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Virtual Issue—Online Only

Current Concepts in the Diagnosis, Pathogenesis, and Management of Nonarteritic Anterior Ischemic Optic Neuropathy
By Neil R. Miller

Go to www.jneuro-ophthalmology.com for the first virtual issue of the Journal of Neuro-Ophthalmology!
Pitfalls in Imaging

Simmons Lessell, MD

Only a devout Luddite could fail to acknowledge the enormous contribution that technology makes to medical diagnosis. One can probably date the modern era of medical technology to Roentgen’s discovery of X-rays that were immediately adopted and adapted by physicians as an aid to diagnosis (1). Plain radiographs, the first fruits of Roentgen’s discovery, literally provided revelations, but their value for neurological diagnosis was limited since the location and nature of the brain, the spinal cord, and nerve diseases could be made only if there were alterations in bone or abnormal calcification of soft tissues. With the introduction of contrast techniques, the ability to evaluate the brain and spinal cord was greatly increased. The current imaging techniques—CT, MRI, and ultrasound—have become the clinician’s indispensable handmaiden. Imaging is invaluable for neuroophthalmic diagnosis. While the history and physical examination remain sovereign, imaging makes an enormous contribution often forming part of the matrix of information that leads to the correct diagnosis. A major advance in imaging occurred in the 1990s with the introduction of optical coherence tomography (OCT), which provides a view of the retina in cross section (2). OCT took retinal imaging from a macro- to a microlevel, and with the refinements and modifications that are certain to occur, we can look forward to a time when OCT will show the details of individual cells. Little wonder that we have become enamored with technology. However, so enamored are we that we are in danger of accepting test results uncritically. This poses potential problems for the clinician and for the clinical investigator. In this issue of the Journal of Neuro-Ophthalmology, 2 interesting and well-written publications warn of some limitations of imaging: the problem of instrument-dependent variation among OCT results in one report and the problem of “pilot error” in neuroimaging in the other.

The value of OCT in glaucoma and primarily retinal disorders is already well established, but OCT is also a valuable resource for the neuroophthalmologist and neurologist. Measurements of central macular thickness and nerve fiber layer thickness are especially useful because these layers are thinned following the death of axons in the optic nerve. After optic neuritis and even in some cases of multiple sclerosis without other evidence of optic neuritis, OCT shows depletion of the nerve fiber layer and thinning of the macula (3). In some situations, these measurements will be made serially or the clinician will wish to compare his or her result with those of OCT performed on a different instrument. OCT can also be used as a surrogate for more expensive and time-consuming tests to assess the effect of drugs on multiple sclerosis. The technology has evolved from image resolution based on time and distance (time-domain OCT [TD-OCT]) to image resolution based on spectral data using Fourier transforms (spectral-domain OCT [SD-OCT]). Several SD-OCT instruments are currently available. Watson et al (4) selected 1 TD-OCT device and 4 Fourier-domain OCT devices to compare the results of nerve fiber layer and macular thickness among this group of instruments. Their 25 study subjects (50 eyes) were patients with multiple sclerosis, optic neuritis, or both, precisely the group of greatest interest to neuroophthalmologists. Each patient’s testing on the 5 instruments was completed on the same day. Watson et al (4) found poor agreement among the results from the 5 devices. One would not have expected this a priori, but another investigation has shown similar interinstrument disagreement in patients with glaucoma (5). The authors suspected that the variations could be from differences in the way the various devices acquire and analyze data. For example, while all the techniques use the internal limiting membrane as the inner boundary for measuring macular thickness, 4 different outer boundaries are used. Whatever the reason for the variation, the

Neuro-Ophthalmology Unit, Massachusetts Eye and Ear Infirmary and Harvard Medical School, Boston, Massachusetts.

Address correspondence to Simmons Lessell, MD, Neuro-Ophthalmology Unit, Massachusetts Eye and Ear Infirmary and Harvard Medical School, 243 Charles Street, Boston, MA 02114; E-mail: simmons_lessell@meei.harvard.edu

implications are clear. First, if one wishes to serially measure retinal nerve fiber layer and macular thickness in patients with multiple sclerosis or optic neuritis, use the same device each time. Second, beware of extrapolating the measurements obtained from one device to another; they are not necessarily interchangeable.

Every July, we emphasize to the new ophthalmology residents that while there is a myriad of neuroophthalmic pseudoemergencies, there are very few true neuroophthalmic emergencies, disorders that require immediate attention. Of these, the most important is the patient with an acute painful third nerve palsy since it may announce the presence of a life-threatening aneurysm that is enlarging and has the potential to rupture. Missing an aneurysm in that setting can result in an otherwise avoidable tragedy. Fortunately, nearly all aneurysms have the potential to be detected by noninvasive means using computerized tomographic angiography or magnetic resonance angiography. The diagnosis, or more exactly the misdiagnosis, of intracranial aneurysms from imaging studies in patients with third nerve palsies is the subject of the report by Elmalem et al (6) at the Emory University. They review instances in which a patient presented to the proverbial “outside hospital” with an isolated third nerve palsy from an aneurysm that went unrecognized despite being evident on the original scans. The palsies were each accompanied by pain or headache (V. Biousse, MD, personal communication, February 2011). There were 8 patients, all of whom had aneurysms of the posterior communicating artery. In each case, the reading radiologist missed the aneurysm when interpreting the initial scans. The authors obtained the original studies in all but 1 case, and in each of them, the aneurysm was easily recognized. One of the missed aneurysms measured 12 mm! One might be inclined to blame these failures on the equipment, the technique, or the technologist. However, since the aneurysms were demonstrated on the original scans, these can be exonerated. Failure to detect the aneurysms resulted from what I’ll call “pilot error” by the reading radiologist. What caused the pilot error in these cases? The authors identified 2 possible factors. One is the expertise of the reading radiologist. Only 2 of the initial reading radiologists were neuroradiologists, but one of them had trained in neuroradiology 20 years earlier and “had been practicing mostly as a general radiologist for many years.” The simple fact is that nonneuroradiologists may lack the training and experience necessary to detect aneurysms on CT and MRI. The superiority of neuroradiologists over general radiologists in detecting intracranial aneurysms on CT or MR images has been documented in the literature (7). There can be no doubt that as the authors remind us that “...the most important step in imaging remains interpretation, which is entirely dependent on the training, skills and experience of the radiologist.” The second factor contributing to nondiagnosis was the poor quality of the information provided to the radiologist. Elmalem et al (6) were able to obtain the information provided to the radiologist in 7 of the 8 cases. Only 2 of the radiologists were advised that aneurysm was a consideration, and in one of them, the side of the suspected aneurysm was not specified. The other requests were vague or downright misleading. Perhaps if the physician ordering the study provided an accurate description of the clinical findings and mentioned concern for the possibility of an aneurysm, the radiologist might have been more likely to recognize the aneurysm. Unfortunately, it seems to be the rule rather than the exception that referring physicians provide the radiologist with inadequate information about what the clinician wants to learn from the radiologist. If you ask the right question, you have a better chance of getting the right answer.

One can assume that there are cases of patients with acute third nerve palsies in which the radiologist failed to detect the aneurysm present on images and who later suffered a subarachnoid hemorrhage that might have been avoided. Elmalem et al (6) are not the first to point out the problem, but it is so important that it is worth reinforcing the message articulated by Chaudhary et al (8). “To avoid diagnostic mishaps, noninvasive studies should be reviewed by at least 1 neuroradiologist before aneurysm is rejected as the cause or before the patient undergoes CCA [catheter cerebral angiography].”

One can say of technology what has been said of fire and the $\chi^2$ test: it is a wonderful servant but a cruel master (9).

REFERENCES
Underdiagnosis of Posterior Communicating Artery Aneurysm in Noninvasive Brain Vascular Studies

Valerie I. Elmalem, MD, Patricia A. Hudgins, MD, Beau B. Bruce, MD, Nancy J. Newman, MD, Valérie Biousse, MD

Background: Expert interpretation of modern noninvasive neuroimaging such as computed tomographic angiography (CTA) or MRA should detect nearly all aneurysms responsible for an isolated third nerve palsy. Whether a catheter angiogram should still be obtained in cases with negative CTA or MRA remains debated and mostly relies on whether the noninvasive study was correctly performed and interpreted. The aim of our study was to review the diagnostic strategies used to evaluate patients with isolated aneurysmal third nerve palsy at a large academic center.

Methods: Retrospective review of all cases with posterior communicating artery (PCom A) aneurysmal third nerve palsies seen at our institution since 2001.

Results: We identified 417 cases with third nerve palsy, aneurysm, or subarachnoid hemorrhage, among which 17 presented with an acute isolated painful third nerve palsy related to an ipsilateral PCom A aneurysm (mean age: 52 years; range: 33–83 years). Patients were classified into 3 groups based on the results of the noninvasive imaging obtained at initial presentation. Group I included 4 cases with subarachnoid hemorrhage on initial noncontrast head CT initially obtained in an emergency department for evaluation of their isolated third nerve palsy. Group II included 5 cases with isolated third nerve palsy and normal noncontrast head CT at presentation, immediately correctly diagnosed with a PCom A aneurysm at the referring institution. Group III included the 8 remaining cases who all had aneurysms that were missed on noninvasive studies at outside institutions. Review of these outside studies at our institution showed a PCom A aneurysm, confirming misinterpretation of these tests by the outside radiologists, rather than inadequate technique. Absence of specific training in neuroradiology and inaccurate clinical information provided to the interpreting radiologist were associated with test misinterpretation at the outside institutions. The average size of PCom A aneurysms causing an isolated third nerve palsy across all 3 groups was 7.3 mm and was similar in each group.

Conclusion: Our study suggests that aside from an accurate history, the training and experience of the interpreting radiologist is probably the most important factor in determining the reliability of a noninvasive scan in patients with isolated third nerve palsies.

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Isolated third nerve palsy can be the sentinel sign of an aneurysm at the junction of the internal carotid artery and posterior communicating artery (PCom A), and evaluation of isolated third nerve palsies remains one of the most challenging situations in neuro-ophthalmology (1–9). Expert interpretation of modern noninvasive neuroimaging such as computed tomographic angiography (CTA) and MRA should detect nearly all aneurysms responsible for an isolated third nerve palsy (9–12). Most clinicians prefer CT/CTA for the initial study in this clinical setting because of CTA’s easy accessibility and rapid acquisition time, although this varies depending on the institution (8,9,11,12). Whether a catheter angiogram should still be obtained in cases of isolated third nerve palsy with negative CTA or MRA remains a difficult decision (8,9). Although recent studies (13) have reported a risk of neurologic complications close to zero for diagnostic cerebral angiographies performed within a high volume neurointerventional practice, the risk of neurologic complications following catheter cerebral angiography was once between 0.9% and 4% (14) and therefore, algorithms trying to avoid routine catheter angiography, especially as a screening test, have
been proposed in the past (1,2,5). Recent publications have emphasized the importance of having presumed negative noninvasive vascular imaging studies reviewed by a skilled neuroradiologist before aneurysm is rejected as the cause of the third nerve palsy or before the patient undergoes catheter angiography (9,12).

The aim of our study was to review the diagnostic strategies used to evaluate patients with isolated third nerve palsy at our tertiary academic center since 2001 and to examine details of those cases with false negative noninvasive neurovascular imaging studies.

METHODS

We performed a retrospective review of all cases with PCom A aneurysmal third nerve palsy seen at our institution from 2001 to 2010. Cases seen prior to 2001 were excluded from this study because high quality noninvasive vascular imaging was not routinely performed prior to that date. Our database was searched for diagnosis codes of third nerve palsy, aneurysm, and subarachnoid hemorrhage, and these charts were reviewed in detail. Reports from outside radiology tests were obtained, and outside films were reviewed with our neuroradiologists whenever possible. We specifically recorded the clinical information provided to the interpreting radiologist on the initial imaging report. We also inquired whether the interpreting radiologist was specifically trained in neuroradiology or not.

We included all cases that initially presented with a nontraumatic isolated third nerve palsy and were later found to have an ipsilateral PCom A aneurysm. Patients who presented initially with symptoms and signs of subarachnoid hemorrhage or who developed a third nerve palsy postoperatively were excluded. Aneurysms in locations elsewhere (such as the intracavernous internal carotid artery, basilar tip, or cerebellar arteries) usually presented with other neurological findings and were thus excluded. The study was approved by our institutional review board.

RESULTS

Four hundred seventeen cases with third nerve palsy, aneurysm, or subarachnoid hemorrhage were identified. Of the 417 cases reviewed, 17 presented with an acute isolated painful third nerve palsy related to an ipsilateral PCom A aneurysm (mean age: 52 years; range: 33–83 years). The characteristics of these 17 patients are detailed in Table 1. Patients were classified into 3 groups based on the results of the noninvasive imaging obtained at initial presentation.

Group I included 4 cases that were found to have evidence of subarachnoid hemorrhage on initial noncontrast head CT obtained in an emergency department for evaluation of their isolated third nerve palsy (Table 1, Case I-1 to I-4; Fig. 1). The presence of subarachnoid hemorrhage on CT facilitated the immediate correct diagnosis of aneurysmal third nerve palsy in all 4 patients. The mean age of these 4 subarachnoid hemorrhage patients was 59.5 years (range: 46–83 years). The size range (greatest dimension, as measured on catheter angiography or intraoperatively) of aneurysms in group I was 5.4–10 mm.

Group II included 5 cases with isolated third nerve palsy and normal head CT without contrast at presentation, correctly diagnosed with a PCom A aneurysm (Table 1, Cases II-5 to II-9; Fig. 2). Of these 5 patients, 4 patients required only noninvasive vascular imaging for immediate correct diagnosis of aneurysm (1 CTA and 3 MRI/MRA). The 1 patient diagnosed by direct catheter angiography could not have a brain MRI because of previous history of anterior communicating artery aneurysmal clipping, which also created an artifact, making the CT difficult to interpret. The mean age of these 5 patients was 56.4 years (range: 41–70 years). Aneurysms in group II ranged in size from 5.5 to 10 mm.

Group III included the 8 remaining Cases (Table 1, Cases III-10 to III-17; Fig. 3) who all had aneurysms that were missed on noninvasive studies. These 8 patients were all initially evaluated at outside institutions. In 1 Case (III-15, Table 1), the patient was transferred from an outside hospital because of high clinical suspicion of aneurysm despite “negative” noninvasive vascular imaging. The outside studies were not available for review and a catheter angiogram was performed immediately on arrival to our institution, which revealed a PCom A aneurysm. In all 7 other Cases (III-10 to III-14, III-16, and III-17; Table 1), review of the outside noninvasive vascular studies by our institutional personnel, including neuro-ophthalmologists, neurologists, neuroradiologists, or neurosurgeons, allowed identification of a PCom A aneurysm. This confirmed misinterpretation of these tests by the outside radiologists, rather than inadequate technique. Two of these patients had normal appearing reconstructed MRA images, but an aneurysm was detected on the source images. Five of the 7 misread noninvasive imaging studies were performed and read by general radiologists who had no neuroradiology training. In 1 case, the interpreting radiologist had received neuroradiology training 20 years prior but had been practicing mostly as a general radiologist for many years. We could not determine the training of the radiologist in 1 Case (III-11), but the test had been performed at a general radiology center with no special expertise in neuroradiology.

