute for TAB to diagnose GCA. The 5 criteria (age older than 50 years, onset of new headache, erythrocyte sedimentation rate greater than 50 mm/h, clinical abnormalities of the...
superficial temporal artery, and positive TAB) endorsed by the American College of Rheumatology (ACR) is most quoted (10). However, a prospective study of TAB vs the ACR criteria has shown that the sensitivity of the ACR vs a positive TAB was 72.7% and the specificity was 61.2% (2). This would seem to eliminate the ACR criteria as a reliable guide to diagnose GCA.

The question often arises: what if the biopsy is negative but GCA is still suspected on clinical grounds? There is no information in the literature to answer this query. I suspect most neuro-ophthalmologists would continue treating the patient with systemic corticosteroids but for a shorter period than if the patient had a positive TAB. I have always stopped the corticosteroids if the biopsy is negative and have never had a patient lose vision in a pattern suggestive of GCA after discontinuing treatment.

**Studies on CDU as a diagnostic tool in patients with suspected GCA**

Ultrasonography of the superficial temporal artery had been used to guide the surgeon to the area of the superficial temporal artery to biopsy. In 1997, Schmidt et al (3) proposed that CDU could substitute for TAB to diagnose GCA. They described the results of duplex ultrasonography performed on patients from January 1994 to October 1996. Thirty patients were diagnosed with GCA. However, only 21 had biopsy confirmed disease. The authors stated that 22 (73%) of these 30 patients had a positive ultrasonographic finding indicated by a dark halo around the lumen of the temporal artery. They also stated that 24 patients (80%) had stenosis or occlusions of the temporal artery segments and that 28 patients (93%) had stenosis, occlusions, or a halo. They further indicated that none of the patients “without temporal arteritis” had halos identified. One of the major problems with this study is that almost one-third of the patients said to have GCA had negative biopsies, and additional criteria, other than positive temporal artery biopsies (TABS), were used to make that diagnosis. On the basis of their data, the authors stated that CDU could replace TAB in the diagnosis of GCA and, therefore, biopsies need no longer be done. However, in an accompanying editorial, Hunder and Weyand (46) correctly (in my opinion) indicated that ultrasonography may not be sensitive enough in the more difficult patients who present with no definite credible signs of GCA on physical examination. They also indicated that the study did not prove the likelihood of ultrasonography diagnosing GCA better than TAB.

**Meta-analyses of studies on the value of CDU in GCA**

Although many ultrasonography articles have appeared, the number of patients in each study has been small. Meta-analyses addressing this subject have appeared. Karassa et al (37) performed a meta-analysis published in 2005. Twenty-three studies involving 2,036 patients were included in this analysis. It was found that the weighted sensitivity and specificity of the halo sign was 69% and 82%, respectively, compared with TAB and 55% and 94%, respectively, compared with the ACR criteria. They indicated that the best use of Doppler was when the pretest probability of GCA was low (10%) in that the ultrasound was normal.

A meta-analysis in 2010 by Ball et al (38) using 17 eligible studies containing 998 patients found that the halo sign on CDU, compared with TAB, had a 75% sensitivity and 83% specificity. Despite the low sensitivity and specificity, these authors recommended that Doppler ultrasonography should replace TAB and that the surgery should be reserved only for patients with negative scans. It should be noted, however, in this meta-analysis that patients were included who were diagnosed as having GCA with a negative TAB on the basis of the ACR criteria.

An earlier study addressed the issue of “biopsy negative GCA” by using ultrasonography and comparing the results only with patients having positive temporal artery biopsies (28). Although the numbers were small, with only 7 patients having positive TABs, 6 were identified accurately on ultrasonography. However, 6 patients were found to have false-positive findings on ultrasonography. This provided a sensitivity of 86% and a specificity of 68% and a positive predictive value of 50% for the use of ultrasound in the diagnosis of GCA. The authors indicated that they could not recommend changing from the routine practice of TAB to diagnose GCA.

**Note of caution**

Major caution has to be used when evaluating studies that claim to compare favorably or unfavorably with TAB. In almost all studies, it is stated that a positive TAB is the “gold standard” for the diagnosis for GCA. Yet, in almost all of the ultrasonography studies, patients have been included as having GCA when they have negative TABs. Even with this manipulation, the ultrasound, which is an indirect method of diagnosing GCA, does not compare favorably with TAB.

**Conclusion**

Finally, the arguments regarding any tests to replace TAB be that ultrasonography, laboratory testing, MRI scanning, or PET scanning involves, to a large extent, circular reasoning. Although patients have negative TABs and a positive TAB is said to be the “gold standard,” almost all these articles continue to include patients as having GCA by using other than the biopsy criteria. This type of circular reasoning cannot lead to an accurate evaluation of any of these modalities. Ultimately, the “gold standard” should be respected and that standard, TAB, should be performed in all patients suspected of having GCA.
Rebuttal: Klara Landau, MD

Dr. Savino poses the crucial question: What does “gold standard” mean in the context of using TAB for GCA diagnosis if false-negative biopsies do occur? How do we determine that a particular patient does have GCA despite a negative biopsy report? The elegant mathematical approach to this problem by Niederkohr and Levin (45) using data from studies with bilateral biopsies comes as close to a definitive albeit theoretical answer as it gets. Their result of 98.7% sensitivity also shows that the “gold standard” contains fewer karats of gold than the “pure 24” that we would wish for.

Let’s face the fact that performing a TAB in a routine clinical setting is not as straightforward as it may seem: patients are not keen to have it done and surgeons often are not eager to perform the procedure. A considerable number of patients will either not have a biopsy done at all or it will stay inconclusive for a variety of reasons, including specimen too small, vein being biopsied instead of artery, performed too long after beginning treatment, and lack of expertise by the pathologist. Dr. Savino points out that in the study by Schmidt et al (3), 30 patients were diagnosed with GCA despite the fact that only 21 were biopsy positive. What about the remaining nine? In only 4 patients (and not in all 9) TAB was negative, but we do not know when in the course of symptoms it was performed. Three patients refused to have a biopsy and in 2 the result was inconclusive.

Dr. Savino’s main criticism points to the “circular reasoning” in recommending CDU instead of TAB for diagnosing temporal arteritis because the results published in studies on the use of CDU include patients who did not have their disease proven by a TAB. But if only patients with a positive TAB were included in such studies, it would be impossible to prove any test more sensitive than the 100% of positive biopsies!

During the Christmas holiday of 2011, my 92-year-old mother developed symptoms highly suggestive of GCA, including headache, jaw claudication, and transient visual loss, as well as elevated erythrocyte sedimentation rate (ESR) and C-reactive protein. I immediately prescribed systemic steroids and asked my colleagues to perform CDU on her temporal arteries. Admittedly, no halos, stenoses, or occlusions were found. I did not opt for a TAB that I considered too stressful for her in view of the immediate relief of signs and symptoms that she experienced after starting steroid treatment. I suppose it was too early for ultrasound or biopsy to have yielded a positive result—as “waiting increases the likelihood of positive biopsy findings, but it also increases the chance of a vascular complication” as addressed by Hunder and Weyand in their editorial in 1997 (46). But the CDU was far less disruptive than the hassle of a TAB during the holiday season would have been for all parties involved. Over a period of 4 months, steroids were tapered and my mother’s symptoms never reappeared. This personal experience exemplified the immense gap between the awareness of evidence-based medicine on one side and the decision making based on an individual patient’s situation on the other.

I agree that a TAB should be performed in patients in whom GCA is possible but equivocal and histological diagnosis will be very helpful to either adhere to a treatment regimen if the biopsy is positive or taper the treatment off rapidly when it is negative. I do not think that TAB must be performed when clinical presentation is highly suggestive of GCA and CDU supports the diagnosis. Similarly, TAB can be omitted in patients with low clinical probability of GCA and normal CDU findings obtained by a skilled examiner.

The editorial by Hunder and Weyand (46) in the New England Journal of Medicine was not quite as critical as described by Dr. Savino. Admittedly, Schmidt et al (3) may have overstated their conclusions because 16 years later, the use of CDU to diagnose GCA remains controversial. Nevertheless, CDU is a powerful method that is increasingly being used as a diagnostic and monitoring technique in patients with suspected GCA, and rightly so.

Rebuttal: Peter J. Savino, MD

Drs. Landau and Gruber have cited numerous articles from the ultrasound literature to support the use of CDU instead of TAB to diagnose GCA. However, a reading of these articles shows that they do not attain the levels of sensitivity and specificity of TAB in diagnosing GCA and therefore, I believe, establishes the point that CDU should not be used in lieu of TAB. A close reading of the cited article shows several additional reasons why they are not “proof of concept”:

1. The range of sensitivities and specificities varies greatly among these publications. One of the reasons is identified by my coauthors themselves when they write that the test “remains highly examiner dependent.” This statement alone should disqualify CDU from replacing TAB at this point in time. Another significant problem is that patients with negative TABs were used in most of these publications to label a patient as having GCA. Patients with negative TABs but with positive CDU studies were accepted as having GCA on clinical grounds. How is it possible for CDU to show indirect positive findings of histologic changes from GCA in the superficial temporal artery when the direct histopathological examination fails to do so? To be credible, a newly proposed test must be compared with the “gold standard” test before the new
test can be proposed as a substitute for standard test. Including so-called biopsy-negative GCA as proof of the validity of CDU is less than convincing.

2. We are in agreement that systemic corticosteroid therapy must be instituted in suspected GCA before confirmatory testing is performed. The histopathological changes of GCA are evident on TAB for 2 weeks at a minimum and usually longer. CDU, however, shows a marked reduction of the diagnostic sensitivity to 50% within 2–4 days (40).

3. Another argument used against TAB is the presence of “skip lesions.” The length of these normal areas in a positive TAB is small so that obtaining a biopsy length of 1–2 cm and sampling various areas of the specimen makes this fact moot.

4. Likewise the often-cited “serious complications” of TAB in the nonsurgical literature. Admittedly, the world’s worst surgeon may experience more than a minor complication with TAB; however, in competent hands, TAB is, for all intents and purposes, devoid of “serious” complications.

5. The authors state that CDU in GCA “can be used for treatment monitoring.” How exactly would this be done? Should corticosteroid therapy be halted or decreased when the repeat CDU improves? Since we know this may occur in less than 1 week, this suggestion is potentially dangerous.

6. The authors admit that CDU cannot distinguish between GCA and “different types of inflammatory changes in the vessel wall.” They state: “This is a minor drawback in comparison with TAB as GCA is by far the most important and most frequently encountered entity that is being diagnosed using TAB.” This would result in patients with all other forms of vasculitis being treated for months with large amounts of corticosteroids even if that is not the appropriate therapy for that specific disorder.

Finally, I am not aware of the medicolegal climate in other countries but the United States is a litigious society. A physician’s best defense, in any matter, is that he or she has adhered to the “standard of care.” Abandoning the “gold standard” of TAB for an indirect diagnostic modality in the diagnosis of GCA would be problematic at best.

**Conclusion: Valérie Biousse, MD, and Andrew G. Lee, MD**

The sensitivity, specificity, and utility of CDU for diagnosing GCA continue to evolve and improve. As with any clinical decision, however, the pretest likelihood of disease (i.e., clinical suspicion of disease) is a much more powerful predictor of disease than the test per se and this applies even to the gold standard of TAB. For example, in an 80-year-old woman with new onset headache, no light perception vision due to pallid disc edema, and jaw claudication, the finding of a normal ESR and C-reactive protein and even a negative TAB would not dissuade us from treating for GCA. Perhaps the question is not whether CDU can replace TAB in the diagnosis of GCA but instead whether CDU could be a sufficiently sensitive and specific adjunctive tool in specific cases to make a diagnosis without a confirmatory TAB. If the clinical findings are highly suspicious for GCA (as in the patient example above) and in the setting of a positive CDU, then the posttest likelihood of disease might be high enough to justify steroid treatment and be sufficient for medical and medicolegal purposes without a TAB. Likewise, in a patient with a very low clinical suspicion for GCA (e.g., 40-year-old man with ESR of 100 mm/h) in whom we might be loath to perform an essentially non-diagnostic TAB, a negative CDU might be very reassuring to the patient and attending physicians.

**REFERENCES**

Daniel M. Jacobson, MD, completed neurology training at the University of Pittsburgh and neuro-ophthalmology fellowship at the University of Iowa. He joined the staff of the Marshfield Clinic in Marshfield, Wisconsin, in the Departments of Neurosciences and Ophthalmology in 1987 with a faculty appointment at the University of Wisconsin. During a 16-year period at the Marshfield Clinic, Dr. Jacobson cared for thousands of patients and authored more than 50 scientific manuscripts in the field of neuro-ophthalmology. He was honored with numerous teaching and research awards and recognized for his ability to apply basic science principles to the investigation of the most pressing clinical issues. The Marshfield Clinic Foundation has established a memorial fund in his name. In recognition of the profound impact Dr. Jacobson had on the field of neuro-ophthalmology, the North American Neuro-Ophthalmology Society has established a lecture to be presented each year at the NANOS meeting.