Review of the indications for these misinterpreted studies in the patients’ medical records revealed that in 6 of 7 cases, the radiologist performing and interpreting the test was given vague, or wrong, clinical history. Misleading clinical indications included “headache, Horner,” “transient ischemic attack, hypertension,” “headache,” and “rule out aneurysm” without mention of the side or location of the suspected aneurysm (Table 1). The mean age for group III was 44.1 years (range: 33–55 years). The size range for the aneurysms that were initially missed (group III) was 3.5 mm (Case III-16) to a bilobed 12 mm aneurysm (Case III-14) (Table 1).
### TABLE 1. Imaging strategies in 17 patients with isolated third nerve palsy related to an ipsilateral posterior communicating artery aneurysm

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (Yrs)/Sex</th>
<th>First Imaging Modalities</th>
<th>SAH on CT</th>
<th>Initial Diagnosis Missed</th>
<th>Clinical Indication on Radiology Report</th>
<th>Read by Neuroradiologist Initially</th>
<th>How Correct Diagnosis Was Made</th>
<th>Side and Size of Aneurysm in Millimeters*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1</td>
<td>60/F</td>
<td>Noncontrast CT, then angiogram</td>
<td>Yes</td>
<td>No</td>
<td>Headache</td>
<td>No</td>
<td>Initial imaging (angiogram)</td>
<td>Right and 6 × 5 × 4</td>
</tr>
<tr>
<td>I-2</td>
<td>46/M</td>
<td>CT/CTA, then angiogram</td>
<td>Yes</td>
<td>No</td>
<td>Right pupil dilation, suspicion of aneurysm</td>
<td>Yes</td>
<td>Initial imaging (CTA)</td>
<td>Right and 5.4 × 3.6</td>
</tr>
<tr>
<td>I-3</td>
<td>59/F</td>
<td>CT/CTA, then angiogram</td>
<td>Yes</td>
<td>No</td>
<td>Head/retro-orbital paralyzed left eye</td>
<td>NA</td>
<td>Initial imaging (CTA)</td>
<td>Left and 10 × 5 × 4</td>
</tr>
<tr>
<td>I-4</td>
<td>83/F</td>
<td>CT, MRI/MRA, then angiogram</td>
<td>Yes</td>
<td>No</td>
<td>Headache with new right third nerve palsy; evaluate for possible aneurysm</td>
<td>Yes</td>
<td>Initial imaging (MRI/MRA)</td>
<td>Right and 6 × 4.5 × 4.5</td>
</tr>
<tr>
<td>II-5</td>
<td>70/F</td>
<td>CT/CTA</td>
<td>No</td>
<td>No</td>
<td>Left CN third palsy</td>
<td>Yes</td>
<td>Initial imaging (CTA)</td>
<td>Left and 6.2 × 3 × 2.7</td>
</tr>
<tr>
<td>II-6</td>
<td>53/M</td>
<td>MRI/MRA</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>Initial imaging (MRI/MRA)</td>
<td>Right and 8 × 5</td>
</tr>
<tr>
<td>II-7</td>
<td>41/F</td>
<td>Noncontrast CT, MRI/MRA</td>
<td>No</td>
<td>No</td>
<td>Stroke, assess for aneurysm</td>
<td>Yes</td>
<td>Initial imaging (MRI/MRA)</td>
<td>Right and 10 × 8 × 7</td>
</tr>
<tr>
<td>II-8</td>
<td>64/F</td>
<td>Noncontrast CT, MRI/MRA</td>
<td>No</td>
<td>No</td>
<td>Right third nerve palsy</td>
<td>Yes</td>
<td>Initial imaging (MRI/MRA)</td>
<td>Right and 5.5 × 4.5 × 4.45</td>
</tr>
<tr>
<td>II-9</td>
<td>54/M</td>
<td>Noncontrast CT, then angiogram (artifact from prior surgical clip)</td>
<td>No</td>
<td>No</td>
<td>Headache with history of cerebral aneurysm</td>
<td>Yes</td>
<td>Angiogram</td>
<td>Left and 9.6 × 8.1 × 5.8</td>
</tr>
<tr>
<td>III-10</td>
<td>55/F</td>
<td>Noncontrast CT, MRI/MRA</td>
<td>No</td>
<td>Yes (misread)</td>
<td>Headache with right Horner</td>
<td>No</td>
<td>Review of outside MRI/MRA showed aneurysm on source images</td>
<td>Right and 5 × 3 × 3</td>
</tr>
<tr>
<td>III-11</td>
<td>53/F</td>
<td>Noncontrast CT, then MRI/MRA</td>
<td>No</td>
<td>Yes (misread)</td>
<td>NA</td>
<td>NA</td>
<td>Review of outside MRI/MRA</td>
<td>Right and NA</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Case</th>
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<th>Clinical Indication on Radiology Report</th>
<th>Read by Neuroradiologist Initially</th>
<th>How Correct Diagnosis Was Made</th>
<th>Side and Size of Aneurysm in Millimeters*</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-12</td>
<td>50/F</td>
<td>CT/CTA, MRI/MRA</td>
<td>No</td>
<td>Yes (misread)</td>
<td>Headaches, evaluate for possible aneurysm</td>
<td>Yes (but mostly performs general radiology)</td>
<td>Review of outside CT/CTA; outside MRI poor quality</td>
<td>Left and 6 x 3</td>
</tr>
<tr>
<td>III-13</td>
<td>39/F</td>
<td>Noncontrast CT, MRI/MRA</td>
<td>No</td>
<td>Yes (misread)</td>
<td>R/o aneurysm right eyelid drop and right-sided headache</td>
<td>No</td>
<td>Review of outside MRI/MRA showed aneurysm on source images</td>
<td>Right, bilobed: 9.4 total and 7.1 x 4.4 x 3.6; 2.3 x 2 x 1.8</td>
</tr>
<tr>
<td>III-14</td>
<td>40/F</td>
<td>Noncontrast CT, then MRI/MRA</td>
<td>No</td>
<td>Yes (misread)</td>
<td>TIA, hypertension</td>
<td>No</td>
<td>Review of outside MRI/MRA</td>
<td>Left, bilobed: 12 total and 3 x 3; 8 x 6</td>
</tr>
<tr>
<td>III-15</td>
<td>33/F</td>
<td>Noncontrast CT, MRI/MRA</td>
<td>No</td>
<td>Yes</td>
<td>Right-sided headache</td>
<td>No</td>
<td>Outside MRI/MRA not available for review; diagnosis on angiogram</td>
<td>Right and 6 x 3</td>
</tr>
<tr>
<td>III-16</td>
<td>46/F</td>
<td>MRI, then CT with contrast, then angiogram</td>
<td>No</td>
<td>Yes (misread)</td>
<td>Migraine headache and CVA</td>
<td>No</td>
<td>Review of initial imaging (contrast CT)</td>
<td>Left and 3.5 x 2.5 x 2.5</td>
</tr>
<tr>
<td>III-17</td>
<td>37/F</td>
<td>CT with and without contrast, MRI/MRA, then CTA</td>
<td>No</td>
<td>Yes (misread)</td>
<td>Headache, Horner syndrome</td>
<td>No</td>
<td>Review of outside MRI/MRA</td>
<td>Left and 7.7 x 4.7 x 4.2</td>
</tr>
</tbody>
</table>

Group I: SAH on initial noncontrast CT; group II: no SAH but aneurysm correctly initially diagnosed; and group III: no SAH and initial diagnosis missed.

*Size of aneurysm in millimeters, as measured on catheter angiography (angiogram refers to catheter angiography).

CN, cranial nerve; CTA, CT-angiography; CVA, cerebrovascular accident; NA, not available; PCOM, posterior communicating artery; r/o, rule out; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.
The average greatest dimension of the aneurysms in each group was 6.9 mm for group I, 7.9 mm for group II, and 7.1 mm for group III. A 1-way analysis of variance test showed no statistically significant difference of aneurysm size among the 3 groups (P = 0.33). The average size of PCom A aneurysms causing an isolated third nerve palsy across all 3 groups was 7.3 mm.

DISCUSSION

Our study demonstrates that the interpretation of non-invasive neurovascular imaging is not easy and that a negative result can only be trusted after verifying that the interpreting radiologist is aware of the correct clinical indication for the study and has appropriate training and experience. Many radiology centers in the United States are equipped with the state-of-the-art CT and MRI scanners, but only a few benefit from experienced technologists who are able to appropriately manipulate the raw data and from neuroradiologists specifically trained to interpret non-invasive neurovascular imaging studies (12). In centers without skilled personnel, patients with an isolated non-traumatic third nerve palsy, should likely undergo a catheter angiogram, which remains the gold standard for the diagnosis of intracranial aneurysms. Unfortunately, it is likely that these centers are also the ones with the highest risk of catheter angiography–related complications because of their lack of experience with invasive neurovascular imaging (13,14). Intracranial aneurysms presenting with an isolated third nerve palsy are relatively rare (9–11,15), and only high volume centers with experienced neuroradiologists, interventional neuroradiologists, and vascular neurosurgeons have enough experience to efficiently “rule out” an aneurysm on noninvasive vascular imaging. Even at our highly specialized center, we could only identify 17 cases with isolated aneurysmal third nerve palsy over a period of 9 years. Many more aneurysmal third nerve palsies presented to our Emergency and Neurosurgery Departments over the same time period, but these were not isolated, manifesting the more typical symptoms and signs of aneurysmal rupture.

In theory, noninvasive vascular imaging (CTA or MRA) should be sensitive enough to detect nearly all aneurysmal third nerve palsies (9–12). Indeed, the smallest PCom A aneurysm reported to presumably cause a third nerve palsy was 3 mm and was missed initially on MRA (16). With this case and our case, III-16 as very rare exceptions, most reports have maintained that a PCom A aneurysm needs to be at least 4 mm to cause a third nerve palsy, within the range of highest sensitivity for both current MRA and CTA machines (3,4,6,9–11,17,18). The sensitivity of 1.5T MRA for aneurysms larger than 5 mm has improved to at least 95%, whereas the sensitivity of 1.5T MRA has been reported to be much lower (around 50%) for smaller aneurysms (10,19). The latter are unlikely to cause a third nerve palsy. The sensitivity of 3T MRA is only slightly better than with 1.5T MRA (19), and MRA of 7T might not significantly increase the sensitivity over the standard 1.5T MRA in diagnosing smaller aneurysms (20). The availability of 64-section multidetector CTA in recent years, compared with the previously used 4- or 16-section CTA, has dramatically improved the quality of the CTA examination and in turn, the sensitivity of CTA in the detection of small aneurysms (11,21,22). With improved spatial and temporal resolution and reduced slice thickness, the sensitivity of CTA for aneurysms above 3 mm is 99%–100% (23). In addition, rapid acquisition time makes CTA practical for emergency evaluation of cerebral aneurysms. However, unless the interpreting physician improves his/her ability for aneurysm detection, these advancements in imaging will not be beneficial.

In 4 of 17 of our cases (group I, Table 1), there was evidence of subarachnoid hemorrhage on the initial noncontrast CT obtained emergently, and the diagnosis of aneurysm was easily made. In the presence of subarachnoid hemorrhage, the index of clinical suspicion for intracranial aneurysm is very high, which improves the chance that the correct sequence of imaging studies will be performed and that the radiologist will meticulously evaluate the images in the search of an aneurysm. The lack of subarachnoid hemorrhage makes the identification of an aneurysm more difficult. The correct diagnosis was immediately made on initial noninvasive vascular imaging in 5 of 13 cases without

FIG. 1. Noncontrast head CT showing subarachnoid hemorrhage (arrow) in a patient with an isolated painful right third nerve palsy (group I).
subarachnoid hemorrhage (group II). Some of these studies were performed at various institutions (including ours), and nothing differentiated these cases from those that were missed. Interestingly, the patients in group II (correctly diagnosed) were older than those in group III (missed) and perhaps should have been less suspected of harboring an aneurysm and more suspected to suffer a microvascular third nerve palsy. The aneurysms' sizes were similar in groups II and III.

All 8 patients with an initial misread as negative noninvasive neurovascular study (group III) had studies performed at outside institutions. When considering these 8 patients with missed aneurysms, our initial inclination was to find fault with the technical quality of the test obtained. However, we were able to easily identify the missed aneurysm on all outside imaging studies (on a CD or plain films, without the ability to reformat the images), confirming that they were of adequate quality. Because of this finding, we chose not to evaluate or report in detail the techniques used to perform the CTAs and MRAs at outside institutions but rather focused on the interpretation of the studies themselves.

In detecting intracranial aneurysm on noninvasive neurovascular studies, it is crucial to carefully examine the source data in addition to the postprocessed reconstructed images. Manual alteration of the window levels and widths at an interpreting workstation can also improve aneurysmal detection. To perform these steps correctly, the radiologist must be given the correct clinical history (eg, left or right third nerve palsy). In 6 of 7 cases, with misinterpreted studies, the radiologist was given vague, or incorrect, clinical history including “headache, Horner,” “transient ischemic attack, hypertension,” and “headache,” without mention of an acute third nerve palsy, or “rule out aneurysm,” without mention of the side or location of the suspected aneurysm (group III, Table 1). It is not surprising that when the history is vague or inaccurate, the radiologist may not focus as carefully on the expected location of the aneurysm and may miss aneurysms that are sometimes seen only on 1 CTA slice or MRA source image.

Aside from an accurate history, the training and experience of the interpreting radiologist is probably the most important factor in determining the reliability interpretation of a noninvasive scan (12). Most (5 of 7) misread noninvasive imaging studies were interpreted by general radiologists who had no formal neuroradiology training. In 1 case, the interpreting radiologist had received neuroradiology training 20 years prior, but had been practicing mostly as a general radiologist for many years.

White et al (24) compared the detection of intracranial

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**FIG. 2.** CTA demonstrating a left PCom A aneurysm (arrow) in a patient from group II.

**FIG. 3.** A. MRA reformatted image from a patient in group III showing a PCom A aneurysm (arrow). B. MRA source image from the same patient showing the aneurysm (arrow).
aneurysms on CTA and MRA by neuroradiologists versus “observers,” which included a neurosurgeon, general radiologist, and radiographer with experience in looking at the neuraxis but no formal neuroradiology training. Neuroradiologists were consistently more accurate. For aneurysms larger than 5 mm on CTA, accuracy for neuroradiologists was 100%, whereas accuracy for the observers was 86%–93%. For MRA, accuracy was 93%–100% for neuroradiologists and 86%–100% for the observers. In another study (25) in which neuroradiologists reinterpreted head and neck imaging in a multidisciplinary cancer center, a change in interpretation occurred in 41% of images, altering management in 98% and prognosis in 95%, most with a worse prognosis, confirming that neuroradiology certification dramatically improves interpretation skills of neuroimaging. While technical improvements in non-invasive neurovascular imaging techniques, including CTA and MRA, have increased their sensitivity in detecting intracranial aneurysms, the most important step in imaging remains interpretation, which is entirely dependent on the training, skills, and experience of the radiologist. Appropriate communication of the correct clinical information and level of suspicion of an aneurysmal third nerve palsy is essential. Previous reports have emphasized the paucity of trained technologists capable of advanced manipulation of the imaging data and of certified neuroradiologists to interpret the study (12). Trobe (9) recently stated that determining whether a negative report is reliable is critical when evaluating a patient with isolated third nerve palsy. Our study suggests that to avoid diagnostic mistakes, all negative noninvasive studies should be reviewed with an experienced neuroradiologist before rejecting aneurysmal compression as the cause of the third nerve palsy or prior to ordering a catheter angiogram. This is obviously institution dependent, and delays resulting from patient or image transfer to a specialized institution must be balanced against the risks of immediate catheter angiogram.

REFERENCES
Comparison of Retinal Nerve Fiber Layer and Central Macular Thickness Measurements Among Five Different Optical Coherence Tomography Instruments in Patients With Multiple Sclerosis and Optic Neuritis

George M. Watson, MD, John L. Keltner, MD, Eric K. Chin, MD, Danielle Harvey, PhD, Audrey Nguyen, MD, Susanna S. Park, MD, PhD

Background: To compare the mean central macular thickness (CMT) and the mean average optic nerve retinal nerve fiber layer (RNFL) thickness in the eyes of patients with a history of optic neuritis and/or multiple sclerosis (MS) using 5 commercially available optical coherence tomography (OCT) instruments.

Methods: Cross-sectional study including 46 patients (92 eyes) with a history of optic neuritis and/or MS. Both eyes were imaged on the same day with 5 OCT instruments: 1 time-domain OCT (Stratus) and 4 different Fourier-domain (spectral-domain) OCT (3D OCT-1000, Cirrus, RTVue-100, and Spectralis).

Results: Twenty-five patients (50 eyes) were included in the final analysis after excluding patients with diabetes, glaucoma, ocular hypertension, or retinal pathology and inadequate scan quality. Randomized block analysis of variance revealed statistically significant differences across instruments ($P < 0.001$) for both eyes for mean CMT and mean average optic nerve RNFL. When testing for significant differences in measurements from instrument to instrument, some difference was noted between the right and left eyes.

Conclusions: Statistically significant differences exist among commercially available OCT instruments in measuring mean CMT and mean average RNFL thickness in patients with optic neuritis and/or MS. These findings likely result from the differences in data acquisition and segmentation algorithm software among OCT instruments. Awareness of these variations among OCT instruments will be important in using these instruments for clinical trials and management of patients with optic neuritis and/or MS.

doi: 10.1097/WNO.0b013e3181facbbd

Optical coherence tomography (OCT) is a quick and noninvasive method of obtaining a cross-sectional image of the retina, aiding clinicians and researchers in understanding numerous pathologic conditions (1). The ability of OCT to quantify retinal nerve fiber layer (RNFL) and macular thickness allows an objective method for monitoring axonal injury and serves as a useful outcome measure in clinical trials of optic nerve disorders (2–6). Accordingly, the neurology community is increasing their reliance on sequential OCT imaging as a potential structural marker for the more time-consuming and expensive MRI imaging in directing clinical response to pharmacotherapy, as well as primary outcomes in drug trials (7). Stratus time-domain OCT (TD-OCT, Carl Zeiss Meditec, Inc, Dublin, CA) has historically been used to quantitate RNFL thinning in patients with multiple sclerosis (MS) and/or optic neuritis, and acceptable
reproducibility has been reported with this instrument (2,4,5,8–12).

Until recently, widespread applications of OCT technology used exclusively TD-OCT, named because image resolution is a function of distance and time (13). Stratus OCT is the most widely used TD-OCT instrument; however, the speed of this class of OCT is limited by the need for a movable reference mirror. In contrast, the newer Fourier-domain OCT (FD-OCT) (spectral-domain OCT) technology offers significant advantages over the traditional TD-OCT techniques (14) by gathering depth information from spectral data using Fourier transformation, eliminating the need for a moving reference mirror, and allowing for more efficient data acquisition (15–17). FD-OCT instruments provide superior image sampling as a greater number of scans are acquired at a faster rate (15). FD-OCT also provides a significant reduction in motion artifacts and an increased signal-to-noise ratio in comparison to TD-OCT (15,18,19). Recent studies comparing central macular thickness (CMT) measurements, that is, central 1-mm zone of the Early Treatment Diabetic Retinopathy Study (ETDRS) map (Fig. 1), among the various commercially available TD- and FD-OCT instruments have shown that measurement differences exist among machines (20–22). Comparative optic nerve and macular thickness data have been reported in both normal and diseased eyes with various TD- and FD-OCT, including ocular hypertension, diabetic retinopathy, traumatic optic neuropathy, macular edema, and chiasmal lesions (11,23–27). More recently, studies have compared RNFL and CMT measurements using various OCT instruments for eyes with glaucoma (20,28–34). Although the majority of these studies illustrate that measurements cannot be compared across 2 different OCT instruments, larger studies comparing greater than 3 instruments are limited. In addition, no study thus far has assessed the variability in RNFL and CMT measurements among commercially available TD- and FD-OCT instruments in eyes with MS and/or optic neuritis.

Before a new diagnostic instrument can be introduced for use in clinical practice, studies aimed at understanding repeatability and reproducibility of measurements, diagnostic accuracy, and ability to detect changes over time must be reported. Furthermore, it is important to determine if measurements from early generation TD-OCT technologies and new generation FD-OCT technologies are compatible and consistent (17–19). Thus, in this study, cross-sectional comparisons of RNFL and CMT measurement were made in patients with MS and/or optic neuritis using 5 different commercially available OCT instruments, including the traditional TD-OCT (Stratus OCT) and 4 different FD-OCT instruments.

METHODS

Participants

Forty-six patients diagnosed with optic neuritis and/or MS were enrolled from the Neuro-ophthalmology Clinic at the University of California Davis Eye Center. Written informed consent was obtained from all participants, and the study was conducted according to a protocol approved by the Institutional Review Board Administration, University of California, Davis, and in adherence to the tenets of the Declaration of Helsinki.

From September through December 2008, all enrolled patients underwent optic nerve RNFL and CMT measurements of both eyes on the following 5 instruments: Stratus TD-OCT and 4 different FD-OCT 3D OCT-1000 (Topcon, Tokyo, Japan), Cirrus (Carl Zeiss Meditec, Inc), RTVue-100 (Optovue Corporation, Fremont, CA), and Spectralis (Heidelberg Engineering, Inc, Heidelberg, Germany) (Table 1). Images were acquired on the same day and setting, by 1 of 3 highly experienced OCT technicians in variable sequence. CMT measurement in this study refers to the thickness of the central 1-mm zone of the macula in the ETDRS macular thickness map (Fig. 1).

All participants included in this study had a diagnosis of optic neuritis and/or MS, regardless of disease subtype, laterality, severity, current activity, or presence of disease-modifying therapy. Participants were excluded if there was a known history of diabetes, glaucoma, ocular hypertension, or other retinal disease that could possibly result in RNFL or macular thickness changes. At the time of image acquisition, OCT scans with gross motion artifacts and segmentation errors were removed by our OCT technicians, and repeat scanning was performed. OCT data with signal strength less than the minimum standard as published by the Diabetic Retinopathy Clinical Research Network (Table 1) and patients with incomplete scans of either eye were excluded from the final analysis.

OCT Instrumentation

Table 1 summarizes the features of the 5 different commercially available OCT instruments used in this study.

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FIG. 1. Macular thickness segmented zones as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS). CMT refers to the central 1-mm zone of the ETDRS macular thickness map as shown.
The following scans were used for each instrument to obtain the RNFL and CMT measurements:

- **Stratus**, software version 4.0, fast macular thickness map protocol was acquired consisting of 6 radial line scans (128 A-scans per line) over a 6-mm diameter circle of the macula centered in the fovea. For the fast RNFL protocol, 3 scans, each composed of 256 A-scans, were acquired consecutively using a 3.46-mm diameter circular scan and an automated computer algorithm delineating the anterior and posterior margins of the RNFL.

- **Topcon 3D-OCT 1000**, software version 3.20, macular and optic nerve protocol consisted of 6 radial line scans (1024 A-scans per line) in a 3-dimensional 6 × 6 mm area (3.6 seconds; 128 raster scans with 512 A-scans per scan). The optic nerve RNFL peripapillary 3.4-mm circle map was centered on the optic nerve.

- **RTVue-100**, software version 2.0, MM6 macular map protocol consisted of 12 radial line scans (1024 A-scans per line) in a 3-dimensional 6 × 6 mm area (2.0 seconds). The optic nerve RNFL NHM4 protocol consisted of 12 radial scans (452 A-scans per line) over 3.45-mm diameter centered on the optic disc.

- **Cirrus**, software version 3.0, macular cube protocol consisted of 128 radial lines (512 A-scans per line) in a 3-dimensional 6 × 6 mm area (2.5 seconds). The optic nerve RNFL 200 × 200 protocol was utilized generating 200 horizontal scan lines (200 A-scans per line) over a diameter of 3.46 mm.

- **Spectralis**, software version 3.2, macular volume protocol consisted of 49 radial lines (512 A-scans per line) in a 3-dimensional 6 × 6 mm area (5 seconds). Optic nerve RNFL measurements consist of 768 A-scans over a 3.45 mm area, however, repeated and averaged over 16 measurements, capable of being performed through eye-tracking software.

**Statistical Analysis**

Means and SDs of CMT and RNFL for each eye were calculated for the 5 instruments. To provide a scaling comparison for each instrument, percent differences from the Stratus mean CMT and RNFL were also calculated. As measurements were available on each instrument for each subject, a randomized block analysis of variance (ANOVA) was used to assess differences across instruments in CMT and RNFL. Post hoc pairwise tests were performed if an overall difference was detected across instruments to identify where differences occurred among the instruments. These post hoc tests were corrected for multiple comparisons using Turkey studentized range (Honestly Significant Differences) test. Because the percent differences are simple linear transformations of the original data, results of the ANOVA and post hoc pairwise comparisons are identical to those for the original data; so results are only presented for the original data. Assumptions of the ANOVA were checked and were met by the data. Analyses were done for each eye separately, because measurements taken from eyes of the same individual cannot be assumed to be independent from one another. In secondary analyses, data from both eyes were used in repeated measures models accounting for the correlation between observations from the same individuals across instruments and eyes to test for differences in CMT or RNFL between eyes. All statistical analyses were performed using SAS, and a P value <0.05 was considered statistically significant.

**RESULTS**

Among 46 patients (92 eyes) imaged and recruited, 21 patients were excluded due to incomplete scans (34 eyes), concurrent retinal disease (6 eyes), or poor signal strength and image quality (2 eyes). Ultimately, 25 patients (50 eyes) were included in our final analysis. Demographic information and clinical diagnoses for included patients are shown in Table 2. The mean ± SD of the respective CMT (Table 3) and average optic nerve RNFL thickness (Table 4) were measured using each of the 5 OCT instruments. Percent differences for CMT and RNFL from the Stratus mean were calculated for each instrument to provide a comparison of scaling as seen in Tables 5 and 6, respectively.

A statistically significant difference was observed for each eye when comparing mean CMT and mean average optic
nerve RNFL thickness across instruments \((P < 0.001)\). Further investigation into the differences in mean CMT showed that in the left eye, all instruments were different from one another \((P < 0.05, \text{corrected for multiple comparisons})\), except for RTVue-100 and Cirrus \((P = 0.12, \text{corrected})\). In the right eye, all instruments were significantly different from one another \((P < 0.05, \text{corrected})\). For RNFL, in the left eye, similarities were seen between 3D OCT-1000 and RTVue-100 \((P = 0.99, \text{corrected})\) and between Cirrus and Spectralis \((P = 0.11, \text{corrected})\), but all other pairings were different \((P < 0.05, \text{corrected})\). In the right eye, RNFL measures obtained from 3D OCT-1000 and RTVue-100 were also similar \((P = 0.99, \text{corrected})\). In addition, Stratus was similar to both of these instruments \((P = 0.36, \text{corrected with 3D OCT-1000 and } P = 0.17, \text{corrected with RTVue-100})\). However, Cirrus was different from all other instruments \((P < 0.05, \text{corrected})\) and Spectralis was different from all instruments with the exception of Stratus, which did not quite reach statistical significance in our study \((P = 0.052, \text{corrected})\).

In models that used the data from both eyes, accounting for the correlation between the eyes from the same individual, there was a significant difference, on average, between the right and left eye on RNFL \((P < 0.001)\) but not on CMT \((P = 0.8)\). RNFL was significantly lower, on average, in left eyes compared to right eyes. To further investigate differences between the eyes, we assessed the eyes for optic neuritis. Two individuals had optic neuritis in both eyes, 9 had it in the left eye only, and 6 had it in the right eye only. For all instruments except 3D OCT-1000 in the right eye \((P = 0.08)\), eyes with optic neuritis had lower RNFL, on average, than those without optic neuritis \((P < 0.01 \text{ for all other instruments, right and left eyes analyzed separately})\). Thus, the lower RNFL measurement noted in the left eye versus the right eye may be partially explained by a difference in the incidence of optic neuritis between the right and left eyes in our study population. There were no differences found on CMT between eyes with and without optic neuritis \((P > 0.5 \text{ for all instruments, right and left eyes analyzed separately})\).