Neuro-Ophthalmology at Iowa

H. Stanley Thompson, MD

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H. Stanley Thompson, the son of Irish missionaries, was born in China. He was educated in China and Ireland and spent the World War II years in a Japanese concentration camp in northern China. After the war, he returned home to Belfast, Ireland, and then, in 1949, he emigrated to the United States. He spent 2 years in the U.S. army as a photographer and then earned BA and MD degrees at the University of Minnesota.

Dr. Thompson’s career in neuro-ophthalmology is intertwined with the history of neuro-ophthalmology at the University of Iowa, the subject of his Jacobson Lecture. Being a man of great humility, Dr. Thompson is quick to give credit to his associates and colleagues; but do not be fooled, as he is also an individual of great intellect, and his contributions to neuro-ophthalmology have been tremendous.

Dr. Thompson has published more than 200 manuscripts, many about making careful use of pupillary signs during routine clinical examination. When ophthalmology residents learn about various pupillary signs and pharmacologic tests, they assume that this body of knowledge has been around for at least a hundred years! They are astonished to discover that many of them were emphasized or introduced into clinical practice by Dr. Thompson. One such example is the diagnostic algorithm dealing with anisocoria (1).

In addition to his contributions to neuro-ophthalmology, Dr. Thompson has found time to serve his profession on the American Board of Ophthalmology, the board of the North American Neuro-Ophthalmology Society, and the International Neuro-Ophthalmology Society. He has attended the International Pupil Colloquium since 1963, not missing a single meeting in 44 years, and he has hosted the meeting twice.

Dr. Thompson has been married for 60 years, and he and his wife, Delores, have raised 5 children and have 8 grandchildren.

THE EARLY YEARS

When Cecil O’Brien started the Ophthalmology Department at the University of Iowa in 1928, ophthalmology had just been separated from the Ear, Nose, and Throat Department by L. W. Dean, the Dean of the Medical College. The Dean had been running the EENT department for 20 years without much enthusiasm for the eye side of things. Dr. O’Brien started his teaching program in ophthalmology in the new University of Iowa Medical Center in 1929. At first there were no subspecialty clinics, and...
O’Brien hired a few professors to help him teach general ophthalmology. One of them was Dr. Placidus Joseph ("P.J.") Leinfelder, who was to become the University of Iowa’s first neuro-ophthalmologist; he came to Iowa City from the University of Wisconsin in 1930, to be one of Dr. O’Brien’s ophthalmology residents. When he finished his residency in 1934, O’Brien asked P.J. to join his faculty as an instructor (Fig. 1).

When, in 1938, O’Brien asked P.J. to head a “neuro-ophthalmology” section in the department, Leinfelder resisted. Dr. Leinfelder always thought of himself as a general ophthalmologist and did not want to call himself a “neuro-ophthalmologist.” Like others of his era, he felt that the term implied that he was neither a neurologist nor an ophthalmologist. Nevertheless, O’Brien went on to brag about the “neuro-ophthalmology” section in his department, and the term eventually became popular. The word was used as a book title by Lindsay Rea (1938), Donald Lyle (1945), Alfred Kestenbaum (1946), and then by Frank Walsh in 1947. There is no doubt, however, that Leinfelder was indeed interested in what we now call “neuro-ophthalmology.” His American Ophthalmological Society thesis, accepted in 1938, was on “Retrograde degeneration in the retina and optic nerves.” He gave courses at the Annual meeting of the American Academy of Ophthalmology (AAO) on neuro-ophthalmic topics from 1937 to 1969. During those same years, his talks to various Midwest state medical societies resulted in publications such as “Papilledema and optic neuritis,” “Misconceptions in neuro-ophthalmology,” “Why test visual fields?,” and “The diagnosis and treatment of ocular neuroses.” Leinfelder continued to do general ophthalmology and cataract surgery but, for the next 30 years, he really was the only member of the Iowa Eye faculty who undertook to help residents with neuro-ophthalmic problems.

Dr. Leinfelder retired in 1971, at age 68, but stayed in the department part-time for another 5 years, taking care of some of his old patients who had known no other ophthalmologist for 30–40 years, making himself available to the residents, and serving as the voice of experience at department faculty meetings. P.J. was a model for all retiring professors—wise, alert, ready with sound advice but not offering it until it became perfectly clear that all of us young fools were going to keep blathering along without ever getting to the heart of the problem. He was kind, avuncular, and approachable, and during those years, he earned from the residents their deepest respect for his knowledge, clinical wisdom, and humanity (Fig. 2).

THE THOMPSON YEARS

In 1966, Dr. Fred Blodi was about to become the new head of the Ophthalmology Department, and he knew that one day he would need to find a replacement neuro-ophthalmologist. I was just finishing my residency in the Department and had some interest in pupil function and in neuro-ophthalmology. In fact, I got hooked on the pupil quite early: I was in medical school in Minneapolis in 1957 when Walsh’s second edition of *Clinical Neuro-Ophthalmology* (“Big Red”) appeared. This is the work that, in later editions, was to become “Walsh and Hoyt,” which today is the gold standard for neuro-ophthalmology texts. I had never before seen a medical book so tightly packed with fascinating details. It soon persuaded me that there was enough material in neuro-ophthalmology to last me a lifetime.

Dr. Blodi, who had known the pupil experts Otto Lowenstein and Irene Loewenfeld when he was at...
Columbia University in New York, saw Loewenfeld at the AAO meeting at the Palmer House in Chicago in 1962. She was demonstrating her new infrared device for continuous recording of both pupils in dark and light. Blodi invited Loewenfeld to visit Iowa City to talk to the Eye Department about her research. I was fascinated and expressed an interest in working with that device. Dr. Blodi and Dr. Maurice W. van Allen of the Neurology Department were, at that moment, applying for National Institutes of Health (NIH) research funds to support a "Neurosensory Center" in Iowa. So soon there were plans to incorporate a Pupillary Research Lab into the University of Iowa Neurosensory Center.

In preparation for this center, Drs Blodi and van Allen purchased a new "electronic pupillograph," developed by Lowenstein and Loewenfeld. Loewenfeld requested that I go to New York for 3 months to learn some of the intricacies of pupillography. This was arranged, and I worked at pupillography until I finished my residency. Blodi’s hope was that I would return to Iowa after spending a year doing a neuro-ophthalmology fellowship with Dr. William Hoyt; and that was indeed the way it worked out. I suspect that Dr. Blodi called Dr. Hoyt and said "You want someone who’ll work on your new pupil chapter?"

At the end of my residency in Iowa, I had been working on a pupillographic demonstration of differences in pupillary input between the 2 eyes (2). This observation had a long history. It had apparently been obvious to Galen in the second century CE, that covering both eyes and then uncovering them one at a time, gave information about the potential for vision in each eye, and Galen refused to couch a cataract in an eye that, when uncovered, failed to show a good pupillary constriction. More recently, Marcus Gunn, Kestenbaum, and Levatin had all emphasized the clinical importance of this sign. Dr. Hoyt and his subsequent fellows began to say "relative afferent pupillary defect," to emphasize the comparison of the pupil reaction in the 2 eyes.

In 1966–1967, Robert Hepler and I were Hoyt’s fellows. We were all working on the third edition of Walsh's book, and Hoyt came in every morning with some new gem of knowledge to pass along. At the end of my fellowship in the summer of 1967, Dr. Blodi had just become the new chief at Iowa, and I returned to Iowa City to join the University of Iowa faculty as a neuro-ophthalmologist. When I arrived back to Iowa City, Dr. Blodi said to me "We don’t have clinic space for you yet, so just start seeing some patients in the general clinic, and we will send you all the neuro-ophthalmology patients that come along" (Fig. 3). This led, very quickly, to an active "Neuro-ophthalmology Clinic."

Starting in 1968, ophthalmology residents began doing a 3-month full-time rotation in the Neuro-ophthalmology Clinic, and since 1971, there has been a steady flow of Neuro-ophthalmology fellows through the service (Fig. 4).

In 1969, I objected to the use of the word "hippus" to describe the behavior of the pupils in patients with Cheyne–Stokes respirations, where the pupils became small in the alarming apneic phase and then enlarged as the patient started to breathe again. This led to a pursuit of the elusive word hippus and resulted in an article done with the help of my sinologist brother Paul, and Albert Franceschetti (3).

In 1971, it seemed worthwhile for me to emphasize that a unilateral fixed dilated pupil due to local atropinic action could be quickly distinguished from a neurogenic mydriasis with a drop of pilocarpine (4). In those days, Iowa cornfields were often contaminated with jimson weed, a plant that is rich in belladonna alkaloids (5).

Throughout the 1970s, I continued to be interested in Adie syndrome. I emphasized that there was a characteristic slit-lamp sign: a regional palsy of the iris sphincter in many patients. Sometimes an odd, back and forth, crawling illusion could be seen called "vermiform movements." When Sattler brought attention to these, "Wurmförmige Zuckungen" in 1911, there was a great deal of head scratching and speculation about their significance. In retrospect, these odd movements may have been nothing more than physiologic hippus in a section of the iris that was still normally innervated (6).
Also at this time I was reviewing possible mechanisms of adrenergic mydriasis Horner syndrome. John Mensher, MD, and I described the utility of topical hydroxyamphetamine drops in differentiating a preganglionic from postganglionic lesion (7).

In 1972, a few months after returning from 6-month training in London at the National Hospital for Neurology and Neurosurgery, Queen Square, I started taking one neuro-ophthalmology fellow per year (see Supplemental Digital Content, Table 1, http://links.lww.com/WNO/A90).

The demand for neuro-ophthalmology service was growing steadily so that, in 1977, James Corbett, a Philadelphia trained neurologist who, like me, had done a fellowship in San Francisco with Dr. Hoyt, joined Dr. Van Allen’s Neurology Department at the University of Iowa as a neuro-ophthalmologist. Dr. Corbett came to the Eye Department every morning for our daily “neuro-ophthalmology rounds,” and on certain days he staffed the Neuro-ophthalmology Clinic all day. This was a great addition to our Neuro-ophthalmology Service leading to a very effective and productive long-time collaboration. I continued my interest in the workings of the pupil, and Dr. Corbett became expert in pseudotumor cerebri.

This Thompson–Corbett team ran the Neuro-ophthalmology Clinic from 1977 to 1990 (Fig. 5). We held our daily Neuro-ophthalmology rounds 5 days a week at 9:00 AM, just after the Eye Department’s “morning rounds.” These daily “service rounds” continue today.

It was, and still is, a teaching and reviewing session that went on for about an hour before we saw any new patients. We reviewed the patients seen the previous day and made suggestions about their follow-up studies. Sometimes we arranged for some visual fields to be done and went to the coffee shop where we spent half an hour reviewing cases and sometimes discussing on-going research projects.

In 1977, we organized a symposium in Iowa City that covered 5 separate areas of neuro-ophthalmology. Each section was set up and run by a Hoyt-trained neuro-ophthalmologist: Lars Frisen, visual fields; Stan Thompson, pupils; Joel Glaser, optic nerve disease; Robert Daroff, eye movements; Michael Sanders, computed tomography. The presentations were published in 1979 as Topics in Neuro-Ophthalmology (8).

In 1984, a first-year ophthalmology resident named Randy Kardon, who had done a PhD in pharmacology as one of the first combined Medical Scientist Training Program MD–PhD students at the University of Iowa College of Medicine, started his research with the premise that the “visual field” could be mapped using pupillary reactivity as an indicator—something that no one had yet done with fundus-based perimetric instrumentation. We made a bold, and, for us, very instructive, preliminary effort, which formed the basis for the next step, gathering quantitative pupil data.

The most important outcome of this project was that after his residency, Dr. Kardon obtained grants from Fight for Sight and Research to Prevent Blindness to continue this work on pupil perimetry and stayed in Iowa City to take a clinical fellowship in Neuro-ophthalmology with Thompson and Corbett while continuing this research. During these very active clinical and research years in the 1980s, we had a number of outstanding fellows, including Dan Jacobson and Kathleen Digre (Fig. 6).

In 1989, Randy Kardon joined the Iowa faculty. He continued to work with pupillary projects and became an active clinical neuro-ophthalmologist, and a much-admired and busy investigator. He was the first ophthalmologist to receive a Career Development Award through the Department of Veterans Affairs. This was later renewed for a second cycle, and it supported his salary and research during his first 9 years on the faculty. This was followed by continuous extramural funding from the Department of Veterans Affairs (VA), Department of Defense, and NIH, which helped define a new model for how a group of academic neuro-ophthalmologists at Iowa could work together in both clinical and research endeavors and receive extramural financial support. In 2008, in recognition for his ongoing research and clinical contributions to neuro-ophthalmology and to the University of Iowa, Dr. Kardon...
was named as the inaugural appointee to the Pomerantz Family Chair in ophthalmology; thanks to a 2 million dollar gift from the Marvin Pomerantz Family to support research and clinical excellence in neuro-ophthalmology and to find cures for vision loss.

In 1990, after 13 active years on the faculty at Iowa, Dr. Corbett received an attractive offer to become the chair of the Neurology Department at the University of Mississippi in Jackson, MS, and moved to Jackson in July 1991. Dr. Corbett and Dr. Kardon continued to collaborate on a number of projects and published together even after 1991. Dr. Corbett has returned to Iowa numerous times as a lecturer or visiting faculty.

Michael Wall joined the Neurology Department as a neuro-ophthalmologist in 1991, after 10 years at Tulane University, and about 2 months after Dr. Corbett left for Mississippi. Dr. Wall’s research was a good fit for Iowa as like Dr. Corbett, one of his main interests was idiopathic intracranial hypertension (IIH). While at Iowa, he has gone on to direct the National Eye Institute–sponsored Idiopathic Intracranial Hypertension Treatment Trial. The goal of this trial is to identify the cause of IIH and to develop evidence-based treatment strategies for the disease. He has also been an investigator in other multi-center investigations, including the Optic Neuritis Study Group. Dr. Wall’s other area of research is studying mechanisms of perimetric variability. While at Iowa, he has developed motion perimetry and has identified using larger kinetic stimulus sizes as a way to reduce variability. This research has been funded since 1994 with a VA Merit review. He has been active in the International Perimetry Society (now the Imaging and Perimetry Society) serving as its President for 8 years and was a leader in the group drafting standards of perimetry practice. Dr. Wall has published extensively on such topics as variability and dynamic range for peripheral visual stimuli of various sizes, IIH, comparisons of sensitivity and specificity of different types of perimetry in disorders, such as glaucoma, homonymous hemianopia, and optic nerve and chiasmal disorders.

After 30 years on the Eye Department faculty (1967–1997), Dr. Thompson retired, to devote himself to projects dealing with the history of ophthalmology, and Dr. Kardon became head of the Neuro-ophthalmology section.

In 2004, the Neuro-ophthalmology Clinic was named “The H. Stanley Thompson Neuro-Ophthalmology Clinic” (Fig. 7). Under Kardon’s direction, both the clinical practice and the associated research have grown vigorously.

**THE POST-THOMPSON YEARS**

Dr. Kardon’s recent research has involved using the pupillary light reflex to measure rod, cone, and melanopsin-mediated responses. He and his colleagues also have measured electromyography of the orbicularis oculi muscle and skin conductance in patients to characterize photosensitivity. Much of this work stems from Dr. Kardon’s role as the Director of The Iowa City VA Center for Prevention and Treatment of Vision Loss. This Center is funded by the Department of Veterans Affairs to study optic nerve and retinal disorders that have relevance to the military population, especially in relation to traumatic brain injury. Kardon concentrates a good deal of his research and clinical efforts on visual disorders related to traumatic brain injury, especially the neuroprotection and treatment of vision loss and the detection, monitoring, and treatment of ocular and central nervous system diseases. The Neuro-ophthalmology service has seen the addition of several faculty members under the direction of Dr. Kardon.

The Neuro-Ophthalmology service has seen the addition of several faculty members under the direction of Dr. Kardon. Dr. Andrew G. Lee moved to Iowa City from Houston, TX, to join the neuro-ophthalmology faculty in 2000. His wife, Dr. Hilary Beaver practiced in our Comprehensive Ophthalmology Service and also was the director of medical student
education. During his time in Iowa, Dr. Lee was very active clinically and also published in several areas of neuro-ophthalmology, including IIH, giant cell arteritis, Leber hereditary optic neuropathy, Charles Bonnet syndrome, infectious neuroretinitis, and neuroimaging. Dr. Lee showed considerable interest in and an aptitude for teaching residents. He was extensively involved in the development and implementation of the Accreditation Council for Graduate Medical Education residency competencies at the University of Iowa and in publications regarding the competencies. In March 2009, Dr. Lee returned to Texas, accepting a position in Houston as Chairman of Ophthalmology at Houston Methodist Hospital where he is a Professor of Ophthalmology, Neurology, and Neurosurgery at Weill Cornell College and on the faculty at Baylor College of Medicine (Adjunct Professor), The University of Texas Medical Branch, Galveston, TX (Clinical Professor), and the UT MD Anderson Cancer Center. Dr. Lee is still an adjunct professor with our Ophthalmology Department at Iowa.

In 1999, Chris A. Johnson, PhD, came to Iowa from Devers Eye Institute and the Discoveries in Sight Research Labs in Portland, OR. At first glance, a PhD in Psychology seems an unlikely addition to a neuro-ophthalmology service, but, in fact, Dr. Johnson’s expertise in visual fields was a natural fit. Dr. Johnson had more than 20 years of experience in developing and managing visual field reading centers at several locations before his arrival at the University of Iowa. He has published extensively on many topics related to visual fields and has had more than 30 years of research funding from the National Eye Institute and other extramural sources. His research interests include perimetry, visual field testing and psychophysical evaluation of eye diseases, development of automated diagnostic test procedures, imaging and topography of the optic nerve head and retinal nerve fiber layer, visual factors related to task performance in transportation/aviation and industry, and motion and flicker perception. He has established a Visual Field Reading Center at the University of Iowa, which evaluates, documents, and stores visual field results from multicenter trials.

In July of 2007, Dr. Steve Stasheff joined the Pediatric Faculty in Neurology with a joint appointment in ophthalmology. Dr. Stasheff completed residencies in pediatrics and pediatric neurology followed by a postdoctoral fellowship in retinal neurophysiology. He simultaneously completed a neuro-ophthalmology fellowship at Beth Israel-Deaconess Medical Center and New England Medical Center under former Iowa neuro-ophthalmology fellows, Jason Barton and Thomas Hedges, III. Before moving to Iowa, Dr. Stasheff was an instructor at Harvard Medical School/Children’s Hospital-Boston/Beth Israel-Deaconess Medical Center in Boston. He sees neuro-ophthalmology patients in the Ophthalmology Department with a special interest in pediatric neuro-ophthalmology and serves as the Medical Director of the Electrophysiology Service in the Eye Department. He has published articles on retinal vs optic nerve disease, cortical visual deficits, ocular motor neuromuscular disease, light adaptation, the pupillary light reflex, retinal degenerations, retinal ganglion cells, and the inner retinal pathways.

In July 2008, Dr. Reid Longmuir joined the faculty. He completed an ophthalmology residency at Iowa, and two 12-month Iowa fellowships, one in neuro-ophthalmology and one in glaucoma. He now functions as neuro-ophthalmology faculty at the University of Iowa and staffs both neuro-ophthalmology and glaucoma patients at the Veterans Administration Medical Center. He is the director of medical student education in the Ophthalmology Department. Dr. Longmuir has published articles on neuro-ophthalmological disorders associated with systemic diseases, such as muscular dystrophy and systemic lupus erythematosus as well as an IIH, Horner syndrome, and optic disc edema.

In December 2010, Dr. Matthew Thurtell was welcomed as the newest addition to the Iowa Neuro-ophthalmology group with a joint appointment in Neurology and the Department of Veterans Affairs Medical Center. Dr. Thurtell trained in Neurology in Sydney, Australia, under the mentorship of Dr. G. Michael Halmagyi, a well-known expert in ocular motility and the vestibular system. He then completed a clinical fellowship with Drs. John Leigh and Robert Tomsak at Case Western Reserve in Cleveland, OH. Dr. Thurtell continued to develop his expertise in eye movement and in the afferent visual system, with special interest in pathophysiology and treatment of raised intracranial pressure as it pertains to the visual system. Dr. Thurtell has added important expertise to the Iowa Neuro-ophthalmology service in central and peripheral aspects of ocular motility physiology and pathology. He also continues his interest and expertise in the afferent visual system, including IIH, which follows a long history of interest in this area at Iowa by Dr. Michael Wall and Dr. James Corbett. And of course, Dr Hayreh’s clinic was always adjacent to ours, and patients with anterior ischemic optic neuropathy were always a shared area of interest. Figure 8 includes the current members of the “neuro-ophthalmology team” at the University of Iowa.

Portions of an Interview With Dr. Thompson
Conducted by Dr. Kardon

Kardon: What was the best thing that has happened in neuro-ophthalmology in the last 30 years?

Thompson: That would be the clear emergence of neuro-ophthalmology as a subspecialty. Drs. Walsh, Hoyt, Smith, and Cogan were the first sparks to ignite an interest in the subspecialty; and neuro-ophthalmology has now come of age and has become an accepted division of both Neurology and Ophthalmology.

This process seems natural enough: if you take an interest in a certain medical topic, and pursue it, then soon other doctors will be referring certain patients to you, or sending someone to you for training. Lawton Smith (who had been a resident at Wilmer when William Hoyt was a fellow with Walsh) started to hold a neuro-ophthalmology...
course in Miami every winter and had some of his colleagues give lectures.

The Annual Walsh Meeting emphasized neuropathologic correlations, and soon Tom Carlow organized the Rocky Mountain Neuro-Ophthalmology Meeting, which grew into the North American Neuro-Ophthalmology Society (NANOS). There was an exciting novelty to it all. The dynamic personality of Lawton Smith had great audience appeal, and he helped to sell neuro-ophthalmology as a worthwhile subspecialty; and the encyclopedic, serious-minded approach of William Hoyt gave it further credibility. So the best thing that happened to neuro-ophthalmology was that it came together as a subspecialty due to the influence of a number of notable people (9).

Kardon: And for the other side of the coin, what would be the worst thing that has happened in neuro-ophthalmology in the last 30 years?

Thompson: One of the burdens that we have to carry in our subspecialty is that our work requires time and thought; and that makes us vulnerable to the economic pressures. The practice of medicine is inevitably influenced by insurance companies who want doctors to provide a prompt answer and move onto the next patient. A neuro-ophthalmologist needs time to put things together while trying to solve the patient's problems, and time to test various possibilities. If all neuro-ophthalmologists were given only seven minutes per patient, our subspecialty would crumble. So, the worst thing has been the “hurry-up” pressure.

A neuro-ophthalmology fellowship should be like any apprenticeship. The fellow in training recognizes that the partnership with his teacher gradually evolves from the teacher-to-student kind, into a colleague-to-colleague relationship. When the teacher and fellow are working together in the same room, the fellow sees how the mentor talks to the patient and how situations are handled, and understands the thought process. The fellow also needs to understand the anxieties of the patient and family, and how this impacts the history as the clinical problem comes to medical attention (especially with “functional” cases) and needs to learn how to effectively communicate with the patient and family. Time constraints interfere with this process. In certain complicated or unusual cases, the fellow will call in the teacher early in the evaluation to see how his teacher handles difficult situations.

Kardon: What makes for the best neuro-ophthalmologist?

Thompson: The best: may be unreachable, but an academic neuro-ophthalmologist should, ideally, be a caring physician willing to be considerate and helpful to patients, and ready and able to explain things to them. There should be a solid knowledge base in ophthalmology, neurology, and neurosurgery that will help to bring together key bits of information to solve clinical problems. In an academic job there needs to be an eagerness to find answers to weird questions, and a willingness to dig vigorously for new knowledge.

An academic neuro-ophthalmologist should also recognize the value of expanding and broadening his or her knowledge in different directions to form useful “knowledge appendages.” This knowledge might then connect with people in other areas of expertise (eg, biostatisticians, biologists, biochemists). This is, of course, one of the reasons for valuing collegiality in an academic institution. An example from my career was working with Michael Brody, PhD, a Professor of Pharmacology, who helped me in differentiating preganglionic from postganglionic lesions in patients with Horner syndrome.

REFERENCES

Literature Commentary


**Purpose:** Scanning laser polarimetry (SLP) reveals abnormal retardance of birefringence in locations of the edematous peripapillary retinal nerve fiber layer (RNFL), which appear thickened by optical coherence tomography (OCT), in non-arteritic anterior ischemic optic neuropathy (NAION). We hypothesize that initial sector SLP RNFL abnormalities will correlate with long-term regional visual field loss due to ischemic injury.

**Methods:** We prospectively performed automated perimetry, SLP, and high-definition OCT (HD-OCT) of the RNFL in 25 eyes with acute NAION. We grouped visual field threshold and RNFL values into Garway-Heath inferior/superior disc sectors and corresponding superior/inferior field regions. We compared sector SLP RNFL thickness with corresponding visual field values at presentation and at >3 months.