**DISCUSSION**

The recent advances in OCT in clinical management and research trials have led to the need for investigating differences among the various instruments, especially between the higher resolution FD-OCT and its predecessor TD-OCT (Stratus). Previous studies have reported statistically significant differences not only between FD and TD classes of OCT instrument but also among the various FD-OCT instruments for both normal and diseased eyes \((22,33,35-37)\). A majority of these studies are limited in comparing only one OCT instrument to another, and large prospective studies comparing greater than 3 different OCT instruments are limited so far. Furthermore, no prior study has compared optic nerve RNFL and CMT measurement among OCT machines in eyes with optic neuritis or MS. Our institution was fortunate to have had access to 5 commercially available OCT machines to compare RNFL and CMT measurements in eyes with optic neuritis or MS. These instruments included Stratus, the prototype TD-OCT, and 4 different commercially available FD-OCT instruments, including Cirrus, TopCon 3D OCT-1000, RTVue, and Spectralis. The results show that both optic

<table>
<thead>
<tr>
<th>OCT Instrument</th>
<th>CMT Right Eye ((\mu\text{m}))</th>
<th>CMT Left Eye ((\mu\text{m}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratus</td>
<td>183 ± 18</td>
<td>184 ± 20</td>
</tr>
<tr>
<td>3D OCT-1000</td>
<td>224 ± 18</td>
<td>223 ± 21</td>
</tr>
<tr>
<td>RTVue-100</td>
<td>246 ± 19</td>
<td>248 ± 21</td>
</tr>
<tr>
<td>Cirrus</td>
<td>253 ± 21</td>
<td>251 ± 23</td>
</tr>
<tr>
<td>Spectralis</td>
<td>266 ± 20</td>
<td>265 ± 20</td>
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**TABLE 4. Mean average RNFL thickness ± SD obtained with each OCT instrument**

<table>
<thead>
<tr>
<th>OCT Instrument</th>
<th>RNFL Right Eye ((\mu\text{m}))</th>
<th>RNFL Left Eye ((\mu\text{m}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratus</td>
<td>94 ± 13</td>
<td>88 ± 15</td>
</tr>
<tr>
<td>3D OCT-1000</td>
<td>96 ± 11</td>
<td>92 ± 12</td>
</tr>
<tr>
<td>RTVue-100</td>
<td>97 ± 13</td>
<td>92 ± 15</td>
</tr>
<tr>
<td>Cirrus</td>
<td>86 ± 13</td>
<td>83 ± 14</td>
</tr>
<tr>
<td>Spectralis</td>
<td>91 ± 15</td>
<td>85 ± 18</td>
</tr>
</tbody>
</table>

**TABLE 5. Percent difference of mean CMT ± SD from Stratus**

<table>
<thead>
<tr>
<th>OCT Instrument</th>
<th>CMT Right Eye</th>
<th>CMT Left Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratus</td>
<td>0.00 ± 0.10</td>
<td>0.00 ± 0.11</td>
</tr>
<tr>
<td>3D OCT-1000</td>
<td>0.23 ± 0.10</td>
<td>0.21 ± 0.11</td>
</tr>
<tr>
<td>RTVue-100</td>
<td>0.34 ± 0.10</td>
<td>0.34 ± 0.11</td>
</tr>
<tr>
<td>Cirrus</td>
<td>0.39 ± 0.11</td>
<td>0.36 ± 0.12</td>
</tr>
<tr>
<td>Spectralis</td>
<td>0.45 ± 0.11</td>
<td>0.44 ± 0.12</td>
</tr>
</tbody>
</table>
nerve RNFL and CMT measurement have statistically significant differences among machines.

In this study, we included eyes with optic neuritis and/or MS. While approximately 80% of patients with MS experience visual impairment (38,39), not all patients who have MS have signs of optic neuritis. In our study, we found a statistically lower mean RNFL thickness measurement for the left eye when compared to the right eye (Table 4). No significant difference was noted in CMT between the right and left eyes. This difference in mean RNFL measurement between the right and left eyes may be partly due to the higher incidence of optic neuritis in the left eye compared to the right eye in our study population since RNFL measurement tends to be lower in eyes with optic neuritis when compared to eyes with MS without optic neuritis. However, patients with MS and a history of unilateral optic neuritis demonstrate RNFL thinning not only in affected eyes but also in the supposed unaffected eyes as demonstrated by TD-OCT (3,40). Additionally, patients with MS without a history of acute optic nerve inflammation have shown decreased RNFL thickness in comparison to eyes of healthy control subjects, as measured by Stratus TD-OCT, and this decrease has been found to correlate well with low-contrast letter acuity and contrast sensitivity in such patients (5,9). Specifically, 4 μm of RNFL thinning was predictive of 1 line worsening of low-contrast letter acuity (5). These findings support that RNFL thinning in patients with MS occurs on a chronic basis and not exclusively from acute optic neuritis, further warranting the use of OCT to follow disease progression and response to therapy.

Quantitative measurements of optic nerve atrophy in patients with MS and optic neuritis with MRI has recently been correlated with optic nerve RNFL thinning as measured by TD-OCT (41,42), further validating RNFL measurement as a potentially more sensitive structural marker for central nervous system imaging in clinical and research investigations in MS. While optic nerve appearance and imaging is of primary interest in evaluating pathology from optic neuritis, the demyelinating damage acts in a retrograde fashion with ultimate retinal ganglion cell loss and subsequent RNFL thinning. As RGCs make up about one third of the total macular thickness, attention has also been placed in following macular thickness reductions in demyelinating disease. An association between optic nerve RNFL thinning and macular volume reduction in patients with optic neuritis with or without MS has been reported with TD-OCT (2). Such findings may be further validated with the superior resolution of FD-OCT, enabling high definition retinal layer segmentation and specific attention to the inner retinal layers.

Our study found significant differences in mean CMT and average optic nerve RNFL thickness not only between TD and FD classes of OCT instruments but also within the FD-OCT class of instruments in this population of patients with MS and optic neuritis. Differences in macular thickness can be partially explained by the reported differences in segmentation algorithm defining retinal boundaries among OCT machines, as well as differences in sampling density (Table 1). All inner macular thickness boundaries begin at the internal limiting membrane; however, the outer boundary is variable (43–45): Stratus measures to the inner segment-outer segment junction of photoreceptor layer, Topcon to the inner retinal pigment epithelium (RPE) layer, Cirrus and Optovue to the outer RPE layer, and Spectralis to Bruch membrane.

Our statistical analysis revealed similar mean CMT values for left eyes between Cirrus and RTVue-100, which may be expected as both instruments measure thickness between the same boundaries. However, this was not a consistent finding when analyzing right eyes as each instrument significantly differed from one another. Similarly, variability in statistically significant differences was found when comparing instruments for mean average RNFL. The clinical significance of such findings is unknown. Ultimately, differences in data acquisition and software among the various OCT instruments should be carefully compared and eventually standardized to provide more consistent and comparable results among OCT machines. Theoretically, future software development aimed at standardizing data acquisition and segmentation boundaries may allow interchangeability of the thickness measurements across OCT instruments.

While our sample size was small, a larger sample would not likely affect our conclusions as differences among instruments are clear and likely resulting from differences in postprocessing algorithms. Our study excluded a large percentage of patients based on incomplete scans or poor signal strength, who otherwise met the inclusion and exclusion criteria. Signal strength has been shown to affect RNFL thickness measurements using Stratus OCT (46,47). Images with lower signal strength were, therefore, excluded from this study. Unfortunately, signal strength scales are not constant across OCT instruments, and this difference among instruments may also have contributed to differences in RNFL and CMT measurements among machines.

In summary, our study demonstrated a statistically significant difference in RNFL and CMT measurements among commercially available TD- and FD-OCT instruments in patients with optic neuritis and/or MS. As retinal thickness measurements among OCT instruments have.

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**Table 6.** Percent difference of mean average RNFL thickness ± SD from Stratus

<table>
<thead>
<tr>
<th>OCT Instrument</th>
<th>RNFL Right Eye</th>
<th>RNFL Left Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratus</td>
<td>0.00 ± 0.14</td>
<td>0.00 ± 0.17</td>
</tr>
<tr>
<td>3D OCT-1000</td>
<td>0.02 ± 0.11</td>
<td>0.04 ± 0.13</td>
</tr>
<tr>
<td>RTVue-100</td>
<td>0.03 ± 0.13</td>
<td>0.04 ± 0.17</td>
</tr>
<tr>
<td>Cirrus</td>
<td>−0.09 ± 0.13</td>
<td>−0.07 ± 0.15</td>
</tr>
<tr>
<td>Spectralis</td>
<td>−0.03 ± 0.16</td>
<td>−0.04 ± 0.20</td>
</tr>
</tbody>
</table>

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been found to vary depending on posterior segment disease (35), it is possible that the variation we found among OCT machines is specific to MS or optic neuritis and not necessarily applicable to other optic neuropathies. Nonetheless, our study raises awareness in the scientific community relying on OCT measurements for clinical decision making and drug trials. Based on our results, the data from these various OCT instruments do not appear to be freely interchangeable in patients with MS and/or optic neuritis.

ACKNOWLEDGMENTS

The authors thank Ellen Redenbo, CRA, ROUB, Mark Thomas, CRA (no longer with University of California Davis Eye Center), and Karisha Chandra, COT, of the University of California Davis Eye Center, for data acquisition. Special thanks also to Norman Siu (Heidelberg) and Eugene Huang, PhD, (Topcon) for making available the FD-OCT instruments used in this study. The authors also thank Jack Werner, PhD, for his valuable advice regarding this study.

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Comparison of Primary Position Measurements and Abduction Deficit Between Type 1 Duane Syndrome and Sixth Cranial Nerve Palsy

Noopur Nikki Batra, CO, Kyle Arnoldi, CO, COMT, James D. Reynolds, MD, Mitchell B. Strominger, MD

Background: Unilateral Duane retraction syndrome type 1 (DRS-I) and unilateral sixth nerve palsy (6NP) present with limitation of abduction, incomitant esotropia, and frequently, a compensatory head turn. The purpose of this study was to compare the mean primary position measurement and to correlate this with the abduction deficit to determine if these measurements may be used to differentiate between the 2 conditions when other clinical signs of DRS-I (globe retraction, changes in lid fissure height, and upshoots/downshoots) are subtle.

Methods: A database search of patients examined over a 5-year period revealed 69 cases of DRS-I and 62 cases of unilateral 6NP. Primary position measurements both at distance and near and limitation of abduction on version testing were recorded and compared.

Results: Mean abduction deficit was \(-3.5 \pm 0.1\) for DRS-I and \(-2.6 \pm 0.2\) for 6NP (\(P = 0.0004\)). Mean esotropia at near was \(8.4 \pm 1.1\) prism diopters (PD) for DRS-I and \(27.2 \pm 2.4\) PD for 6NP (\(P < 0.0001\)). Mean esotropia at distance was \(10.3 \pm 1.3\) PD for DRS-I and \(36.4 \pm 2.4\) PD for 6NP (\(P < 0.0001\)). The mean distance-near disparity for DRS-I was \(1.94 \pm 0.62\) PD and \(9.19 \pm 1.28\) PD for 6NP (\(P < 0.0001\)). The age-group of \(\leq 2\) years consisted of 23 DRS-I and only 2 6NP cases. The age-group between \(>2\) years and \(<18\) years had 41 DRS-I and 16 6NP cases, respectively. Finally, the age-group of \(\geq 18\) years had only 5 DRS-I and 44 6NP cases (\(P < 0.0001\)).

Conclusion: Patients with DRS-I showed greater abduction deficit yet significantly less esotropia in primary position than those with 6NP. Patients with 6NP were more likely to have a significant distance-near disparity. In addition, patients with DRS-I tended to be younger than those with 6NP. This report documents that DRS-I and 6NP can be differentiated based on magnitude of primary position esotropia, comparison of primary position esotropia with severity of abduction deficit, distance-near disparity, and patient age.
condition (5). Differentiating these 2 entities is usually straightforward. Acquired 6NP produce new onset diplopia in older children and adults with no history of a motility disorder dating from early childhood. However, presentation in young children may be accompanied by an incomplete historical observation that fails to note the congenital onset, inadequate evidence of diplopia vs suppression, and clinical features that are subtle or difficult to detect. Caputo et al (6) studied 24 patients with abduction deficits before 36 months of age and found that classic findings of DRS, such as lid fissure narrowing on adduction, upshoots or downshoots, and globe retraction in adduction, may not manifest until early childhood.

The purpose of this retrospective study was to compare the mean primary position strabismus measurement at distance and near and to correlate this with the abduction deficit to determine if these measurements may be used to differentiate between DRS-I and 6NP.

METHODS

Patients diagnosed and treated for unilateral DRS-I and unilateral 6NP within a 5-year period at the Floating Hospital for Children at Tufts Medical Center in Boston, MA, and at the Ross Eye Institute in Buffalo, NY, were included in this retrospective chart review. At the Ross Eye Institute, data were collected on patients diagnosed with DRS-I or 6NP consecutively with no selection bias. At Tufts Medical Center, 9 DRS-I cases were excluded because both distance and near measurements were not recorded. Six unilateral 6NP patients were excluded due to the lack of distance or near measurements, and 10 cases were omitted because they had been treated for the initial 6NP elsewhere and had been referred for possible surgery for a long-standing partially resolved paresis. All patients with a history of eye muscle surgery were excluded. The records of a total of 131 subjects were identified: 69 DRS-I patients and 62 6NP cases. Each patient underwent a complete ophthalmologic and orthoptic examination. Sex, age at first visit with accurate measurements, degree of version restrictions, side of the affected eye, and strabismic measurements in primary position at both distance and near were recorded in each case. Measurements in primary position were determined by Krimsky or Hirschberg method, or prism cover test. To simplify analysis, patients were only included if the records included all these required fields of data.

Since the quantification of the degree of version restriction is subjective, the degree number obtained at the first visit was usually compared to other consecutive visits to compare and judge for reliability of the assessment during the initial visit. The same pediatric ophthalmologist confirmed the abduction deficit in the charts to ensure intraobserver reliability. Abduction deficits were graded on a 0 to −5 scale with 0 equaling no observable abduction deficit and −5 equaling an inability to achieve even the midline. We grouped the size of the abduction deficit into 3 categories: severe (greater than −3), intermediate (−3), and mild (less than −3).

All statistical comparisons were performed using the SAS system for Windows (version 9.2) (SAS Institute, Cary, NC). Primary position measurements at near and distance for DRS-I were compared to 6NP measurements using the Wilcoxon 2-sample test. Distance-near disparity between the 2 groups was also compared using the Wilcoxon 2-sample test. The χ² tests were used to assess age distributions between DRS-I and 6NP patients in 3 different age-groups: 2 years or younger, older than 2 years and younger than 18 years, and 18 years and older. Finally, we used logistic regression models to evaluate the magnitude of associations, as estimated by odds ratios (ORs) and 95% confidence intervals (CIs), between near or distance measurements and age and the 2 conditions.

RESULTS

Among the 131 unilateral cases evaluated, 69 cases were DRS-I and 62 cases were 6NP. Of DRS-I cases, 42 (61%) were women and 27 (39%) were men. Of the 6NP cases, 34 (55%) were women and 28 (45%) men. The left eye was involved in 52 (75%) and the right eye in 17 (25%) of the DRS-I cases. In the 6NP cases, the left eye was involved in 34 (55%) and the right eye in 28 (45%) of cases. The age distribution of patients with DRS-I ranged from 7 months to 34 years (median = 4 years), and the mean (±SE) age was 66.0 ± 0.9 years. The mean age for 6NP patients was 46.9 ± 3.7 years with a range of 7 months to 87 years (median = 54 years).

The age-group of ≤2 years consisted of 23 DRS-I and 2 of 6NP cases. The age-group between >2 years and <18 years consisted of 41 DRS-I and 16 6NP cases. The age-group of ≥18 years had 5 DRS-I and 44 6NP cases (Table 1). Calculated by χ² test, the P value was <0.0001, indicating that the age distribution of DRS-I and 6NP cases is significantly different.

In evaluating the abduction deficit in DRS-I cases, 51 (74%) were in the severe category, 10 (14%) were in the intermediate category, and 8 (12%) were in the mild category. For the 6NP cases, 24 (39%) were in the severe category, 10 (16%) were in the intermediate category, and 28 (45%) were in the mild category. There were a significantly larger number of severe and intermediate cases with DRS-I (61 [88%]), than

<table>
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<tr>
<th>TABLE 1. Age group distribution within DRS-I and 6NP patients</th>
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Values represent n (%).
with 6NP (34 [55%]). The mean (±SE) degree of abduction deficit in DRS-I cases was −3.5 ± 0.1, and the median (interquartile range) was −4.0 (−4.0 to −3.0). For 6NP cases, the mean deficit was −2.6 ± 0.2 and the median was −3.0 (−4.0 to −1.0). Using the Wilcoxon 2-sample test, the P value equaled 0.0004.

The mean (±SE) primary position measurement at near for DRS-I was 8.4 ± 1.1 prism dipters (PD) (range, 1 PD exophoria to 30 PD of esotropia). At distance, the mean was 10.3 ± 1.3 PD (range, orthophoria to 35 PD of esotropia). For 6NP, the near mean was 27.2 ± 2.4 PD (range, orthophoria to 90 PD of esotropia). At distance for 6NP, the mean was 36.4 ± 2.4 PD (range, 6 PD to 90 PD of esotropia). The P value for near measurements between the 2 groups was <0.0001 and for distance was <0.0001.

From a logistic regression model, which included eye position near measurements and age as covariates, the ORs and 95% CIs for DRS-I and 6NP were 1.14 (1.07–1.23) and 1.10 (1.06–1.15), respectively. A model including distance measurements and age produced similar results (OR, 1.15; 95% CI, 1.07–1.22 and OR, 1.09; 95% CI, 1.05–1.14, respectively).

When comparing the distance-near disparity between DRS-I and 6NP by Wilcoxon 2-sample test, we found that the difference was significant with P < 0.0001. The mean (±SE) distance-near disparity for DRS-I was 1.94 ± 0.62 PD (median = 0 PD) and 9.19 ± 1.28 PD (median = 9.5 PD) for 6NP. The maximum disparity in DRS-I cases was 16 PD. The maximum disparity in 6NP was 40 PD, more than double the DRS-I disparity. There was a disparity of 5 dipters or less in 52 (75%) of DRS-I cases and only 21 (34%) of 6NP cases.

Our data suggest that there is definite overlap between the 2 conditions. To better understand if this is significant, we looked at the mean ± SD for both near and distance within the 3 abduction deficit categories: mild, intermediate, and severe (Table 2). Then, the OR could be calculated with regards to the abduction deficit categories. When looking at the effect between mild and severe, the point estimate equaled 7.437. Therefore, without other information, if a patient’s abduction deficit is between −2.5 and 0, then the odds of being 6NP is 7.43 times to a patient whose abduction deficit is between −5 and −3.5 (P < 0.0001). However, if the patient’s abduction deficit is less than −3, then the odds of being 6NP is only 2.12 times to the patient whose abduction deficit is between −3.5 and −5, and this was not significant (P = 0.1403) (Table 3).

To go one step further, we looked at 6 groups by abduction deficit (mild, intermediate, and severe) and near primary measurements with a cutoff at the median or 14 PD (ie, −1≤near ET≤14 and 14<near ET≤90). We then calculated OR estimates using the reference group as 14<near ET≤90 and −5.0≤abduction deficit≤−3.5 (Table 4).

### DISCUSSION

The mean primary position deviations for near and distance measurements were significantly different between patients with DRS-I and 6NP. The mean measurements for 6NP exceeded DRS-I measurements for primary position esotropia at near by 18 PD and 26 PD at distance.

Wagner et al studied patients who presented with an abduction deficiency during infancy. Their patients were followed until a diagnosis of either DRS-I or 6NP was established. They found that of the 24 patients younger than 2 years, 13 were diagnosed with DRS-I, only 1 was diagnosed with 6NP and 10 had an uncertain diagnosis.

The average esotropia in DRS-I cases was 18 PD and 80 PD in 6NP cases. Of the 10 uncertain cases, 8 developed narrowing of the palpebral fissure, retraction of the globe, and upshoots or downshoots on adduction by 35 months of age. The remaining 2 patients still had uncertain diagnosis. Wagner et al concluded, “Other findings suggestive of DRS include a smaller angle of esotropia and abduction deficits manifesting as esotropia in contralateral gaze and convergence insufficiency” (5). Our study also shows smaller angles of esotropia for DRS-I (maximum 35 PD) vs 6NP (maximum 90 PD).

The patient samples of these 2 conditions had a wide range of ages. We assessed this by dividing the cases into 3 different age-groups. Interestingly, for DRS-I cases, 59% were between ages 2 and 18 years, while 71% of the 6NP cases were older than 18 years. Only 2 6NP cases (3%) were in the age-group of ≤2 years. This supports the finding that congenital 6NP is extremely rare (6).

There are limitations to our study. We realize that secondary medial rectus fibrosis can develop in long-

| Table 2. Mean near and distance measurements (±SD) of DRS-I and 6NP patients within the 3 abduction deficit categories: mild (−2.5 to 0), intermediate (−3), and severe (−3.5 to −5) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Abduction Deficit | n | Near | Distance | n | Near | Distance | P Value for Near | P Value for Distance |
| −2.5 to 0 | 8 | 4.63 ± 7.31 | 8.88 ± 12.14 | 28 | 19.04 ± 13.20 | 28.00 ± 14.77 | 0.0063 | 0.0059 |
| −3 | 10 | 2.90 ± 5.22 | 1.60 ± 3.20 | 10 | 23.40 ± 19.77 | 30.70 ± 16.87 | 0.0024 | 0.0012 |
| −5 to −3.5 | 51 | 10.04 ± 9.45 | 12.25 ± 11.07 | 24 | 38.38 ± 19.21 | 48.63 ± 18.09 | <0.0001 | <0.0001 |
standing DRS-I or 6NP, creating a secondary restrictive component that can alter the abduction deficit or eye position in primary gaze. Unfortunately, we did not have data on forced ductions in every case and could not analyze this potential effect. Also, it is difficult to compare abduction deficits in DRS-I cases, which are relatively stable but can change with fibrosis, to 6NP cases, which may have a more variable range of presentation and continue to change based on etiology. However, we noticed a greater degree of abduction deficit in DRS-I than in 6NP cases and felt that it is important to look at the abduction deficit between the 2 groups to see if a trend or difference exists when comparing it to primary position measurements. We attempted to minimize the variations within either group by analyzing the measurements at initial presentation and omitting resolving or long-standing paresis.

Unfortunately, it is not possible to estimate the degree of abduction deficit based on just primary position measurements for 6NP. Even though a general progression in esotropia was seen as the abduction deficit increased, there was a wide range of esotropia measurements for each degree of abduction deficit (0 to −5). However, as seen on Table 3, if a patient has an abduction deficit of −2.5 or less, it is 7.43 times more likely that this is due to 6NP than DRS-I.

When clinical signs such as globe retraction, lid fissure changes and an upshoot or downshoot, are difficult to detect in patients with an abduction deficit, it is important to obtain primary position strabismus measurements both at distance and near. By looking at the magnitude of primary position esotropia, comparing this esotropia measurement with the severity of abduction deficit, and also looking at the distance-near disparity of the measurements, one can obtain important information that will aid in differentiating DRS-I from 6NP. In addition, the age of the patient was also a distinguishing factor with those less than 18 years more likely to have DRS-I and older than 18 years to have 6NP.

When measuring young children, most clinicians can get a near measurement either by Krimsky or Hirschberg method. Therefore, we found ORs by looking at near measurements and abduction deficit (Table 4). We used the reference group 14< near ET<90 and −5.0≤abduction deficit<−3.5. If a patient has a −5 to −3.5 abduction deficit and near ET ≤14 PD, the relative odds of this being 6NP is 0.078 times (P = 0.0002). If a patient has a −2.5 to 0 abduction deficit and near ET >14 PD, the relative odds of this being 6NP is 12.852 times (P = 0.0185).

ACKNOWLEDGMENT

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REFERENCES

Bitemporal Visual Field Defects in Ethambutol-Induced Optic Neuropathy

Richard C. Kho, MD, Majed Al-Obailan, MD, Anthony C. Arnold, MD

Background: Ethambutol-induced optic neuropathy is well documented and most frequently associated with central or cecocentral scotomas. We designed a study to characterize the subset of patients who exhibit bitemporal visual field defects.

Methods: A computer search was performed for patients evaluated in a university academic neuro-ophthalmology consultative practice to identify those with the diagnosis of ethambutol-induced optic neuropathy. Clinical features were tabulated, including dose and duration of ethambutol use, time to onset of visual loss, initial and follow-up visual acuities, automated perimetry, optic disc appearance, and MRI features. Assessments for bitemporal visual field defect with alignment on vertical midline and for visual improvement after discontinuing ethambutol were performed.

Results: Nineteen cases of ethambutol-induced optic neuropathy were identified; all but 2 eyes demonstrated visual field defects worse in the temporal fields, most with margination along the vertical midline with superimposed central or cecocentral scotomas. Six cases (12 eyes) showed bitemporal defects with such margination without superimposed scotomas. Median time to onset of visual loss was 6.0 months. Visual improvement occurred (of 17 cases with data available) by at least 3 Snellen lines in 17 of 34 eyes (50%); mean visual acuity improvement was 3.74 lines (median, 3.0). Visual improvement by at least 3.0 decibels (dB) mean deviation (MD) on automated perimetry occurred in 27 of 34 eyes (79%); mean improvement in MD was 7.82 dB (median, 7.86). Median follow-up was 8.0 months. None had MRI abnormality in the chiasmal region.

Conclusion: Bitemporal visual field defects are common in ethambutol-induced optic neuropathy. The pattern may mimic chiasmal compression, and neuroimaging is required. It may reflect susceptibility to toxicity of chiasmal crossing fibers.

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Ethambutol is a well-documented cause of optic neuropathy, with dose-related severity (1). Previous reports have most frequently described a pattern of visual field loss common in toxic optic neuropathy, with symmetric bilateral central or cecocentral scotomas. Isolated cases of bitemporal visual field loss have been described but have been considered unusual. The degree to which the field loss pattern mimicked chiasmal compression rather than bilateral temporal field loss due to cecocentral depression has been unclear. We reviewed cases of ethambutol-induced optic neuropathy to assess the frequency of bitemporal visual field loss and to establish whether the defects present showed features of chiasmal injury or were more consistent with individual bilateral optic nerve damage.

METHODS

A computer search was performed for patients evaluated in the consultative practice of 1 investigator (A.C.A.) in the years from 1986 to 2010, coded as “optic neuropathy, toxic.” Inclusion criteria included evidence of progressive, bilateral, simultaneous visual field loss within the central 30°, dyschromatopsia, diminished pupillary light responses, normal or pale optic discs, and the use of ethambutol at the time of visual loss. Exclusion criteria included history of vasculitis, demyelinating disease, or other cause of optic neuritis; optic disc edema; and optic nerve or chiasmal abnormality visible on MRI. Clinical features were tabulated, including dose and duration of ethambutol preceding visual loss, initial and follow-up visual acuities, automated perimetry (Humphrey Field Analyzer, Carl Zeiss Meditec, Inc, Dublin, CA and Octopus Perimeter, Haag-Streit USA, Mason, OH), and optic disc appearance.
RESULTS

Computer record search revealed 56 cases of toxic optic neuropathy. Twenty-two cases of ethambutol-induced optic neuropathy were detected. Nineteen cases (38 eyes) with sufficient documentation of clinical and neuroradiologic data were included for this study (Table 1; Figs. 1–3). Age ranged from 23 to 84 years; 15 patients were women and 4 were men. Ethambutol dosage ranged from 500 to 1200 mg/day, with duration 3–24 months (mean, 9.1; median, 6.0) prior to documented visual loss; additional antituberculous medications were used in all cases, including clarithromycin in 11, rifampin in 11, isoniazid in 7, and azithromycin in 2. Thirty-six eyes (95%) demonstrated visual field loss worse in the temporal hemifields. Thirty-one of 38 eyes (82%) showed visual field loss with some degree of margination along the vertical midline, of which 26 had superimposed central or cecocentral scotomas. Six cases (12 eyes) (32%) revealed bitemporal visual field loss marginaling along the vertical midline without superimposed central or cecocentral scotomas.

Visual improvement occurred (of 17 cases with data available) by at least 3 Snellen lines in 17 of 34 eyes (50%); mean visual acuity improvement was 3.74 lines (median, 3.0 lines). Visual improvement by at least 3.0 decibels (dB) mean deviation (MD) on automated perimetry occurred

| TABLE 1. Clinical features of 19 cases with ethambutol-induced optic neuropathy |
|---------------------|--------|--------|--------|--------|----------------|----------------|----------------|----------------|
| Patient no. | Age/Sex | VA1 | VA2 | TX-VA1, m | C/V-VA2 | Fundus | VF 1 Pattern | MD1 (dB) | MD2 (dB) |
| 1          | 69/M    | 20/30 | 20/20 | 10      | 13      | NL    | Temp           | –8.78       | –1.99       |
| 2          | 76/F    | 20/80 | 20/20 | 6       | 3       | 1–2+ OA | Temp           | –15.71      | –2.22       |
| 3          | 84/F    | 20/40 | 20/200 | 5      | 14      | NL    | Temp           | –15.77      | __________ |
| 4          | 63/F    | CF   | 20/60 | Tr OA   | 2+ OA   | Temp + cent | –18.83      | –9.99       |
| 5          | 78/F    | 20/400 | 20/80 | 8       | 3       | 2+ OA | Gen contr     | –12.53      | –5.54       |
| 6          | 77/F    | 20/300 | 20/100 | 9      | 3       | NL    | Temp           | –8.21       | –4.71       |
| 7          | 71/F    | CF   | 20/200 | 24      | 12      | Equiv OA | Temp + cent  | –29.54      | –6.63       |
| 8          | 84/F    | CF   | 20/200 | 20/25 | 15      | NL    | Sup temp       | –6.89       | –3.24       |
| 9          | 69/M    | 20/300 | 20/30 | 9      | 2       | NL    | Sup temp       | –5.76       | –2.22       |
| 10         | 23/F    | —    | 20/100 | 4      | 25      | 1–2 + OA | Temp + mild nasal | –25.33      | –10.91      |
| 11         | 66/F    | 20/200 | 20/30 | 4      | 4       | NL    | Temp + mild nasal | –26.41      | –10.82      |
| 12         | 72/F    | 20/200 | 20/40 | 4      | 3       | NL    | Temp + cent    | –7.22       | –2.35       |
| 13         | 76/F    | 20/300 | 20/40 | 9      | 26      | Equiv OA | Temp + cent   | –14.49      | –3.97       |
| 14         | 64/M    | 20/200 | 20/50 | 5      | 11      | NL    | Temp + cent    | –10.53      | –2.15       |
| 15         | 69/F    | 20/200 | 20/200 | 16     | 5       | 1–2 + OA | Temp + cent   | –10.53      | –3.87       |
| 16         | 75/F    | 20/500 | 20/100 | 1      | 0 + OA | 1 + OA | Temp + cent    | –13.14      | –5.27       |
| 17         | 56/F    | 20/200 | 20/80 | 4      | 120     | 1 + OA | Temp + mild nasal | –22.54      | __________ |
| 18         | 59/F    | CF   | 20/400 | 20/400 | 6      | 18      | 1 + OA | Temp + cent    | –17.67      | –16.65      |
| 19         | 76/M    | CF   | 20/500 | 3      | 16      | NL    | Temp + cent    | –13.64      | –0.45       |

VA, visual acuity; TX-VA1, time from treatment to initial VA; D/C-VA2, time from discontinuing medication to final VA; VF, visual field; CF, count fingers; OA, optic atrophy; temp, temporal defect; cent, central defect; contr, contraction; sup, superior defect; scot, scotoma; gen, generalized; NL, normal; Equiv, equivocal; Tr, trace; MD, mean deviation.
in 27 of 34 eyes (79%); mean improvement in MD was 7.82 dB (median, 7.86 dB). Time from discontinuing ethambutol to final visual measurement ranged from 2 to 120 months (mean, 15.7 months; median, 8.0 months) after discontinuing ethambutol.