**Results:** At presentation, 12 eyes had superior sector SLP reduction, 11 of which had inferior field loss. Six eyes, all with superior field loss, had inferior sector SLP reduction. No eyes had reduced OCT-derived RNFL acutely. Eyes with abnormal field regions had corresponding SLP sectors thinner (P = 0.003) than for sectors with normal field regions. During the acute phase, the SLP-derived sector correlated with presentation (r = 0.59; P = 0.02) and with >3 months after the presentation (r = 0.44; P = 0.02) corresponding superior and inferior field thresholds.

**Conclusions:** Abnormal RNFL birefringence occurs in sectors corresponding to regional visual field loss during acute NAION when OCT-derived RNFL shows thickening. Since the visual field deficits show no significant recovery, SLP can be an early marker for axonal injury, which may be used to assess recovery potential at RNFL locations with respect to new treatments for acute NAION.

The authors expand upon their previous work on SLP and OCT in optic disc edema of various causes (1). In the current study, they evaluated patients with acute NAION, and, not surprisingly, the OCT showed thickening of the RNFL. Meanwhile, the SLP in the acute phase showed thinning of the RNFL in areas corresponding to permanent visual field loss and normal RNFL in corresponding areas that eventually showed improvement in the visual field.

Why would this be? SLP does not directly measure the actual dimensions of the RNFL. Instead, SLP depends upon the birefringence of the parallel structural organization of the RNFL. The birefringence induces a delay, called retardance, in 1 of 2 orthogonal beams of polarized light. The retardance is then used to calculate the RNFL thickness. Presumably, permanently damaged axons develop a disrupted parallel structure, which affects the calculated RNFL.

The findings of this report could be extremely helpful in predicting whom to enroll in clinical trials of NAION. Clinically, it could represent a useful tool in counseling patients with acute NAION.

—Michael S. Lee, MD

OCT has overtaken SLP in the clinical world as the main retinal imaging tool with few ophthalmology practices using the GDx (Carl Zeiss Meditec, Dublin, CA). However, this study demonstrates a major advantage of SLP in the patient with acute NAION (and in the prior study (1) with optic neuritis). Being able to predict recovery of vision using SLP in a patient with optic nerve ischemia will be very helpful in counseling patients and evaluating future clinical trials.

—Mark L. Moster, MD

**REFERENCE**


**Objective:** Although accumulating evidence suggests that a malfunction of the CSF system in idiopathic intracranial hypertension (IIH) may give rise to olfactory dysfunction, little objective knowledge is available at present about the olfactory capacity of patients with this condition.

**Methods:** Seventeen patients with IIH and 17 age- and sex-matched controls were included. The extended Sniffin’ Sticks procedure was used to test odor threshold, discrimination, and identification (TDI).

**Results:** Median (interquartile range) values of the composite TDI score (29 [26.5–35.5] vs 35 [34–37]; P = 0.003) were reduced in patients with IIH. Furthermore, Spearman
correlation revealed reduced TDI values in patients with a recent clinical deterioration of IIH (r = 0.66; P = 0.004). **Conclusions:** Our pilot study provides new evidence that olfaction is impaired in patients with IIH, especially in those who have been newly diagnosed or who have experienced a recent clinical deterioration.

This study found that olfactory function was decreased in IIH patients compared with controls and that patients with acute IIH or recent worsening had the most impaired olfactory function. Although only 29% admitted to olfactory problems on review of systems, more were found to have deficits. Forty-one percent of IIH patients and 80% of those with acute IIH had absolute hyposmia. The mechanism may be similar in dysfunction of the olfactory nerve as in the optic nerve. Although we will not likely be testing smell in our patients, we may want to query our IIH patients about it. Who knows, perhaps we will find transient olfactory obscurations with change in posture!

—Mark L. Moster, MD

I believe that hyposmia and anosmia tend to alter the taste of food and that many individuals with altered smell add more sugar and/or salt to improve food flavor. Hyposmia may affect the ability of IIH patients to lose weight effectively, and testing olfactory function could help us counsel IIH patients regarding weight control.

—Michael S. Lee, MD

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**Objective:** To identify the source of delayed visual evoked potential (VEP) latencies in the fellow eyes of patients with optic neuritis (ON) and determine whether these latencies stem from clinically silent demyelination or reflect an adaptive process for synchronization with the affected eyes.

**Methods:** The study sample comprised 17 patients whom we followed for 12–26 months after unilateral first-ever ON diagnosis and 17 age-matched controls. To avoid confounding effects of axonal loss, only intact fellow eyes (except for VEPs) were included. Subjects underwent standard visual evaluation, motion perception, and static- and time-constrained stereo tasks. Assessments included VEP, optical coherence tomography, high-resolution magnetic resonance imaging, and diffusion tensor imaging.

**Results:** We observed delayed VEP peaks (P100) in both affected and fellow eyes. However, while these were derived from prolonged time to start in the affected eyes, supporting the existence of demyelination, time to start in the fellow eyes was intact. VEP latencies in the fellow eyes could not be explained by demyelinating lesions along postchiasmal pathways (assessed by diffusion tensor imaging). Delayed peaks in fellow eyes resulted from a wider waveform, which evolved over time and occurred with a concomitant decrease in the gap in time between VEP peaks of both eyes. These changes offered a functional advantage: synchronization of inputs highly correlated with improved time-constrained binocular perception.

**Conclusion:** Delayed latencies in the fellow eyes may reflect adaptive mechanisms at the cortical level that improve binocular integration over time to adjust for the damage incurred. These data provide a unique demonstration of temporal reorganization that compensates for delayed transmittal of visual information to the cortex.

The authors retrospectively evaluated individuals with unilateral optic neuritis and good visual recovery. They found a delay in the P100 among affected eyes (AE) and fellow eyes (FE). In the AE, the width of the VEP waveform was similar to controls, but the time to start was significantly delayed compared to controls and FE. For the FE, the time to start was similar to controls, but the width of the waveform was wider than controls (but the width was not statistically different from the AE). The authors conclude that the widening of the waveforms in the FE may reflect an adaptive delay to more closely match the AE and provide more symmetric input from each eye.

This is an interesting concept, which needs further validation. I think it would be interesting to see if this adaptive delay occurs in the FE of patients with other optic neuropathies. I also wonder how quickly this adaptation takes place. The FE showed delayed VEP time to peak at presentation compared to controls, suggesting that if the adaptation occurs, it does so in the acute phase. In this study over time, a significant increase in the time to peak in the FE did not occur (described as a “trend”), which could be explained by an adaptive change or perhaps the small number of patients.

—Michael S. Lee, MD

This is a very interesting study, which suggests that delayed VEP waveforms in the fellow eye of optic neuritis patients represent a central adaptation mechanism rather than a primary abnormality of the optic nerve. Although this is plausible, I don’t think this study has proven the concept. First, Michael, I agree with your concern that the delayed VEP in the FE is present at the time of the optic neuritis, a bit early for central adaptation. This study also conflicts with prior papers in which the FE at onset often has a normal VEP latency.

A second concern is the claim that the optic nerve in the FE is not demyelinated because the motion perception task is normal in these eyes. Although this may be correct, there is no real proof that it is, particularly with less of a delay in the FE than the AE, where motion perception is impaired.

I do think that central adaptation may be a mechanism contributing to the delayed VEP in the FE. In particular, the prolonged waveform with an essentially normal N75 peak latency would support this. An interesting follow-up study would be prospective in multiple sclerosis patients who have normal baseline VEPs prior to developing unilateral
optic neuritis. We will then see VEP changes in the FE from baseline along with those in the AE.

—Mark L. Moster, MD


Purpose: The objective of this study was to determine whether transneuronal retrograde degeneration (TRD) of the retinal ganglion cells (RGCs) could be detected by optical coherence tomography (OCT) in humans with lesions other than that of the occipital lobe or visual cortex. In addition, whether laterality and severity of retinal nerve fiber layer (RNFL) damage correlated with 3 other variables was determined: laterality of hemispheric damage, arterial territory of infarct, and age of infarct.

Design: Cross-sectional, case-control design.

Participants: Forty-six patients with cerebral ischemic infarction diagnosed based on brain magnetic resonance imaging and 46 normal controls were enrolled.

Methods: All subjects underwent a complete ophthalmic examination including OCT. Cerebral infarction was categorized by arterial territory: anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA). Eyes on the same side of the infarction were referred to as ipsilateral eyes, and eyes on the opposite side of the infarction were referred as contralateral eyes.

Main Outcome Measures: RNFL thickness.

Results: Average, superior, temporal, inferior, and nasal RNFL thicknesses were different significantly between patients with cerebral infarction and normal controls. The RNFL thicknesses were reduced significantly at the superior, inferior, and nasal quadrants in the contralateral eyes and at the superior, inferior, and temporal quadrants in the ipsilateral eyes. The RNFL thickness reduction was greater in patients with PCA infarction, followed by MCA and ACA infarction, respectively. Factors related to the average RNFL thickness were time after stroke onset and infarction territory based on both univariate \((P = 0.027\) and \(P = 0.036\), respectively) and multivariate \((P = 0.036\) and \(P = 0.047\), respectively) analyses.

Conclusions: RNFL thickness was reduced in patients with cerebral infarction, providing evidence for TRD of the RGCs. TRD was more pronounced in the nasal nerve fiber layer of the contralateral side and in the temporal nerve fiber layer of the ipsilateral side of cerebral damage.

Although the classic teaching is that patients with posterior visual pathway lesions from early in life develop transsynaptic degeneration, recent reports with OCT have shown this occurring in acquired lesions in adults. Therefore, some of the findings in the current study are to be expected. This includes eventual loss of RNFL after stroke and the predication for temporal loss ipsilateral to and nasal loss contralateral to the side of the infarct. What is a bit surprising is the loss of RNFL after anterior cerebral artery (ACA) infarct. These patients do not have hemianopias and presumably spare visual pathway fibers. However, in this study, patients with ACA infarcts had a mean deviation on the ipsilateral and contralateral visual field (VF) almost as great as the middle cerebral artery infarcts and much less than posterior cerebral artery infarcts. Unfortunately, the VFs are not described in this article, and there was no attempt to correlate the VF with the RNFL loss. I wonder whether the patients described with ACA infarcts really had other territories involved and had an homonymous hemianopia. If not, perhaps, the RNFL loss is not a result of the cerebral infarct but associated as part of a more diffuse vascular process. On a practical level, one must be cautious in attributing RNFL loss to a primary optic neuropathy if the patient has had a prior cerebral infarct.

—Mark L. Moster, MD

Transneuronal retrograde degeneration seems to occur in human and animal histologic studies, and this article supports the idea that it also happens in vivo. To me, these data bolster the contention that vision restitution therapy should not logically improve homonymous hemianopia among those individuals who suffered a stroke years ago since significant retinal ganglion cell atrophy already has taken place.

—Michael S. Lee, MD


Objective: To describe the prognosis and retinal location in patients presenting with acute traumatic maculopathy and extramacular retinal injuries.

Design: Retrospective, noninterventional case series.

Participants and Controls: All patients presenting with commotio retinae or sclopetaria retinae to the Birmingham Midland Eye Centre Eye Casualty from October 1, 2007, to February 23, 2011.

Methods: The notes of all patients presenting with ocular trauma in the specified period were examined to identify suitable patients, and demographic and injury data were extracted.

Main Outcome Measures: Outcome was assessed by visual acuity (VA).

Results: For macular commotio retinae, 53 patients were identified, of whom 34 had adequate follow-up to determine the final VA. The median presenting VA was 20/40; 25 patients (74%) recovered to 20/30. The median extent of visual recovery was 0.18 logarithm of the minimum angle of resolution (logMAR). For extramacular commotio retinae, 117 patients were identified, of whom 58 had adequate follow-up to determine the final VA. The median presenting VA retinae was 20/30; 55 patients (95%) recovered to 20/30. The median extent of visual recovery was logMAR 0.076. There was 1 case of extramacular sclopetaria retinae. The 3 most common retinal locations of extramacular
commotio retinæ, in order of frequency, were inferotemporal (37%), temporal (17%), and superotemporal (17%); <5% of cases were in a nasal location.

Conclusions: This is the first report on the prognosis of acute traumatic maculopathy and extramacular commotio retinæ. After macular injury, 26% of patients were left with a VA of ≤20/30, although the proportion with visual impairment is higher than this because 1) a deterioration from 20/15 to 20/30 is significant to many patients and 2) additional patients are visually impaired by symptomatic paracentral visual field defects, despite a normal VA. Reduced VA after extramacular commotio retinæ may represent occult macular injury or previously undiagnosed visual impairment in the affected eye. Extramacular commotio occurs mostly in an inferotemporal to temporal location, consistent with direct trauma to the sclera overlying the injured retina.

Recently, I overheard an ophthalmologist talking on the phone with the trauma service about a patient. He told them that the patient had commotio retinæ, and he would almost certainly recover. In fact, I recall hearing the same schpiel when I was in residency, and I have repeated it myself. This article evaluated a relatively large group of patients and showed that about one-fourth with macular commotio and 3% with extramacular commotio had final visual acuities of 20/30 or worse. This prognostic information is very helpful in counseling patients with blunt ocular trauma, especially those with macular commotio.

As neuro-ophthalmologists, we often encounter individuals who claim visual loss after an ocular injury. Looking carefully at multifocal electroretinogram and the outer retina on OCT may help detect organic loss among these patients.

—Michael S. Lee, MD

I agree that this is a helpful study that gives us data to back up the clinical impression that patients with commotio retinæ may or may not have a reasonable degree of recovery.

—Mark L. Moster, MD

Methods: The study sample consisted of 37 patients from a clinical practice, 11 men and 26 women. Inclusion criteria consisted of patients treated a minimum of 15 consecutive years for facial dystonia. Seven patients had hemifacial spasm, 4 Meige syndrome, and 26 benign essential blepharospasm. Main outcome measures consisted of treatment efficacy and adverse events.

Results: Mean treatment duration was 19.4 years (SD, 2.2) with an average of 62 (SD, 22) treatments of 70.2 (SD, 20.8) neurotoxin units. Mean duration of treatment efficacy was 127 days (SD, 37) with a 5% physician-reported minor adverse event rate and no major adverse events over each patient’s clinical course. Patients reported no major and 20% incidence of minor adverse events over the treatment course.

Conclusion: Results suggest that long-term botulinum toxin treatment produces clinical success in the alleviation of facial dystonia symptoms. Treatment produced a low incidence of major adverse events and minor adverse events. Previous studies may underreport clinical success and overreport adverse events because of study design.

This retrospective study from a single oculofacial plastic surgery group looked at patients who had been treated with botulinum toxin A for at least 15 years. By using the fourth injection (presumably beyond a “titration phase”) as a baseline, Czyz et al found little change over the years, with excellent success, and a stable duration of response to each injection and a low incidence of adverse events.

The authors claim that prior studies may have underreported efficacy and overreported adverse events because of study design. However, the current study design, which only included patients treated over 15 years, would filter out patients with suboptimal efficacy or more adverse events and is biased toward better results.

—Mark L. Moster, MD

I hate to admit it, but I agree with you, Mark. There is tremendous selection bias since these patients are well established in a single practice. The patients from this practice with poor outcomes or more/worse adverse events might easily have left the practice before the 15-year threshold and missed the study. For instance, I had a patient whom I have injected for several years. She developed diplopia following a botulinum toxin injection earlier this year, and she later informed me that she was extremely close to finding another provider but decided to give me one more try. She might have left my practice before 15 years without my knowledge. It would have been better to see all of the data from all the patients in this practice to compare botulinum toxin dose and duration.

—Michael S. Lee, MD
Optic Disc Doubling or Pseudo-Optic Disc in Colobomatous Retinal Abnormality?

In their Photo Essay, Padhi et al (1) described a patient with optic disc doubling. We examined a similar case (Fig. 1) and believe that the case reported by Padhi et al, like ours, has a coloboma located inferiorly to the true optic disc.

First, the optical coherence tomography (OCT) image in the report by Padhi et al shows naso-temporal asymmetry of the nerve fiber characteristic of a true optic disc, but convergence of the inner retinal layers toward the second disc. This finding is typical of retinal coloboma (2). Second, inferior retinal colobomas often are associated with abnormal retinal vasculature. Third, on OCT imaging, typically there is a discontinuation of the IS/OS junction near a coloboma (3). This finding may be present in the patient of Padhi et al, although it is difficult to assess due to the quality and angulation of the scan.

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REFERENCES
Reply—Optic Disc Doubling or Pseudo-Optic Disc in Colobomatous Retinal Abnormality?

We thank Gerth-Kahlert and Wildberger for their comments on our article dealing with optic disc doubling (1). In their case, the blood vessels that appear to arise from the coloboma inferior to the disc are actually a continuation of the blood vessels emerging from the optic disc. This is an example of a lesion simulating the optic disc or pseudo-disc doubling.

In contrast, in our patient, there is no connection on the surface of retina between the 2 groups of vessels. The emerging retinal vasculature from the optic disc has a normal configuration except for an absent inferotemporal venous trunk. The supenor temporal part of the inferior disc is occupied by the cup, and the inferonasal portion shows the origin of another independent but incomplete retinal vascular system. It consists of superotemporal and inferotemporal venous and superotemporal and inferonasal arterial arcades, converging at one point. There is a single foveal avascular zone corresponding to the true optic disc at a level slightly lower than its normal position. The inferotemporal portion of the perifoveal capillary net is formed by the tributaries from the superotemporal vascular arcade from the second disc. Fundus fluorescein angiography shows simultaneous and similar filling patterns of both vascular systems.

The arcuate visual field defect in our patient demonstrates that the inferior optic disc is nonfunctioning. The hypopigmented bridging track possibly indicates an embryological relationship between the 2 discs. The 2 separate vascular systems, the presence of 2 blind spots on visual field testing, and the crater-like depression over the inferior disc in optical coherence tomography (OCT) suggest that our patient has true doubling of the optic disc.

With regard to our OCT findings, unfortunately we do not have a horizontal line scan passing across the inferior disc to show nasotemporal asymmetry of the nerve fiber layer. We agree with Gerth-Kahlert and Wildberger that discontinuation of the junction of the inner and outer photoreceptor segment is difficult to assess because of the quality and angulation in the scan. Ultrahigh resolution OCT passing across both optic discs would give better delineation of the adjacent retinal architecture.

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REFERENCE

Idiopathic Intracranial Hypertension in a Child With Obstructive Sleep Apnea Cured by Tonsillectomy/Adenoidectomy

We read with interest Dr Michael Wall’s editorial on idiopathic intracranial hypertension (IIH) (1). We describe a surgically treatable case of IIH associated with obstructive sleep apnea (OSA).

A 9-year-old girl presented to our emergency department with complaints of diplopia, headaches, nausea, and vomiting for 5 days associated with mild neck stiffness. She was taking no medications. Her height was 62 inches, weight 159 lbs for a body mass index of 29, (over the 95th percentile for girls her age and height).

Visual acuity was 20/40, right eye and 20/25, left eye. Pupillary reactions, color vision, and confrontation visual fields were normal. Extra-ocular motility demonstrated limited abduction bilaterally. Funduscopic examination revealed mild bilateral optic disc swelling with dilated retinal vessels without hemorrhage or exudate. Neurological examination was normal. Automated visual fields performed 3 days later showed superior arcuate scotomas in each eye and a nasal step in the right eye.

Magnetic resonance imaging of the brain was normal as was magnetic resonance venography. Opening pressure on lumbar puncture was greater than 50 cm H2O, and cerebrospinal fluid analysis was normal. The patient was diagnosed with IIH and prescribed 500 mg of acetazolamide 4 times a day. This was eventually reduced to 500 mg twice a day. Her diplopia resolved, but 6 months later, she complained of...
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intractable headaches and had worsening papilledema. Opening pressure on repeat lumbar puncture was 44 cm H₂O.

At this point, the patient’s mother reported that the child had OSA, which was diagnosed 2 years previously. Polysomnographic studies had demonstrated severe OSA with a respiratory disturbance index of 21 events per hour. The patient was irregularly using a continuous positive airway pressure machine.

On physical examination, the patient was found to have hypertrophic tonsils and adenoids with complete obstruction of her nasopharynx. She underwent adenotonsillectomy and postoperatively reported immediate relief of her headaches. At her last visit, she had complete resolution of all symptoms referable to IIH and subjective improvement in her sleeping pattern.

Recent studies have suggested a potential relationship between IIH and OSA (2–6). The nocturnal hypoxemia and hypercarbia present during apneic episodes cause cerebrovasodilatation and secondary increased ICP (7). OSA may be a risk factor in the worsening of IIH, the importance of which is compounded by the fact that the 2 conditions frequently coexist in patients with obesity. Screening for papilledema is recommended in all patients with OSA who have visual symptoms (8,9). In children who are found to have OSA and IIH, airway obstruction caused by adenotonsillar enlargement should be considered. We are not aware of previously reported cases where the removal of adenotonsillar tissue led to significant improvement in OSA and resolution of intracranial hypertension.

Evelyne Kalyoussef, MD
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A Limited Form of Neuromyelitis Optica With a Lesion of the Fourth Nerve Nucleus

We read with great interest the review article “Neuromyelitis optica” by Morrow and Wingerchuk (1). The authors referred to several reports of abnormal eye movements in association with brainstem lesions in NMO (2–4). We evaluated a patient with a limited form of NMO with a fourth nerve palsy.

A 62-year-old woman with a history of numbness in the legs, nausea, and repeated vomiting presented with vertical diplopia and numbness in the left arm and chest. Neuroophthalmic testing demonstrated visual acuity of 20/20 in both eyes, full visual fields, and normal ophthalmoscopy. The patient had a right hypertropia that increased in left gaze and head tilt to the right. Ocular motility was otherwise unremarkable.

Magnetic resonance imaging (MRI) showed hyperintense areas in the midbrain, pons, and medulla (Fig. 1) and in the spinal cord from C5 to T1 (Fig. 2). NMO antibody was positive, whereas acetylcholine receptor, nuclear, SS-A, and SS-B antibodies were all negative. Cerebrospinal fluid analysis revealed no oligoclonal bands.

The patient was diagnosed with a limited form of NMO due to the presence of NMO antibody and longitudinally extensive spinal cord lesions. She was treated with intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days) followed by oral prednisolone (10 mg/day with gradual taper). Two months after the third pulse, vertical diplopia had almost disappeared.

The authors report no conflicts of interest.

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totally resolved with a decrease of the hyperintense areas on MRI.

Our patient with a right fourth nerve palsy had a form of NMO, a subtype of NMO spectrum disorder. Reports of cases of NMO or NMO spectrum disorder with ophthalmoplegia are rare. Gilmore et al (5) described a patient with Parinaud syndrome, in which MRI abnormalities were found in periaqueductal gray matter. Shinoda et al (3) found a midbrain tegmentum lesion adjacent to the aqueduct on MRI causing wall-eyed bilateral internuclear ophthalmoplegia syndrome in a patient with NMO spectrum disorder. In our patient, MRI showed a high-intensity lesion in the area of the fourth nerve nucleus causing vertical diplopia. In addition, our patient had a history of nausea and vomiting likely due to NMO involving the medullary floor of the fourth ventricle and area postrema (6,7).

![FIG. 1. A. Sagittal T2 magnetic resonance imaging (MRI) shows hyperintense lesions in the midbrain and pons (arrowheads). Axial FLAIR MRI reveals hyperintense lesions in the midbrain (B, arrowhead), pons (C, arrowhead), and left side of the medulla oblongata (D, arrowhead).](image)

![FIG. 2. Sagittal T2 spine magnetic resonance imaging demonstrates a hyperintense lesion extending for five vertebral segments (C5 to T1; arrowheads).](image)

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Spontaneous Cerebrospinal Fluid Otorrhea and Rhinorrhea in Idiopathic Intracranial Hypertension Patients

The article by Rosenfeld et al (1) described cerebrospinal fluid (CSF) leaks caused by chronically increased intracranial pressure (ICP) in 4 patients with idiopathic intracranial hypertension (IIH). The impression given by the authors is that spontaneous CSF leaks occur with equal frequency in the settings of normal and increased ICP. However, evidence indicates that the majority of spontaneous CSF leaks are associated with intracranial hypertension. Spontaneous CSF leaks traditionally have had a high recurrence rate after surgical repair (25%–87%), compared to less than 10% for most other etiologies (2–4). Identification of this underlying etiology has led to the widespread use of acetazolamide and, in some cases, permanent CSF diversion to control the ICP.

In a prospective evaluation of more than 5 years, 46 patients (average age, 51 years) with a cumulative 56 spontaneous CSF leaks were treated by the senior author (5). The data presented in the study provided concrete evidence that the majority of spontaneous CSF leaks are secondary to intracranial hypertension. Lumbar drain pressure measurements averaged 32.3 ± 9.0 cm H₂O and demographics mirrored IIH, where a large proportion of the patient cohort consisted of obese middle-aged women. Successful treatment of elevated ICP in combination with endoscopic repair can provide high success rates (93% primary and 100% secondary).

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We thank Vaphiades et al for their interesting comments. Our manuscript (1) describes 4 patients with idiopathic intracranial hypertension (IIH) and increased intracranial pressure (ICP) (range, 270–370 mm H₂O) that developed an unusual complication of spontaneous rhinorrhea or otorrhea (one as the initial chief complaint and the others later in the clinical course). Our study does not address the issue of whether most cases of spontaneous cerebrospinal fluid (CSF) leak occur in patients with high ICP or not. In a recent publication by Chaaban et al (2), it was reported that the majority of spontaneous CSF leaks are secondary to increased ICP, and that successful treatment of elevated ICP together with endoscopic repair can provide cure for most patients. This conclusion contradicts an earlier publication by Shugar et al (3) who have reported that 55% of cases of nontraumatic rhinorrhea described in the literature are associated with normal ICP and 45% with elevated pressure. Spontaneous rhinorrhea or otorrhea is rare in patients with IIH. One goal of our report was to raise awareness among clinicians to these unusual manifestations.