**DISCUSSION**

Ethambutol-induced optic neuropathy has been reported to most commonly result in bilateral and relatively symmetric central or cecocentral visual field defects. While typical

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**FIG. 1.** Case 1. *Top:* Initial automated perimetry demonstrates bitemporal visual field defects with alignment on vertical midline in each eye. *Bottom:* Follow-up automated perimetry 13 months later shows near complete resolution of defect in the right eye and partial resolution in the left eye.
FIG. 2. Case 19. **Top:** Initial automated perimetry demonstrates bitemporal visual field defects with alignment on vertical midline in both eyes. There are superimposed central scotomas in the left eye more severe than in the right eye. **Bottom:** Follow-up automated perimetry 12 months later shows near complete resolution of field defects in both eyes.
Cecocentral scotomas may mimic field loss from compressive chiasmal damage, they are usually readily distinguishable from the latter in their lack of margination along the vertical midline and their restriction to the central portion of the temporal visual fields. Rarely, focal posterior chiasmal compression may produce bitemporal hemianopic central scotomas. Bitemporal visual field defects that respect the vertical midline are considered to result from preferential damage of crossing chiasmal fibers, most commonly from compressive lesions.

Twenty-two anecdotal cases of bitemporal visual field defects secondary to ethambutol toxicity have been previously reported (1–15). These present a mix of perimetric techniques and results including both large cecocentral scotomas and clear bitemporal defects aligning on the vertical midline. To our knowledge, no other medication currently in use has been associated with this pattern.

We add 19 cases in which high-resolution neuroimaging ruled out idiopathic or infectious chiasmal inflammation, tuberculoma, and unrelated compressive lesion and in which quantitative static perimetry allowed precise analysis of defects. In our cases, the most common pattern of field loss was bitemporal depression with some degree of margination on the vertical midline and superimposed cecocentral defect (Figs. 2, 3). Six cases showed no superimposed scotomas and were highly suggestive of chiasmal injury (Fig. 1). Although sampling bias may have played a part, in this series, the predominant pattern of loss was not pure cecocentral or central scotoma but varying patterns of bitemporal loss.

Artifactual margination of visual field defects along both vertical and horizontal meridians has been documented with the Humphrey perimeter, presumably due to the algorithm for initialization by quadrant (16). It is possible that this factor contributed, in some cases, to the prominent margination seen in our cases. However, the correlation of these cases with similar features previously reported with various perimeters and with the experimental data described below suggests that it represents more than artifact. Moreover, in 1 case (Fig. 3; Case 17), Octopus perimetry, which does not rely on the same initializing algorithm and is not susceptible to this artifact, revealed similar margination.

Experimental animal studies by several investigators have confirmed histopathologic evidence of central chiasmal damage as an early sign of ethambutol toxicity (16–20). A single human study of brain and eye histopathology also indicated focal chiasmal demyelination (16). No study to
date, however, has confirmed the etiology for specific involvement of crossing fibers. Lessell (19) postulated factors such as 1) selective deposition in chiasm and adjacent optic nerves and 2) local variations in microvascular supply, contact with cerebrospinal fluid, enzymatic activity, and glial cell populations, any of which might predispose to chiasmal damage. His subsequent study suggested that chiasmal glial subpopulations did indeed differ from those in more distal optic nerves (21). Our findings corroborate these studies.

Several authors have addressed evidence that ethambutol may be directly toxic to the retina. Heng et al (22) studied ethambutol toxicity in rats and concluded that ganglion cells were specifically susceptible via an excitotoxic (glutamate-mediated) pathway. Zoumalan et al (23) also concluded that ganglion cell injury was a significant mechanism for visual loss from ethambutol, citing patterns of retinal nerve fiber loss as measured by optical coherence tomography. Lai et al (24), Kardon et al (25), and Liu et al (15) have reported abnormalities of the multifocal electroretinogram in cases of ethambutol-associated visual loss, suggesting a primary injury to deeper layers of retina. Three of the reported cases demonstrated bitemporal visual field loss but were more in keeping with a cecocentral pattern. Cases in our series predominantly revealed a pattern more suggestive of preferential involvement of chiasmal crossing fibers, with more widespread visual field loss and with margination on the vertical midline. These findings in aggregate suggest that damage from ethambutol may involve several regions: deeper retinal layers (given reports of multifocal electroretinographic findings) papillomacular retinal nerve fibers (documented by optical coherence tomography) and crossing fibers within the chiasm (supported by bitemporal visual field loss demonstrated in our cases).

Previous reports vary regarding prognosis for visual recovery after discontinuation of the drug. In general, prognosis has been said to depend on the degree of optic nerve injury at discovery. In the only other large series of cases with follow-up data (26), 6 of 10 eyes (60%) showed visual acuity improvement by at least 2 Snellen lines, with 7 of 9 (78%) showing visual field improvement. Our data in a larger number of cases indicate a similar favorable prognosis with relatively early detection. Some 50% showed visual acuity, and 79% showed visual field improvement. Available data on dose of ethambutol were insufficient to correlate with visual loss and recovery.

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Epidemic Optic Neuropathy Is Evident in the Somalian Population

Abdirisak A. Dalmar, PhD, MD, Katherine E. Hodson, MSc, Gordon T. Plant, MD

Background: Optic neuropathy epidemics have proven to be a serious public health problem around the world. Recently, documented outbreaks have occurred in Cuba and Tanzania, with almost identical clinical presentation. Investigations of both epidemics have implicated nutritional deficiencies as part of a multifactorial etiology, and thus, it is proposed that there may be many undetected epidemics in other food-deprived nations. Somalia, a country subject to prolonged droughts and civil war, may be at particular risk of nutritional deficits. We conducted a case series in Mogadishu, the Somalian capital, with the aim of identifying and characterizing any cases of epidemic optic neuropathy.

Methods: Cases were recruited at the Al-Noor Eye Hospital, Mogadishu, between 2002 and 2004. Individuals were screened by trained ophthalmic nurses, and a full ophthalmic examination was undertaken by an experienced ophthalmologist. Patients also completed a lifestyle questionnaire to identify any common risk factors.

Results: One hundred five acute cases of optic neuropathy were identified. Progression from hyperemia to pallor of the optic discs and greatest visual loss occurred over the first month. Our findings are similar to those reported in the Tanzanian epidemic, including involvement of young patients (mean age: 24 ± 5.3 years) and evidence of peripheral neuropathy.

Conclusion: Epidemic levels of optic neuropathy are evident in Somalia. The extent of visual loss in the first month emphasizes the need to initiate treatment early in the course of the disease. Training and establishing health surveillance systems in community clinics may form a central component to this strategy.

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Optic neuropathy epidemics around the world have affected tens of thousands of individuals in the past century. In many cases, poor nutrition or toxic dietary factors have been attributed as central features of the underlying etiology. Strachan syndrome, for example, first described in the Caribbean (1) was later documented in Canadian prisoners of war subject to malnourishment in Japanese concentration camps during World War II (2). Tropical ataxic neuropathy (TAN) in Nigeria (3), and a form of acute paralysis known as “Konzo” in Democratic Republic of Congo (formerly Zaire) (4), Mozambique (5), and Tanzania (6) was associated with cyanide toxicity secondary to cassava consumption (although in the case of TAN, the link with cyanide intoxication is not well established). More recently, population-wide B-vitamin deficiency, in combination with cassava consumption, tobacco smoking (7,8), and, to a lesser extent, low-level chronic methanol consumption (8), was implicated in an epidemic of optic neuropathy in Cuba. Widespread B-vitamin supplementation largely resolved the outbreak (7). The clinical features of the Cuban epidemic closely resemble an outbreak in Tanzania, which was first reported in 1988 and is now more appropriately regarded as endemic in the secondary school population in Dar es Salaam (9). Reports from Tanzania (10,11) described bilateral, simultaneous, usually painless, visual failure over 2–12 weeks, loss of nerve fibers in the papillomacular bundle associated with central or cecocentral scotomas, impaired color vision, and peripheral neuropathy. The finding that the Tanzanian epidemic also occurred in a B-vitamin deficient population (A. A. Dalmar et al, unpublished data, 2010) suggests a similar multifactorial etiology to that demonstrated in Cuba.

The common involvement of nutritional deficiencies in these epidemics has focused attention on the potential for undetected epidemics occurring in other African countries suffering from food shortages. As a country that has been affected by prolonged droughts and civil war since 1991, and in which agriculture makes up 65% of gross domestic
product (12), Somalia is particularly sensitive to failing crop yields. Generalized poor agricultural performance, suspected widespread micronutrient deficiencies, and a diet that is predominantly cereal based suggest that the population is at risk of nutritional deficiencies and thus potentially to epidemics of optic neuropathy. No survey of epidemic optic neuropathy has ever been conducted in Somalia.

We carried out a case series in Mogadishu, the Somalian capital, with the aim of identifying and characterizing any cases of epidemic optic neuropathy, comparing its features to those presenting in Tanzania.

**METHODS**

Based on previous case definitions of epidemic optic neuropathy (9), patients were recruited from the Al-Noor Eye Hospital, Mogadishu, Somalia, over a period of 2 years (2002–2004).

Nurses trained in interviewing techniques administered a questionnaire concerning sociodemographic characteristics and exposure to any known toxins. The information collected also included date of onset, the duration for visual loss to reach its worst level, past and present medications, food intake and weight loss over the previous few months, and drinking/smoking habits. A full clinical examination was undertaken.

A certified ophthalmic nurse determined best-corrected visual acuity and assessed color vision using Ishihara pseudoisochromatic color plates. The principal author charted visual fields on a 1-m tangent screen with the use of 1- to 10-mm red test objects, carried out slit-lamp examination and tonometry, and performed a complete fundusoscopic examination.

**Data Analysis**

All data were entered into an Excel data sheet. Double entry was not performed, but all variables were coded and checked, and data cleaning was performed where necessary.

The data set was imported into SPSS for Windows software and descriptive statistics generated. Data from Somalia were compared with data collected by the authors in a similar study in Tanzania.

**Ethics**

The Ministry of Health, Somalia, granted ethical approval for this research.

**RESULTS**

A total of 105 cases were seen over the 2 years of the study, and clinical findings are summarized in Table 1. The mean age (±SD) of the optic neuropathy cases was 24 ± 5.3 years, with an almost identical age distribution compared to the Tanzanian epidemic (Fig. 1). Of the affected individuals, 65% were men, and 30% presented within a month of symptom onset. On examination, the optic discs were either normal or had dilated capillaries and blurred margins and over 4 weeks developed temporal pallor with loss of the cecocentral nerve fiber layer.

In terms of peripheral symptoms, 59% reported numbness in the legs and 29% hearing loss, once again demonstrating similar levels to those seen in Tanzania (Fig. 2). Almost half of cases reported weight loss, and more than 50% (16 of 31) of women of breastfeeding age (age > 16 years) were breast-feeding at the time of symptom onset, but this comprised only 15% of the total study population. No common medication or dietary factors were evident.
DISCUSSION

In contrast to previously published Tanzanian data, which predominantly focused on chronic cases of optic neuropathy (10,13), the individuals in this study represent acute cases, with over half presenting within 3 months of onset of symptoms. Our results document progression of the symptoms of optic neuropathy over the first 12 weeks. The prominent features were bilateral loss of visual acuity with central or cecocentral scotomas and diminished color vision. There was evolution of optic disc hyperemia to pallor over the first month. Greatest visual loss occurred during the first 4 weeks and continued to deteriorate over the subsequent 8 weeks. These findings are virtually identical to those reported from Tanzania, including similar age groups and associated peripheral neuropathy, and hearing loss. Our data support the hypothesis that the clinical syndrome in Somalia and Tanzania is the same entity. Given their similarity to the Cuban epidemic (7,8), and their shared clinical features with Leber hereditary optic neuropathy (14), it seems likely that both the Somali and Tanzanian optic neuropathies are disorders resulting from mitochondrial dysfunction. This has already been proposed for the Cuban epidemic (7–15).

In the Somali and Tanzanian populations (10,16), smoking prevalence was low, thus suggesting that cyanide toxicity from tobacco smoking plays no role in the etiology of this optic neuropathy. This is in contrast to the Cuban epidemic in which smoking was an important risk factor for optic neuropathy (7,8). In Cuba, the underlying mechanism was thought to involve inhibition of oxidative phosphorylation due to a combination of the following: 1) cyanide from tobacco smoking and/or cassava consumption; 2) formate accumulation due to methanol consumption; and 3) B-vitamin deficiency affecting the detoxification of endogenous formate (8,15). This combination of factors would lead to inhibition of adenosine triphosphate (ATP) production, on which neuronal activity is dependent. In the absence of ATP, mitochondrial transport to the site of energy requirement (the nodes of Ranvier and distal axon terminal) cannot occur, leading to neuronal degeneration (15). Papillomacular bundle nerve fibers and long axons have particularly high ATP requirements and may be selectively targeted by this mechanism (15).

A common feature of the Somali and Cuban epidemics is weight loss reported at onset of symptoms, suggesting a possible nutritional deficiency with stomatitis occurring in almost one third of our patient cohort. B-vitamin deficiency (riboflavin, niacin, vitamin B₁₂, and vitamin B₁₅) may play a causal role. However, given the lack of a control group in our study and the poor nutritional status of the Somali population in general, the role of B vitamins in the etiology of Somali optic neuropathy remains uncertain.

Previous studies in Tanzania have suggested that lactation is particularly a strong risk factor for optic neuropathy (13). In our study, more than 50% of women of breastfeeding age reported the onset of optic neuropathy with initiation of lactation. If epidemic optic neuropathy is associated with nutritional deficiencies, the increased demands of pregnancy followed by lactation might also be a contributing factor. With optic neuropathy in Tanzania now classed as endemic (9), and evidence presented here for the first time of its prevalence in Somalia, more effective treatment strategies are required. Current treatment of B-vitamin supplementation based on its use in the Cuban epidemic (7,8) has proven very successful in acute cases in Tanzania (Dalmar et al, unpublished data, 2010), and the large extent of visual loss reported over the first month in Somalia places emphasis on the need for early diagnosis and treatment through:

- Training community eye care workers.
- Establishing a surveillance system in community health clinics to provide data on patterns of disease occurrence and monitor any changes.
- Developing national guidelines for the treatment and prevention of epidemic optic neuropathy.