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Pseudotumor Cerebri Syndrome Associated With Giant Arachnoid Granulation

In the March 2013 issue of the Journal, we read with great interest the articles dealing with various disorders initially thought to be idiopathic intracranial hypertension, including spinal leptomeningeal lymphoma (1) and Sheehan syndrome (2). We describe a rare case of pseudotumor cerebri (PTC), associated with a giant arachnoid granulation (GAG) in the transverse venous sinus.

A 26-year-old healthy, nonobese man complained of horizontal diplopia for 1 month. Visual acuity was 20/25 in each eye, pupillary reactions were normal, and ocular motility revealed bilateral abduction deficits. Funduscopy demonstrated bilateral papilledema, and automated visual fields showed enlarged blind spots. Optical coherence tomography of the peripapillary retinal nerve fiber layer (RNFL) confirmed optic disc edema, with average RNFL thickness of 171 μm for the right eye and 275 μm for the left eye.

Computed tomography (CT) of the brain revealed no mass lesion or hydrocephalus but a hypodense filling defect at the origin of the right transverse sinus (Fig. 1A). Contrast-enhanced magnetic resonance imaging (MRI) and magnetic resonance venography confirmed a 3.5-cm filling defect, noted to be isointense to cerebrospinal fluid (CSF) (Fig. 1B, C). Because these findings initially were interpreted as subacute or chronic venous sinus thrombosis, a hypercoagulability work-up was initiated and the patient was started on daily aspirin (81 mg). On further review of the neuroimaging studies and based on the filling defect being isointense to CSF, the diagnosis was changed to GAG of the transverse sinus.

Lumbar puncture revealed an elevated opening pressure of 56 cm water, with normal CSF composition. The diagnosis of PTC was made, and treatment was initiated with oral acetazolamide 500 mg twice daily. Despite titrating doses of acetazolamide up to 1,000 mg twice daily, the patient’s diplopia persisted, and he developed more severe headaches with worsening papilledema.

Because of progressive symptoms and signs, intervention via an endovascular approach was offered to the patient. Cerebral venography revealed intact venous flow around the intraluminal obstruction in the right transverse sinus. Manometry showed pressure proximal to the GAG of 14 mm Hg and 3 mm Hg distal to the GAG. Because the appearance and pressures within the left transverse and superior sagittal sinuses were normal, stenting was not performed.
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The patient continued on medical treatment alone, with his doses of acetazolamide increased to 1,000 mg 3 times daily. A repeated lumbar puncture showed opening pressure of 32 cm water. His headaches and papilledema slowly improved and were resolved by 6 months. Repeat MRI revealed no change in the size of the hypodense filling defect in the right transverse sinus.

Arachnoid granulations filter CSF across the lining of the arachnoid into the cerebral venous system. GAGs are believed to be a normal variant (3,4), with an estimated prevalence of 0.3%–1.0% in adults (4). GAGs may mimic other entities and may be misdiagnosed as venous sinus thrombosis. However, venous sinus thrombosis is hyperintense on both CT and T1 axial MRI and enhances with contrast. Alternatively, GAGs are hypointense on CT and T1 axial MRI and do not enhance (4).

Although usually asymptomatic, GAGs have been reported in association with increased intracranial pressure (ICP) and PTC in only a handful of cases (5–8). Arjona et al (6) described a 51-year-old nonobese man who presented with transient visual obscurations and bilateral papilledema. The patient was found to have a GAG at the right transverse sinus–sigmoid sinus junction, with hypoplasia of the left transverse sinus. Opening pressure on lumbar puncture was 27 cm water. Unfortunately, the authors did not discuss the management of this case but believed GAG to be responsible for the elevated ICP. Choi et al (7) reported a 66-year-old woman with occipital headaches who was initially diagnosed as having dural sinus thrombosis. MRI confirmed the diagnosis of GAG, and a normal venous pressure gradient was found across the symptomatic lesion. The patient’s headaches were managed with medical therapy. Zheng et al (8) described a unique case of a patient with GAG in the dominant left transverse sinus and elevated pressure proximal to the GAG. Stenting of the transverse sinus reduced the pressure gradient across the lesion, as well as the ICP, and led to symptomatic improvement.

The cause of GAG formation is uncertain. It has been postulated that increased CSF volume and pressure may cause hypertrophy of the arachnoid granulations, with subsequent formation of a GAG (4). However, if this were the case, then many more patients with ICP from various etiologies would develop GAGs. Alternately, they may represent hyperplasia of preexisting arachnoid granulations or benign neoplasm of mesenchymal origin (3).

The clinical course of our patient raises the question of whether the GAG caused PTC or whether its presence was purely coincidental. Normal venous sinus pressures proximal to the GAG make it less likely that GAG raised venous sinus pressure and led to increased ICP. With medical therapy alone, PTC completely resolved in our patient. There is still the possibility that the GAG had caused increased ICP, and venous collaterals developed with time, facilitating venous outflow. We did not perform a follow-up cerebral venogram after our patient’s PTC resolved to evaluate this possibility.

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The authors report no conflicts of interest.
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Optic Perineuritis Secondary to Acute Retinal Necrosis

Optic perineuritis (OPN) has been recognized as a form of idiopathic orbital inflammatory disease, where the specific target is the optic nerve sheath (1-4). Most reported cases are isolated and idiopathic, but some have been associated with specific infectious or inflammatory disorders, including Wegener granulomatosis, giant cell arteritis, syphilis, and viral meningitis (5-8). A recent report by Townsend et al (9) documented OPN as a presenting finding in a patient with leukemia. We evaluated a patient with acute retinal necrosis (ARN) who subsequently developed OPN.

A 67-year-old man reported decreased vision in his left eye. Examination revealed visual acuity of 20/80 with cells in the anterior chamber, multiple patchy areas of necrosis in the peripheral retina, retinal vasculitis, optic disc swelling and vitritis (Fig. 1A). He was diagnosed with ARN and treated with acyclovir 800 mg intravenously 3 times a day. Despite antiviral therapy, vision declined to 20/200 in the left eye. Ganciclovir (2 mg/0.1 mL) was injected into the vitreous cavity, and the patient was prescribed oral famciclovir 500 mg, 3 times a day. On day 7, oral prednisolone (60 mg/day) was added. Prophylactic vitrectomy was performed with a silicone oil tamponade, and the patient’s vision gradually improved to 20/100 (Fig. 1B).

Systemic corticosteroids were tapered over 3 weeks and then discontinued, while maintaining oral famciclovir. After 3 days, the patient reported pain with left eye movement and had no light perception in the left eye. The fundus appearance was unchanged, and a fluorescein angiography showed no specific findings to explain the vision loss. Flash visual evoked potential was nonrecordable in the left eye. Although magnetic resonance image (MRI) of the brain appeared normal, there was enhancement of the left optic nerve sheath (Fig. 2). Cerebrospinal fluid analysis was unremarkable. The patient was given high-dose intravenous methylprednisolone (1 g/day) for 3 days, followed by oral steroids and maintained on famciclovir. Visual acuity in the left eye recovered to 20/500 at 2 months, without further improvement over the following 10 months.

Optic nerve involvement in ARN has been reported in 47%-57% of cases (10-12). Proposed mechanisms include intraneural vasculitis, direct viral invasion of the optic nerve,
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FIG. 1. A, Left fundus shows peripheral retinal necrosis, optic disc swelling, and vitreous haziness. B, After systemic therapy and vitrectomy with silicone oil tamponade, there is resolution of retinal necrosis and optic disc swelling with sheathing of the retinal vessels and optic disc pallor.
and compression caused by inflammatory exudate within the optic nerve sheath (11,13,14). Our case is consistent with the last proposed mechanism producing the neuro-imaging findings of OPN. Sergott et al (11) demonstrated enlargement of the optic nerve sheath in 2 patients with ARN. Because their report preceded the advent of MRI, they based the proposed mechanism on operative findings of optic nerve fenestration in 1 patient. After incision of the nerve sheath, they described: “a large gush of serosanguinous CSF,” which led to an improvement in visual acuity.

Once antiviral therapy has been initiated, systemic steroid therapy often is used in patients with ARN and ARN-associated optic neuropathy to reduce inflammation. However, the effect and duration of steroid treatment remains controversial, because there are no controlled studies of its efficacy.

Optic perineuritis associated with ARN has not been reported previously. In our patient, it developed during antiviral treatment and shortly after steroid therapy was discontinued. It may have been because of relapse or delayed onset of disease within the optic nerve.

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FIG. 2. Postcontrast T1 axial orbital magnetic resonance imaging with fat suppression shows enhancement of the left optic nerve sheath (arrow).
Ethambutol Optic Neuropathy in a Hemodialysis Patient Receiving a Guideline-Recommended Dose

We read with interest the review of mitochondrial optic neuropathies by Wang and Sadun (1). We report a case of ethambutol optic neuropathy in a patient receiving maintenance hemodialysis, who was treated with an ethambutol dose of 20 mg/kg 3 times per week. Other published reports of ethambutol optic neuropathy in patients receiving hemodialysis cite a daily ethambutol dose (2,3). The dose in this case was prescribed 3 times per week according to the Centers for Disease Control and Prevention (CDC), in conjunction with the American Thoracic Society and the Infectious Diseases Society of America, tuberculosis treatment guidelines for patients with renal dysfunction (4).

A 79-year-old woman weighing 60 kg presented to our outpatient ophthalmology clinic with progressive visual difficulty occurring over 4 weeks. Her medical history included atrial fibrillation, diabetes mellitus, and chronic kidney disease requiring hemodialysis three times per week.

Approximately 1 year previously, evaluation of dyspnea included chest computed tomography (CT) that showed multiple calcified lung nodules, thickening of the interlobular septae and pleural fissures on the right, opacities in the right upper lobe with tree-in-bud appearance, and multiple borderline enlarged mediastinal lymph nodes. QuantiFERON-TB Gold testing was positive. Initial results from a bronchoalveolar lavage showed acid-fast bacilli, and cultures from these samples grew Mycobacterium tuberculosis.

The patient began tuberculosis treatment with isoniazid 300 mg daily, pyridoxine 25 mg daily, rifampin 600 mg daily and pyrazinamide 1500 mg (25 mg/kg) three times per week. The medications were given after hemodialysis and followed the recommendations of the CDC (4). Within 24 hours of treatment initiation, she developed confusion and somnolence that worsened over the next 7 days. She was admitted into the hospital for further evaluation. Cerebrospinal fluid, blood, and urine cultures did not reveal an infectious cause of her symptoms. A non-contrast brain CT was normal. Isoniazid-induced central nervous system toxicity was suspected, and her medications were changed to an alternative CDC-recommended regimen that included ethambutol 1200 mg (20 mg/kg), rifampin 600 mg, and pyrazinamide 1500 mg (25 mg/kg),

FIG. 1. Automated visual fields show bilateral central scotomas consistent with toxic optic neuropathy.
given after each hemodialysis session thrice a week. With this change, her mentation returned to normal.

One year before starting antituberculosis therapy, baseline best-corrected visual acuity was 20/25 in both eyes. During her 6 months of ethambutol treatment, the patient underwent monthly vision screening with Ishihara color plates administered by a county health care worker in accordance with a Michigan Health Department protocol. She was always correct in interpreting the color plates over this period. Visual acuity testing with a Snellen chart, which is also recommended as part of the monitoring protocol, was not performed. During the sixth month of the treatment, she reported blurred vision in both eyes.

Our examination revealed visual acuity of 20/100 in the right eye and 20/70 in the left eye. She was able to identify only the control Ishihara color plate with each eye. Both pupils constricted normally to light without relative afferent pupillary defect and ophthalmoscopy was normal. Automated visual fields showed bilateral central scotomas with mean deviations of −5.6 dB in the right eye and −5.9 dB in the left eye (Fig. 1). Visual evoked potentials revealed P100 waves with a latency greater than 200 milliseconds (Fig. 2). Brain CT was normal, as were laboratory tests including vitamin B12 and folic acid levels.

The diagnosis of optic neuropathy from ethambutol was based on bilateral decreased visual acuity, impaired color vision, central scotomas, and increased latency of the P100 waves on visual evoked potential testing (5,6). Ethambutol was promptly discontinued; she only had 1 dose left to complete her 6-month course of treatment. Before her follow-up neuro-ophthalmologic examination could be performed, she died from unrelated medical issues. An autopsy was not performed.

Our patient developed ethambutol optic neuropathy despite the increased dosing interval recommended by the CDC (4). This case serves as a reminder that even a renally adjusted ethambutol dose may not be safe in patients receiving hemodialysis. If ethambutol must be prescribed to patients on hemodialysis, they should be advised of the risks. Published expert opinion suggests obtaining informed consent and monthly ophthalmic examinations in all patients who have an increased risk for toxicity, including renal failure (7). Our report indicates that patients receiving hemodialysis should be monitored as carefully as those with renal dysfunction who are not on hemodialysis.

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Obituary: Harvey Birsner

On May 25, 2013, the doors of the Santa Monica Drive-Thru Brain Surgery Center in Santa Monica, CA, closed forever. Its resident neurosurgeon, Dr Harvey Birsner, passed away on that date, and the North American Neuro-ophthalmology Society (NANOS) lost one of its only neurosurgeon members and Fellows.

Harvey Birsner was born in San Francisco on February 24, 1941, to Harry Mackler and Helen Nicholson Mackler. He was raised in Bakersfield, CA, and graduated from Bakersfield High School in 1958. In high school, Harvey was voted “least likely to succeed.”

Harvey attended Bakersfield Junior College and San Francisco State College. He received his medical degree from the University of California San Francisco in 1965 and started postgraduate neurosurgical training at Parkland Memorial Hospital in Dallas, TX. Part way through his residency, Harvey received a letter from the United States Government directing him to report for active duty, and he subsequently served 2 years as the Chief of Neurosurgery at Naval Hospital, Philadelphia. While on active duty, Harvey decided that he wanted to do a neuro-ophthalmology fellowship with William Hoyt. Dr Hoyt accepted him with the stipulation that he read Walsh & Hoyt’s textbook in its entirety before starting. Harvey did and from 1970 to 1971 he was a neuro-ophthalmology Fellow at UCSF alongside Myles Behrens and Ernesto Rios-Montenegro. Dr Hoyt said that Harvey was the only neurosurgeon in the United States who could identify the retinal nerve fiber layer with an ophthalmoscope.

After finishing his neurosurgical training at Parkland Hospital in 1972, Harvey arrived in Antelope Valley (AV), California. He was AV’s first neurosurgeon and served on the medical staff of each of the Valley’s hospitals. He was elected to various positions including Chief of Surgery and Chief of Medical Staff at AV Hospital. In addition to multiple medical staff appointments, he was a Trustee of the Antelope Valley Healthcare District between the years 1980 and 1996. He served in various capacities including board Chairman.

Harvey married Donna Harris in 1974. After Harvey and Donna retired, they moved to Park City, UT, in 1997 to pursue their love of skiing and travel. At last count, Harvey and Donna had visited 83 countries, always in style. While living in Park City, Harvey regularly attended grand rounds in neurosurgery at the University of Utah—and pushed the neurosurgeons to use their ophthalmoscopes and report the results of their patients’ visual acuities and fields. Harvey prided himself in being a thinking neurosurgeon.

Harvey Birsner had been a fellow of NANOS since 2001. He was recently remembered by the then Chief of Neurosurgery at the University of Utah as “the Utah version of William Hoyt.” We suspect that Harvey was quite proud of that comparison. Dr Hoyt was his mentor and his friend, and Harvey regularly hosted a dinner for him and a few close friends at the annual NANOS meeting. The only stipulation for the guests was that they endure Harvey’s barbs, which were effusive but clearly came from his heart.

Harvey faced his final illness of cholangiocarcinoma in typical Harvey fashion. He declined chemotherapy after the first dose made him too ill. Instead of chemotherapy, he ordered a case of his favorite wine, dined and entertained life-long friends, emailed everyone, and then finally passed away with Donna at his side.

Harvey was preceded in death by his parents and his adoptive father, Dr J. W. Birsner. In addition to Donna, Harvey is survived by his 2 sisters, Elizabeth and Margaret, his brother, John, who is a practicing physician in AV, and, of course, his neuro-ophthalmology colleagues.

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Tumors of the Pediatric Central Nervous System


Intended audience: Pediatric neuro-oncologists, neurosurgeons, neurologists, radiation oncologists, radiologists, pathologists, neuro-ophthalmologists, and pediatricians.

Written by leading experts in the field of pediatric neuro-oncology, this textbook provides an essential, comprehensive resource for those involved in the care of children with central nervous system tumors. The text opens with a fascinating historical overview on pediatric neuro-oncology, a recognized field for less than 100 years that is continually advancing based on the latest research. All aspects of the medical management of pediatric central nervous system tumors including clinical, pathological, radiological, and surgical perspectives are thoroughly explored. High-quality color images, figures, and radiographic findings are integrated into the text along with practical pearls and pitfalls summaries of the key points for each tumor location and tumor type. This second edition contains updated and expanded chapters in all previous areas and 19 new chapters on topics such as the latest advances in cytogenetics and molecular biology. It is an outstanding reference on pediatric central nervous system tumors, and neuro-ophthalmologists will find the chapters on neurodiagnostic principles and optic pathway gliomas especially useful.

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The North American Neuro-Ophthalmology Society held its 39th annual meeting at Snowbird, Utah from February 9–14, 2013. The week was filled with outstanding educational venues advancing our knowledge in neuro-ophthalmology.

Valérie Biousse, MD, from Emory University, chaired The Frank Walsh Session. Pat Hudgins, MD, Professor of Neuroradiology, and Daniel J Brat, MD, PhD, Professor of Neuropathology, also from Emory University, provided expert opinions on neuroradiology and pathology. The session had 2 new educational features: an expert panel comprised of Steven Galetta, Andrew Lee, and Neil Miller; and following each section specific teaching points were presented. The best Walsh case was presented by Chantal J. Boisvert, MD (Doheny Eye Institute, Los Angeles) for: “OMG, I can’t C.”

A variety of symposia highlighted the meeting. “Journal Club” featured recent clinical trials in retina, thyroid eye disease, multiple sclerosis, cerebrovascular disease, and migraine. In another session, recent advances were outlined in the treatment of giant cell arteritis, neuro-ophthalmic sarcoid, neuromyelitis optica, and stem cell therapy. An update of the management of idiopathic intracranial hypertension covered visual loss, weight loss, and headache management as well as reviewed the surgical treatment options including cerebrospinal fluid diversion (shunts), optic nerve sheath fenestration, and cerebral venous sinus stenting. A session dedicated to improving diagnostic capabilities discussed distinguishing retinal disorders from optic nerve dysfunction, newer techniques to distinguish pseudo-papilledema from other optic neuropathies, the best techniques in viewing/measuring retinal nerve fiber layer, and not allowing diagnostic techniques to lead us astray. The final symposium helped us to understand the direction and potential impact of telemedicine in neuro-ophthalmology.

The optional symposia were excellent, as well. A neuroimaging symposium featured Pat Hudgins, MD (Emory University) along with Anne Osborn, MD and Karen Salzmann, MD (University of Utah). Topics included imaging of the optic nerve, cranial nerves and central nervous system lymphoma. Amin Kassam, MD (Ottawa) performed live endonasal endoscopic cadaveric prosection, demonstrating various approaches to reach the pituitary and other cranial nerves. Sue Vicchrilli COT, OCS (Salt Lake City and the American Academy of Ophthalmology San Francisco) discussed the perils and pitfalls of medical coding.

The scientific platform and poster sessions reflected active neuro-ophthalmologic research. The best presentation by a fellow was given by Kimberly Winges, MD (University of Iowa): “The Ganglion Cell Layer Across the Vertical Meridian in Hemianopsia: I Get No Respect!” The resident awardee was Cynthia Yu-Wai-Man, MBBS, FRCOphth (Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom) who discussed “Extraocular muscle atrophy and central nervous system involvement in chronic progressive external ophthalmoplegia—a structural and spectroscopic magnetic resonance study.” The medical student

FIG. 1. Stan Thompson and his wife Delores stand next to long-time colleagues, James Corbett, Michael Wall, and Randy Kardon. Former fellows, faculty, and residents from the University of Iowa, Department of Ophthalmology stand behind them.
prize went to Ali S. Saber Tehrani (Johns Hopkins University) for: “Quantitative video-oculography for diagnosing stroke at the bedside in acute vertigo: an ‘ECG’ for the eyes.”

Robert A. Avery, DO, presented “Hand-held optical coherence tomography during sedation detects visual acuity and visual field loss in young children with optic pathway gliomas.” He received the 2013 Thomas and Susan Carlow Young Investigator Award.

The 2013 Jacobson Lecture entitled “Neuro-Ophthalmology at Iowa” was presented by H. Stanley Thompson, MD (University of Iowa) (Fig. 1).

There were 415 registrants for this North American Neuro-Ophthalmology Society (NANOS) meeting representing 24 countries. Janel Fick and her outstanding staff hosted a very well-organized meeting. We are already looking forward to next year’s meeting in Puerto Rico (March 1–6, 2014)—it will be NANOS’ 40th anniversary!

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The 11th European Neuro-Ophthalmology Society (EUNOS) meeting took place in Oxford, England, April 10–13, 2013, at the Examination Schools in the center of the city. Surrounded by many steeple-rich colleges coupled with a well-organized meeting, attendees has a very rich educational experience.

Christopher Kennard, President of EUNOS and the organizing committee, hosted 290 attendees from 40 countries—and almost every continent (Fig. 1).

The meeting included minisymposia dealing with idiopathic intracranial hypertension, novel therapeutic approaches, optical coherence tomography (OCT), radiotherapy, visual hallucinations, and functional and unusual visual symptoms. There also were scientific sessions on optic neuropathies, OCT and visual pathway lesions, eye movements, and orbit, pupils, and photophobia. Poster sessions were held in the afternoon of 2 days in the exhibit hall.

In between these sessions, we were treated to 4 keynote lectures. John Leigh (Cleveland, OH) treated us to an erudite lecture on “Using eye movements to study recovery from neuromuscular disease.” Andrew Parker (Oxford, England) gave an insightful lecture, “The extraordinary visual cortex: the seeing-machine in our heads.” Russell Foster (Oxford, England) delivered a dynamic lecture on the circadian rhythm and discovery of the melanopsin pathway entitled “Keeping an eye on Time.” Finally Dan Milea (Copenhagen, Denmark) updated the “Inherited optic neuropathies.”

The social events were wonderful. We opened our visit in the historic Ashmolean Museum surrounded by artifacts collected over hundreds of years. The gala dinner was held at the Oxford Town Hall. Surrounded by Victorian decorated walls, the delegates feasted and enjoyed lively conversation with other neuro-ophthalmologists from Europe and around the world.

The next EUNOS meeting is scheduled for Ljubljana, Slovenia in 2015. A EUNOS update will be held in 2014 in Zurich, Switzerland.

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Festschrift for Simmons Lessell, MD

A Festschrift was held in honor of Simmons Lessell, MD, at the Massachusetts Eye and Ear Infirmary (MEEI) on May 25, 2013, the day of his 80th birthday. This Festschrift offered a reflection of the many contributions that Dr Lessell has made to the careers and lives of the 39 fellows whom he has trained.

The event began with an overview of the social, political, and scientific state of the world at the time that Dr Lessell was born in 1933. This was followed by a summary of Dr Lessell’s educational and professional background, including photographs of Dr Lessell while he was a student at the renowned Stuyvesant High School in New York City, and a commentary on Dr Lessell’s educational years at Amherst College and Cornell Medical School, where he also served as an intern. Dr Lessell studied under George Schumacher, MD, then Chairman of the Department of Neurology at the University of Vermont. He quickly applied his neurological expertise by studying the recently discovered Lytic-Brudz disease while serving in Guam within the Epidemiology and Genetics Branch of the National Institute of Neurological Diseases and Blindness of the National Institutes of Health. Upon his return to the United States, Dr Lessell became a research fellow for 2 years in the Howe Laboratory at the MEEI. During this time, his interest in neuro-ophtalmology was born while working with David G. Cogan, MD, then Chairman of the Department of Neurology and the founder of the neuro-ophthalmology service at the Institute. Dr Lessell completed an ophthalmology residency at MEEI and immediately was recruited as the first neuro-ophthalmologist at Boston University School of Medicine, where he remained for 18 years. In 1984, he was recruited back to the MEEI as director of the neuro-ophthalmology service, a position he held until 2005.

The meeting in Dr Lessell’s honor was organized around 20-minute lectures given by 20 fellows who traveled from as far away as Australia. The fellows presented a summary of their scientific or clinical work, with emphasis on ways in which Dr Lessell has impacted their lives and professional careers. These reflections produced some tears, shed in happiness and with gratitude.