ACKNOWLEDGMENTS

The authors thank all the staff at the Al-Noor Eye Hospital, Mogadishu, and especially manager Mrs Anab Hussein Jama, for their kind support during data collection.

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Functional Constriction of the Ocular Motor Field: Description and Preliminary Evaluation of a New Technique to Help Distinguish Organic From Nonorganic Visual Field Loss

Nadeem Ali, MA, MB BChir, MRCOphth, FRCSEd(Ophth)

Background: To describe and evaluate a novel clinical method to assess patients with constricted fields using the Goldmann perimeter, with the aim of distinguishing nonorganic from organic field constriction.

Methods: Ten patients with constricted visual fields who were undergoing kinetic perimetry as part of their routine workup were included. Five of them had suspected functional visual loss (FVL), and 5 had organic field loss. Patients were assessed on the Goldmann perimeter using a test that combines kinetic perimetry (visual field) with a modified uniocular field of fixation (motor field). The main outcome measure was the size of the visual and motor fields.

Results: In all patients with organic visual loss, the motor field was expanded relative to the visual field, as would be expected ($P = 0.02$). In all patients with suspected FVL, the motor field was markedly constricted and was not significantly different from the visual field ($P = 0.27$). The motor fields of the 2 groups were significantly different sizes ($P = 0.001$).

Conclusion: Patients with FVL may exhibit functional behavior on a motor task, believing that it is a test of vision. Functional constriction of the ocular motor field may help distinguish organic from nonorganic visual field loss, but further evaluation is required.

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Subjectively impaired vision without a detectable organic basis is termed functional visual loss (FVL). Patients with FVL pose significant diagnostic and therapeutic challenges to ophthalmologists and may also present to other medical specialties (1–4).

FVL can present as loss of visual acuity, visual field, or both (5). In all cases, an underlying organic cause must first be excluded. A common pattern of functional field loss is marked visual field constriction. The field area is often the same at different testing distances (a tubular field), a feature that helps distinguish it from a physiological conical field. In some patients, however, it can be difficult to be certain that marked field constriction is functional rather than organic.

The Goldmann perimeter is an ideal tool to demonstrate functional features in suspected nonorganic field loss. Overlapping of isopters, spiraling, stellate patterns, and centrifugal expansion are evidence of functional behavior (6,7). However, the Goldmann perimeter has also been used as a way of measuring ocular ductions in conditions such as thyroid eye disease (8–10) and chronic progressive external ophthalmoplegia (11). The quantitative record of the ocular motility obtained, which is plotted on standard kinetic perimetry paper, is called the Uniocular Field of Fixation (UOF). The Goldmann perimeter provides the opportunity to switch from a visual task (perimetry) to a motor task (UOF) without changing the testing environment.

In our study, we aimed to determine 1) if functional behavior observed on perimetry would be translated into functional motor behavior when the task was switched and 2) if the responses obtained might be helpful in distinguishing a functional cause from an organic cause of field constriction.

METHODS

Ten patients undergoing kinetic perimetry as part of their standard ophthalmic workup were studied. All had previously demonstrated constricted visual fields with preserved central vision and no limitation of ocular motility. The first group (“organic”) comprised 5 patients with known disease thought to be wholly responsible for their visual field loss.
Their characteristics are shown in Table 1. The second group (“functional”) comprised 5 patients with suspected FVL, based on typical functional features as shown in Table 2. Three of these functional patients (#6, 7, 8) had no concurrent organic ophthalmic or neurological disease and were considered to have pure FVL. In the remaining 2 patients, the diagnosis of FVL on a background of organic disease (functional overlay) had been made. Case 9 had long-standing hydrocephalus, and Case 10 had craniopharyngioma resection earlier in life.

Immediately following conventional perimetry, the right eye of each patient was retested using the procedure described below. Testing was performed in all cases by an experienced perimetrist (N.A.).

The testing method was designed to be quick, simple to understand, repeatable, and easily incorporated into a routine kinetic perimetry session. It consisted of 2 steps: the first visual and the second motor. The first step was a simplified visual field plot using a single stimulus target (V4e). The patient was instructed to “look at the central spot all the time and press the buzzer when the light first appears.” The target was moved toward the center along each of the 8 cardinal meridians in random order, and the responses were plotted in the standard way. This was termed the “visual field.”

The second step was a modified UFOF and followed immediately. The patient was instructed, “Now the target is going to start in the centre and move outwards, but this time you should follow it with your eyes as it moves. Press the button as soon as it disappears.” The V4e target was then moved centrifugally from the center along each of the 8 cardinal meridians, and the responses were plotted. This was termed the “motor field.”

For quantitative analysis of the visual and motor fields, the mean radial distance from the center for each of the plotted responses was measured in millimeters, and the 8 distances summed to give a total field score. T tests (5% level, 2 tailed), paired for within group and independent for between group, were performed on SPSS (ver 17).

<p>| TABLE 1. Patients with organic visual field loss |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Gender</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46/Male</td>
<td>Idiopathic intracranial hypertension with chronic papilledema</td>
</tr>
<tr>
<td>2</td>
<td>61/Male</td>
<td>Advanced retinitis pigmentosa</td>
</tr>
<tr>
<td>3</td>
<td>21/Male</td>
<td>Chronic relapsing idiopathic optic neuropathy</td>
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<tr>
<td>4</td>
<td>84/Male</td>
<td>Advanced primary open angle glaucoma</td>
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<tr>
<td>5</td>
<td>38/Female</td>
<td>Advanced pigmentary retinopathy</td>
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</table>

<p>| TABLE 2. Patients with functional visual field loss |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Gender</th>
<th>Functional Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>19/Female</td>
<td>Crossing isopters, factitious hemianopia on automated field (not present on kinetic field)</td>
</tr>
<tr>
<td>7</td>
<td>15/Female</td>
<td>Spiraling isopters on kinetic perimetry</td>
</tr>
<tr>
<td>8</td>
<td>40/Male</td>
<td>History of pseudohemiparesis and pseudoseizures; triplopia on 4 prism-diopter base up test</td>
</tr>
<tr>
<td>9</td>
<td>16/Female</td>
<td>Improvement in visual acuity with minimal prescription; Ishihara numbers traced accurately but not read</td>
</tr>
<tr>
<td>10</td>
<td>60/Female</td>
<td>Tubular fields; normal visuomotor behavior incompatible with claimed fields</td>
</tr>
</tbody>
</table>

RESULTS

The visual and motor field plots for each patient are shown in Figure 1. Table 3 shows the visual field and motor field scores. All patients had markedly constricted visual fields, the size of which was not significantly different between the 2 groups (mean field scores: organic, 139 ± 44; functional, 111 ± 30; P = 0.61).

For the organic group, the motor fields were significantly larger than the visual fields (mean field scores: visual, 139 ± 44; motor, 446 ± 48; P = 0.02). For the functional group, the motor fields were markedly constricted and were, on average, the same size as the visual fields (mean field scores: visual, 111 ± 30; ocular motor, 142 ± 30; P = 0.27). Comparing the motor fields between the 2 groups, the difference was highly significant (mean field scores: organic, 446 ± 48; functional, 142 ± 30; P = 0.001).

DISCUSSION

Most of the techniques for demonstrating functional features in patients with suspected nonorganic visual loss are tricks (7). They rely on the patient’s inadequate understanding of visual physiology. In the technique described here, the patient is led to believe that step 2 is another visual field task when in reality, because the target is foveated as it moves, it is a test of ocular motility. We found that patients with suspected FVL demonstrated a functional gaze paresis, which mapped quantitatively in visual space to their perceived field of vision, a feature that can distinguish them from patients with organic field loss.

Other techniques have been described to expose functional field loss. A commonly used method is to tell the...
patient to make saccades to targets in the supposed blind field, disguising the test as an assessment of eye movements (7). This has recently been examined quantitatively for its value in discriminating organic from nonorganic visual loss (12). More objective tests, which demonstrate intact visual pathways and are less reliant on patient cooperation, include

**FIG. 1.** Visual (blue) and motor (red) fields plotted with the V4e stimulus for all patients.
pupil perimetry (13,14) and measuring multifocal visual evoked potentials (15).

The technique described in this study differs from these in that no attempt is made by the examiner to prove sight in the blind field. Rather the goal is to demonstrate additional unequivocally functional behavior, in this case restriction of ocular ductions where none exists. This is a limitation of the technique since other tests would still be needed to prove a scotoma is factitious.

The advantages of our technique are that it is simple to perform and can be used within the setting of the Goldmann perimeter as soon as functional perimetry features are suspected. In addition, in this preliminary series of patients, there were no false-positive results. This technique may prove to be a useful way of distinguishing organic from nonorganic field loss. However, larger patient groups are required to validate sensitivity and specificity and to see whether patients with pure FVL differ from patients with functional overlay. We are planning additional studies to address these issues.

### REFERENCES


### TABLE 3. Individual field score (in millimeters)

<table>
<thead>
<tr>
<th>Patient</th>
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<th>Motor</th>
<th>Patient</th>
<th>Visual</th>
<th>Motor</th>
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<td>377</td>
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<td>37</td>
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<td>167</td>
<td>186</td>
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<tr>
<td>5</td>
<td>172</td>
<td>419</td>
<td>10</td>
<td>65</td>
<td>79</td>
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<tr>
<td>Mean</td>
<td>139</td>
<td>448</td>
<td>111</td>
<td>142</td>
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</tr>
<tr>
<td>SE</td>
<td>44</td>
<td>48</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

SE, standard error.
Statin or Nonsteroidal Anti-Inflammatory Drug Use Is Associated With Lower Erythrocyte Sedimentation Rate in Patients With Giant Cell Arteritis

Ryan Hegg, MD, Andrew G. Lee, MD, Nathan T. Tagg, MD, M. Bridget Zimmerman, PhD

**Background:** Previous studies have found that nonsteroidal anti-inflammatory drugs (NSAIDs) and statins may impact erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels in patients. The current study was performed to determine if NSAID or statin use is associated with lower ESR and CRP in patients with biopsy-proven giant cell arteritis (GCA).

**Methods:** A retrospective cross-sectional study was conducted that included 161 patients via chart review. Charts of patients with GCA seen at the University of Iowa Hospitals and Clinics from 1960 to 2008 were reviewed. Inclusion criteria were adequate medication records, serum ESR and/or CRP on record, no prior corticosteroid use, and biopsy-positive GCA. Exclusion criteria were the presence of diseases known to elevate ESR or CRP. Main outcome measures included ESR and CRP values measured while evaluating patients for GCA but prior to receiving treatment.

**Results:** Statin nonusers had an ESR of 85.0 mm per hour (interquartile range [IQR] = 60–110 mm per hour) and a CRP of 8.7 mg/dL (IQR = 2.7–16.2 mg/dL). Statin users had an ESR of 57.5 mm per hour (IQR = 35–85) and a CRP of 2.4 mg/dL (IQR = 0.8–15.9 mg/dL). Statin use was associated with a lower ESR ($P =$ 0.005), while there was no significant association with a lower CRP ($P =$ 0.127). NSAID nonusers had an ESR of 98.0 mm per hour (IQR = 64–116) and a CRP of 8.0 mg/dL (IQR = 2.1–16.2 mg/dL). NSAID users had an ESR of 75.0 mm per hour (IQR = 46–98.5 mm per hour) and CRP of 8.0 mg/dL (IQR = 1.5–16.2 mg/dL). NSAID use was associated with a lower ESR ($P =$ 0.004), but there was no significant association with a lower CRP ($P =$ 0.522).

**Conclusion:** Statin use and NSAID use were associated with a lower ESR; however, they were not associated with lower CRP values. Clinicians should be aware that statin or NSAID use is associated with lower ESR in patients with GCA, and this test may therefore have lower sensitivity and specificity for recognizing patients with GCA, and CRP may be a superior test to evaluate patients for GCA.
CRP of 2.78 mg/L in controls, 2.73 mg/L in patients on aspirin alone, 2.29 mg/L in patients on statins alone, and 2.03 mg/L in patients on both aspirin and statins (8). These results suggest that statins are associated with lower CRP values, and this may be synergistic with aspirin in patients without inflammatory diseases. Kinlay reported on the CRP-lowering effects of simvastatin vs simvastatin/ezetimibe. The author found that simvastatin lowered baseline CRP by 14.3% and that simvastatin/ezetimibe lowered CRP by 31.0% (9). A meta-analysis of studies analyzing the association between cholesterol-lowering therapies and CRP values found that across all studies (58% of which were statin-only treatment studies), there was a 28% (95% CI: 26%–30%) drop in CRP, with greater drops occurring in statin treatments than with other cholesterol-lowering therapies (10). However, 89%–98% of the decrease in CRP associated with using cholesterol-lowering agents was found to be related to the low-density lipoprotein (LDL)–lowering effects of the treatments (10). These findings suggest that while statin use is associated with lower CRP values, this association may be directly related to lower LDL levels produced by the statins.

For ophthalmologists considering the diagnosis of GCA in patients taking NSAIDs or statins, artificially low or normal inflammatory marker levels might lead to error in clinical judgment (increased false-negative rate). To the best of our knowledge, there has been no prior study that searches for an association between NSAID or statin use and ESR or CRP in patients with biopsy-proven GCA. Because these 2 serum markers are often pivotal in the evaluation of patients with suspected GCA, it is critical to know if these medications are associated with lower ESR and CRP values in this patient population. In this study, we report on the associations between use of statins or NSAIDs and serum ESR and CRP in patients with biopsy-proven GCA.

METHODS

A retrospective chart review of all patients with the primary diagnosis of GCA seen in the H. Stanley Thompson Neuro-Ophthalmology Clinic at the University of Iowa Hospitals and Clinics from 1960 to 2008 was conducted. Institutional review board approval was obtained prior to data collection, and the collection was compliant with Insurance Portability and Accountability Act. This included patient age, date of diagnosis, initial serum ESR and/or CRP, temporal artery biopsy result, and medication profile, particularly the use of NSAIDs or statins. Patients were included only if they had adequate documentation of their medications, a serum ESR and/or CRP measurement prior to the initiation of corticosteroid treatment, and biopsy-proven GCA. Patients were excluded for the following reasons: 1) they had inadequate documentation of their medications; 2) they had inadequate documentation of serum ESR and/or CRP measurements; 3) they had initiation of steroid treatment before initial ESR and/or CRP measurements; 4) they had a history of other collagen vascular or inflammatory disease that could also produce an elevated ESR/CRP; or 5) they did not have biopsy-proven GCA.