Those who presented at the meeting included: Patrick Sibony, MD (Stony Brook University Medical Center, Stony Brook, NY); Jon Currie, MBBS, FRACP (Melbourne Medical School, Melbourne, Australia); Alfredo Sadun, MD, PhD (University of Southern California, Los Angeles, CA); Joseph F. Rizzo (Harvard Medical School, Boston, MA); Nancy Newman, MD (Emory University School of Medicine, Atlanta, GA); Nicholas Volpe, MD (Northwestern Feinberg School of Medicine, Chicago, IL); Leonard Levin, MD, PhD (McGill University Health Center, Montreal, Canada); Charlotte Thompson, MD (University of South Carolina, Columbia, SC); Howard Pomeranz, MD (Hadassah Hospital, Jerusalem, Israel); Behzad Mansouri, MD (Geisel School of Medicine at Dartmouth, Hanover, NH); Marc Dinkin, MD (Weill Cornell Medical College, New York, NY); Gena Heidary, MD, PhD (Harvard Medical School); Rebecca Stacy, MD, PhD (Harvard Medical School); and Cristiano Oliveira, MD (Weill Cornell Medical College).

Others fellows whom Dr Lessell trained include: James Coppeto, MD; Michael Cohen, MD (Headache and Neurologic Center of Philadelphia, Philadelphia, PA); Robert Gise, MD (Worcester, MA); Irma Lessell, MD (Lexington, MA); Neal Snebold, MD (Boston, MA); Nancy Canter Weiner, MD (Atlanta, GA); Steve Hamilton, MD (Seattle, WA); Judith Warner (University of Utah, Salt Lake City, UT); Misha Pless (Harvard Medical School, currently in Lucerne, Switzerland); Glenna March, MD (Los Angeles, CA); Michelle Banks, MD (Los Angeles, CA); Kenneth Chang, MD (Harvard Medical School); Adam Cohen, MD (Harvard Medical School); Ellen Mitchell, MD (University of Pittsburgh Medical Center, Pittsburgh, PA); Ming He, MD (New Jersey Neuroscience Institute, JFK Medical Center, Edison, NJ); Ivey Thornton, MD (Cleveland, OH); Joshua Kruger (Hadassah Hospital, Jerusalem, Israel); Behzad Mansouri, MD, PhD (University of Winnipeg, Winnipeg, Canada); and Philip Skidd, MD (University of Vermont, Burlington, VT). Figure 1 depicts those in attendance.

Among these fellows, four of them serve as Department Chairs (Sibony, Levin, Volpe, and Pless) and one serves as an Associate Dean (Pepin). Thirty of the 39 fellows are at academic centers.

I had the opportunity to present 2 interludes reflecting on special aspects of Dr Lessell’s life. The first was dedicated to his wife of 58 years, Irma Lessell, MD, who has provided inspiration and love to Simmons throughout his career. The second interlude was dedicated to 2 individuals who were mentors to Dr Lessell: George Schumacher, MD, and David G. Cogan, MD. There was also a special moment to reflect on the life of Ephraim Friedman, MD, a dear friend and close colleague of the Lessells who passed away in 2011; Dr Friedman is the namesake of one of the Lessell’s sons.
A final session provided comic relief. Bedecked with a sultan’s hat and a black cape, Dr. Lessell was asked to play the role of the great sage of television from decades past, Carnac the Magnificent. I was the stand-in for sidekick, Ed McMahon, who handed sealed envelopes that contained provocative clues of thought to Carnac (Fig. 2). With ceremonial flourish in opening each envelope, Dr. Lessell, aka “Carnac,” used his unique magical powers to divine questions that provided insight into the meaning of the clues. No topic was off limits, and off-limit topics were plentiful, to the delight of all.

The fellows presented Dr. Lessell with a commemorative ceramic bowl, which rests upon a square mahogany base lined with 4 bronze plaques engraved with the names of the fellows whom Dr. Lessell has trained. Dr. Lessell closed the festivities with a remarkably humble statement of appreciation to all of his fellows and to the many others who were in attendance. This Festschrift was not held as a retirement party, nor was it a fishing trip (which also would have delighted Dr. Lessell). Rather, adhering to the classic connotation, this Festschrift was an opportunity to reflect upon the profound impact that an exceptional mentor has had on the lives of others. We were able to savor this glorious day with the added benefit of knowing that we still have further opportunity to learn from Dr. Lessell and to laugh with him, experiences that have fostered admiration from so many of us who cherish him.
Neuro-Ophthalmology in Switzerland

Klara Landau, MD

Historical Background

Neuro-ophthalmology in Switzerland stands on the shoulders of giants. One hundred fifty years ago, Friedrich Horner was the first ophthalmologist to hold an independent chair at the University of Zurich. Hans Goldmann invented—among many other examination techniques—the kinetic perimeter named after him while teaching and working at the University of Bern. Adolphe Franceschetti made important contributions to the understanding of genetic diseases and to color vision while at the University of Geneva. While serving as chair in Lausanne, Marc Amsler developed his famous “Amsler grid,” thus pointing out the importance of the central visual field. Volker Henn made seminal contributions in the fields of ocular motor and vestibular research in the Department of Neurology in Zurich.

Close collaboration with 2 famous neurosurgeons in Zurich, Hugo Krayenbühl and “Neurosurgeon of the Century” M. Gazi Yasargil, brought Alfred Huber’s career to fame far beyond the Swiss borders. His book “Eye Signs and Symptoms in Brain Tumors,” which first appeared in 1956 in German and was later translated into English, represents a marvelously documented account of his vast clinical experience as the first Swiss neuro-ophthalmologist (Fig. 1). Alfred Huber together with Tom Hedges founded the International Neuro-Ophthalmology Society (INOS) and together with Adolphe Neetens from Belgium established the European Neuro-Ophthalmology Society (EUNOS). Two INOS meetings have taken place in Switzerland, the third meeting in 1980, organized by Alfred Huber in Valbella in the mountains of Grisons, and the 15th meeting, organized in 2004 by Avinoam Safran in Geneva. Zurich was the site of the first EUNOS meeting in 1993.

Switzerland’s Society and Health System

What is special about Switzerland and how does it affect our subspecialty? It is a country of 7 million people who speak 4 different languages (German, French, Italian, and Romansh). Despite such diversity, the Swiss have a very stable political system that is based on direct democracy and on autonomy of each of its 23 cantons. The main political and social attitude is pragmatic collaboration between all parties, requiring the willingness to compromise. This organization works well including the country’s health care system. Five Swiss Universities offer teaching of medical students: 3 in German (Basel, Bern, and Zurich) and 2 in French (Geneva and Lausanne). Less than 1000 medical students graduate each year, a number that is not sufficient to cover the country’s demand.

That is why physicians from other EU countries, mainly from neighboring Germany, Austria, France, and Italy move to Switzerland to work, both in hospitals and in private clinics.

Why is Switzerland so attractive for physicians? There are several reasons including the stability of the country, the

FIG. 1. Alfred Huber, MD, the founder of neuro-ophthalmology as a subspecialty in Switzerland.
high quality of health care, and universal access. In addition, 10 years ago, a sophisticated reimbursement system was implemented that is quite unique. It is not technical procedures, but rather time that physicians spend with their patients. For neuro-ophthalmologists, this represents a major advantage.

**Neuro-Ophthalmology in Switzerland**

Today each large teaching hospital, not just those that are affiliated with the 5 medical schools, have at least a small unit staffed with a fellowship-trained neuro-ophthalmologist (Table 1). These units are mostly, but not exclusively, based in ophthalmology departments and some are located in neurology. Frequently, the neuro-ophthalmologist combines his or her practice with other subspecialties, such as pediatric ophthalmology and strabismus, electrophysiology or orbital disease. There exists no formal Swiss Neuro-Ophthalmology Society, but rather a group of colleagues who share their common interest and communicate well. Main neuro-ophthalmology centers are currently located in Aarau, Bern, Basel, Lausanne, Luzern, St Gall, and Zurich. For a period of 6 years, 2 of the 5 ophthalmology chairs were neuro-ophthalmologists: Avinoam Safran in Geneva (1998 till 2010) and Klara Landau (since 2005) in Zurich.

The Swiss Ophthalmological Society annual meeting is held each fall alternating among 3 language regions of Switzerland: German (Interlaken), the French (Montreux, Fribourg) and the Italian (Lugano, Locarno). The scientific program always includes a neuro-ophthalmology session. In addition, the group from Lausanne holds regular local neuro-ophthalmology teaching courses in French. In the German part of Switzerland, the neuro-ophthalmologists teach in German at their respective hospitals. For decades, a national Winter Ophthalmic Seminar has been held in one of the beautiful Swiss ski resorts with international expertise.

**TABLE 1. Currently active neuro-ophthalmologists in Switzerland**

<table>
<thead>
<tr>
<th>Name</th>
<th>City</th>
<th>Training</th>
<th>Mentor, City</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matthias Abegg, Bern</td>
<td>Bern</td>
<td>Ophthalmology</td>
<td>Jason Barton, Vancouver</td>
</tr>
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<td>Yael Bellaliche Shavit, Zurich</td>
<td>Ophthalmology</td>
<td>Neil Miller, Baltimore</td>
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<tr>
<td>Anne-Caroline Bessero, Sion</td>
<td>Ophthalmology</td>
<td>James Acheson, London</td>
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<td>Francois Xavier Borrut, Lausanne</td>
<td>Ophthalmology</td>
<td>Michael Sanders, London</td>
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<td>J. Lawton Smith, Miami</td>
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<tr>
<td>Anna Fierz, Zurich</td>
<td>Ophthalmology</td>
<td>Eric Eggenberger, East Lansing</td>
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<td>Christina Gerth-Kahlert, Zurich</td>
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<td>Ray Buncic, Toronto</td>
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<td>Oliver Job, Lucerne</td>
<td>Ophthalmology</td>
<td>Agnes Wong, Toronto</td>
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<tr>
<td>Aki Kawasaki, Lausanne</td>
<td>Neurology</td>
<td>Joel Glaser, Miami</td>
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<td>Huspeter Killer, Aarau</td>
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<td>Ron Burde, New York</td>
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<tr>
<td>Klara Landau, Zurich</td>
<td>Ophthalmology</td>
<td>William F. Hoy, San Francisco</td>
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<td>Otmar Meienberg, Binningen</td>
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<td>William F. Hoy, San Francisco</td>
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<tr>
<td>Daniel Mojon, St Gall</td>
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<td>Jeff Odel, New York</td>
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<td>René Müri, Bern</td>
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<td>Charles Pierrot-Desilligny, Paris</td>
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<td>Anja Palmowski-Wolf, Basel</td>
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<td>Erich Sutter, San Francisco</td>
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<td>Misha Pless, Lucerne</td>
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<td>Simmons Lessell, Boston</td>
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<td>Dominik Straumann, Zurich</td>
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<td>David Zee, Baltimore</td>
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<td>Veit Sturm, St Gall</td>
<td>Ophthalmology</td>
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<td>Nadja Tajouri, Sion</td>
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<td>Christa Vollrath-Junger, Zurich</td>
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<td>Konrad Weber, Zurich</td>
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<td>Hannes Wildberger, Zurich</td>
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<td>Michael Halmagyi, Sydney</td>
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<td>Ian Curthoys, Sydney</td>
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<td>Fried van Lith, Rotterdam</td>
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<tr>
<td></td>
<td></td>
<td>Harold Henkes, Rotterdam</td>
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guests teaching neuro-ophthalmology in English, hosted by local organizers from Lausanne and Zurich. Because of difficulties related to sponsoring regulations, this popular tradition had to be modified and is now available to a rather limited number of practitioners in the German part of Switzerland alone. Irene Gottlob, who used to be in charge of the Neuro-Ophthalmology and Strabismus unit in St Gall before moving to the United Kingdom, established a 2-day spring meeting featuring case presentations in neuro-ophthalmology and strabismus. It has been continued by Daniel Mojon and currently by Veit Sturm. In the summer of 2012, a very successful 2-day practical course in neuro-ophthalmology was held at a lakeside castle near Zurich. The format and the content were prepared by Jonathan Trobe, who delivered introductory lectures followed by intensive work in small groups, supervised by Dominik Straumann, Konrad Weber, and Klara Landau. This course will be repeated in June of 2014 with David Zee joining Jonathan Trobe. It will represent the second EUNOS update course for residents.

Outlook

The future of neuro-ophthalmology in Switzerland will be determined by curious, creative, and passionate young physicians with a genuine interest in answering the many unsolved questions in our subspecialty. It is our responsibility to motivate them and, at the same time, to preserve our favorable health system structures. Looking at the developments in Germany, where neuro-ophthalmology is rapidly losing ground because of shortsighted political decisions and is disappearing from the teaching programs, every effort should be made to avoid a similar development in Switzerland. We owe this to our patients, our colleagues, and our founders including Friedrich Horner, Adolphe Franceschetti, Marc Amsler, Hans Goldmann, Alfred Huber, Volker Henn, and Avinoam Safran.

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Worldwide Neuro-Opthalmology

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