All patients were categorized into 1 of 2 groups: those exposed to the study medications (NSAIDs and/or statins) and those not exposed to the study medications at the time of their first evaluation. The initial ESR and CRP in patients from both groups were compared using the Wilcoxon rank sum test. The proportion of patients with a normal initial ESR measurement (defined as ESR of 37 mm per hour or less) and those with a normal initial CRP measurement (defined as CRP of 0.5 mg/dL or less) were computed and then compared between patient groups using Fisher exact test. We defined a normal ESR at a cutoff of 37 mm per hour because the average patient age was 75 years and if divided by 2 this is 37.5, which is a method sometimes used as a reference for ESR since it varies by age (12). However, we do recognize that this is a somewhat arbitrary cutoff. We defined a normal CRP as <0.5 mg/dL because this was the laboratory’s reference value. In addition to assessing the effect of either statin or NSAID use on a defined normal ESR, logistic regression analysis was performed with either NSAID use or statin use as the independent variable, and age as a covariate to account for the known effect of age on ESR. This same analysis was also performed for patients with a defined normal CRP. Power calculations were performed based on the number of subjects with recorded ESR and CRP values. Using Fisher exact test ($P \leq 0.05$; power = 0.8), we estimated that a statistically significant difference between study group patients could be detected if 30% of statin users (n = 24) and $\leq$6% of statin nonusers (n = 137) had a normal ESR. Similarly, we estimated that a statistically significant difference between study group patients could be detected if 25% of NSAID users (n = 80) and $\leq$8% of NSAID nonusers (n = 81) had a normal ESR. For comparisons involving CRP levels, Fisher exact test ($P \leq 0.05$; power = 0.8) was estimated to detect significant differences between study groups if 25% of the statin user group (n = 17) and $\leq$1.3% of the statin nonuser group (n = 90) had normal CRP levels. For NSAID users (n = 53) vs nonusers (n = 54), we estimated that a group difference could be detected with 0.80 power if CRP was normal in 20% of NSAID users and $\leq$2% or less of NSAID nonusers.

RESULTS

Of the 742 charts reviewed, 161 patients (22%) were included and 581 patients (78%) were excluded. Of the included patients, 161 had measurements for ESR and 107 of them had CRP measurements; the difference occurred because mostly all clinicians ordered ESR and not all ordered CRP. It was rare for clinicians to have only ordered CRP. The patients in the study were composed of 118
women (73%) and 43 men (27%). The mean patient age was 75.7 years (SD = 8.5 years, range = 53–95 years). Of the 161 patients included in our study, 81 patients used NSAIDs. Of these, 62 patients used NSAIDs but not statins, 19 used both NSAIDs and statins. Of the 24 patients using statins, 19 patients used both statins and NSAIDs and 5 patients used only statins. Of the total 161 patients, 75 patients used neither class of medication. NSAIDs used by patients in the study included aspirin, ibuprofen, naproxen, piroxicam, celecoxib, valdecoxib, salasalate, diclofenac, ketorolac, rofecoxib, ketoprofen, and nabumetone, with aspirin outnumbering all the other NSAIDs combined. The statins used by patients in this study included simvastatin, atorvastatin, pravastatin, lovastatin, fluvastatin, and rosuvastatin, with simvastatin being the most common statin used.

The median ESR of statin users was 57.5 mm per hour (interquartile range [IQR] = 35–85 mm per hour; IQR = 25th to 75th percentile; range = 17–136 mm per hour), which was significantly lower than the median ESR of statin nonusers (median = 85.0 mm per hour; IQR = 60–110 mm per hour; range = 6–150 mm per hour; P = 0.005). The median ESR of NSAID users was 75 mm per hour (IQR = 46–98.5 mm per hour; range = 6–143 mm per hour), which was significantly lower than the median ESR of NSAID nonusers (median = 98 mm per hour; IQR = 64–116 mm per hour; range = 11–150 mm per hour; P = 0.004).

Comparison of median CRP values showed no significant difference between statin users and nonusers (P = 0.127), with a median CRP of 2.4 mg/dL (IQR of 0.8–15.9 mg/dL; range = 0.5–18.8 mg/dL) for statin users and 8.7 mg/dL (IQR of 2.7–16.2 mg/dL; range = 0.4–61.5 mg/dL) for statin nonusers. There was also no significant difference in CRP (P = 0.524) between those who used NSAIDs (median of 8.0 mg/dL; IQR of 1.5–16.2 mg/dL; range = 6–143 mg/dL) and those who did not (median of 8.7 mg/dL; IQR of 2.1–16.2 mg/dL; range = 0.4–61.5 mg/dL).

In our population of patients with biopsy-proven GCA, ESR was normal in 29.2% (7 of 24) of statin users compared with 13.1% (18 of 137) of statin nonusers; however, this was not statistically significant (P = 0.064). After using logistic regression analysis to correct for the effect of age on ESR, this comparison was still not significant (P = 0.055). The odds for a normal ESR were 2.94 (95% CI: 0.89–9.15) times higher in statin users compared with statin nonusers. The ESR was normal in 17.5% of NSAID users and was normal in 13.6% of NSAID nonusers, and this difference was not significant (P = 0.521). The odds for a normal ESR were 1.33 (95% CI: 0.52–3.51) times higher in NSAID users compared with NSAID nonusers. The CRP was normal in 17.6% of statin users and was normal in 8.9% of statin nonusers, and this difference was not significant (P = 0.376). The odds for a normal CRP were 2.58 (95% CI: 0.38–13.57) times higher in statin users compared with statin nonusers. CRP was normal in 11.3% of NSAID users and was normal in 9.3% of NSAID nonusers, and this was not significant (P = 0.740). The odds for a normal CRP were 1.53 (95% CI: 0.34–7.96) times higher in NSAID users compared with NSAID nonusers.

**DISCUSSION**

Our study demonstrated that patients with biopsy-proven GCA who were taking NSAIDs or statins at the time of initial laboratory evaluation had a significantly lower median ESR than those not taking these medications. This finding was expected for NSAIDs given the previous similar findings by Helms et al (7). The finding that statins have an effect on ESR was expected on a theoretical basis in our patient population given the possible anti-inflammatory effects of statins. The finding that statin use was not associated with decreased CRP levels was unexpected, given the previous studies that found the opposite (8–10). As expected, patients with a higher ESR tended to be older and patients with a lower ESR tended to be younger. Our finding that statin or NSAID use was associated with lower median ESR values is important because this may mean that the ESR measurement may have lower sensitivity and specificity for patients with GCA. It should be emphasized that despite the focus on ESR and CRP in this study, the diagnosis of GCA is a clinical one and clinicians should interpret the results of ESR and CRP values in the context of the entire clinical picture when considering a diagnosis of GCA (14).

We recognize the limitations of our work. First, this study is retrospective and susceptible to the flaws of such a design, including recall, selection, and ascertainment bias. Patients may not have been asked specifically about over-the-counter use of NSAIDs, and thus, we may have excluded additional cases from our study. Second, patients on NSAIDs or statins may have been receiving those medications for the treatment of disorders that could influence the ESR and CRP values; however, we attempted to exclude all patients with diseases known to affect ESR and CRP. Third, we did not have independent verification (e.g., pharmacy records) that the patients were taking the reported medications consistently, and for many cases, we did not know the dosage. Thus, dose-related analysis of the association between NSAID or statin use and the reduction in acute-phase reactants seen in our study could not be performed. Finally, the sample size may limit the general applicability of our conclusions. Despite these limitations, we believe that the results of our study suggest that biopsy-proven GCA patients treated with NSAIDs or statins have a lower median ESR than those not treated with these medications.

**REFERENCES**

Low-Density Lipoprotein Receptor–Related Protein Is Decreased in Optic Neuropathy of Alzheimer Disease

Lloyd M. Cuzzo, BA, Fred N. Ross-Cisneros, BA, Kenneth M. Yee, BS, Michelle Y. Wang, MD, Alfredo A. Sadun, MD, PhD

Background: Alzheimer disease (AD) is associated with optic nerve degeneration, yet the underlying pathophysiology of this disease and the optic nerve disorder remain poorly understood. Low-density lipoprotein receptor–related protein (LRP) is implicated in the pathogenesis of AD by mediating the transport of amyloid-β (Ab) out of the brain into the systemic circulation. As a key player in the reaction to central nervous system injury, astrocytes associate with LRP in AD. This study investigates the role of LRP and astrocytes in the pathogenesis of AD optic neuropathy.

Methods: To investigate the role of LRP and astrocytes in the pathogenesis of AD optic neuropathy, we conducted immunohistochemical studies on postmortem optic nerves in AD patients (n = 11) and age-matched controls (n = 10) to examine the presence of LRP. Quantitative analyses using imaging software were used to document the extent of LRP in neural tissues. Axonal integrity was assessed by performing immunohistochemistry on the subjects’ optic nerves with an antibody to neurofilament (NF) protein. Double-immunofluorescence labeling was performed to investigate whether LRP colocalized with astrocytes, expressing glial fibrillary acidic protein.

Results: LRP expression was decreased in AD optic nerves compared to that in controls (P < 0.001). LRP immunoreactivity was observed in the microvasculature and perivascularly in close proximity to the astrocytic processes. Colocalization of LRP in the astrocytes of optic nerves was also demonstrated. The presence of optic neuropathy was confirmed in the AD optic nerves by demonstrating greatly reduced immunostaining for NF protein as compared to controls.

Conclusions: The reduction of LRP in the AD degenerative optic nerves supports the hypothesis that LRP may play a role in the pathophysiology of AD optic neuropathy.

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Alzheimer disease (AD) is the leading cause of dementia in the elderly, affecting 5.3 million people in the United States and 40% of people older than 85 years (1,2). AD may also manifest as optic nerve degeneration (3–7). This presents clinically in patients with mild to moderate AD as abnormal visual evoked responses, poor contrast sensitivity, and a reduction of retinal nerve fiber layer on OCT; in severe AD, there may be impaired visual acuity, visual fields, and color vision (4,8–11). Visual complaints in AD are often attributed to impaired cognition and may be overshadowed by higher cortical visual dysfunction, which occurs frequently in AD patients.

The major pathological hallmark of AD is the accumulation of amyloid-beta protein (Aβ), a neurotoxic peptide centrally involved in the pathogenesis of AD (12–16). This may be due to faulty clearance of Aβ from the central nervous system (CNS) (15,17–24). The blood-brain barrier (BBB), largely maintained by tight junctions between cerebrovascular endothelial cells (25), limits the transport of polar solutes, such as Aβ. Receptor mediated–transport accounts for most Aβ transported across the BBB (17,19,24,26–28). Low-density lipoprotein receptor–related protein (LRP) is the major receptor at the BBB responsible for clearing Aβ from the CNS (19,29,30). A decreased amount of LRP is found in the cerebral microvasculature in both human AD brains and transgenic AD animal models and is associated with regional accumulation of Aβ as compared to controls (23,24,30–32).
LRP also exists in a soluble form (sLRP) in plasma and has been shown to bind to 70%–90% of plasma Aβ preventing its access to the CNS (33,34). In AD individuals, levels of sLRP in plasma are reduced, thereby allowing free Aβ in plasma to enter the CNS (29).

LRP is also found in astrocytes (35–37). In response to injury, astrocytes undergo both hypertrophy and hyperplasia displaying prominent fibrous ramifying processes, enhanced immunoreactivity for glial fibrillary acidic protein (GFAP), and increased release of bioactive molecules. LRP is expressed by astrocytes in normal human brains but expression is increased in AD (35,37).

Since the optic nerve is part of the CNS, we hypothesized that LRP was decreased in optic nerves of AD patients possibly contributing to Aβ accumulation as part of the pathogenesis of AD optic neuropathy. We conducted an immunohistochemical study, first to histologically verify the presence of AD optic neuropathy and second to characterize the presence of LRP and the extent of its association with the microvasculature and astrocytes in AD optic nerves.

**METHODS**

**Human Autopsy Specimens**

Postmortem retrobulbar optic nerves were obtained from 11 AD patients (81.0 ± 12.0 years) and 10 control subjects (72.8 ± 13.9 years). AD tissues were provided by the Alzheimer’s Disease Research Center at the University of Southern California, and controls were obtained from the Lions Eye Bank of Oregon. The diagnosis of AD was confirmed clinicopathologically (38–40). Control optic nerves were from subjects with no history of neurodegenerative disorders. Patient data are summarized in Table 1.

**Tissue Processing**

Nerves were immersion fixed in 10% neutral buffered formalin immediately following enucleation of eyes with optic nerves attached. Dissections of the optic nerves into longitudinal profiles 5 mm in length were performed approximately 7–10 mm behind the globe. Tissues were dehydrated in ethanol and processed for paraffin embedding. The paraffin tissue blocks were cut at 5 μm on a retractable microtome, and the tissue sections were placed on electrostatically charged glass microscope slides for immunohistochemistry.

**Immunohistochemistry: Immunoperoxidase Labeling**

Tissue sections were deparaffinized and rehydrated, and the antigen retrieval was performed in a 1× citrate buffer, pH 6.2 (BioGenex, San Ramon, CA) within a steamer bath. The bath was microwaved at 480 W for 10 minutes. The sections were rinsed with tris-buffered saline, and endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide. Tissue sections were incubated with a monoclonal mouse anti-human LRP primary antibody (EMD Chemicals, Inc, Gibbstown, NJ) at a dilution of 1:1000 in a humidity chamber for 1 hour. Negative control sections were incubated in antibody diluent (Dako North America, Inc, Carpinteria, CA) in the absence of primary antibody. Tissue sections were next incubated in a goat anti-mouse secondary antibody conjugated to horseradish peroxidase (Dako) for 30 minutes. The substrate 3,3′-diaminobenzidine (Dako) was added to produce a brown reaction product (chromagen). All AD and control tissue sections were either counterstained with Mayer’s hematoxylin (Dako) for general nuclear morphology or immunostained for LRP without counterstain for densitometry analysis. Finally, the sections were dehydrated in alcohol, cleared in xylene, and coverslipped. The stained nerves were observed on a Zeiss Axioskop light microscope, and the images were captured with a Spot II digital camera.

To examine the axonal integrity in both control and AD optic nerve samples, immunoperoxidase staining was performed with a monoclonal mouse anti-human neurofilament (NF) protein primary antibody (Dako) at a dilution of 1:500 and counterstained with hematoxylin utilizing the methodology above.

**Table 1. Demographic and clinical data of donor optic nerves**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (Years)</th>
<th>Sex</th>
<th>Braak Stage</th>
<th>Duration of Disease (Years)</th>
<th>Postmortem Interval (Hours)</th>
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<td>52</td>
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<td>5</td>
<td>56</td>
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<td>99</td>
<td>F</td>
<td>III</td>
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Braak system of staging Alzheimer disease (AD) (38). M, male; F, female; N/A, not available.
Immunohistochemistry: Double-Immunofluorescence Labeling

Tissue sections were deparaffinized, rehydrated, and subjected to antigen retrieval as described previously. Sections were washed with phosphate-buffered saline (PBS) and incubated with 1% BSA with 0.1% Triton X-100 in PBS for 15 minutes. Tissues were incubated with a monoclonal mouse anti-human LRP primary antibody (EMD Chemicals), as used previously for immunoperoxidase staining, at a dilution of 1:1,000 at 37°C for 1 hour in a humidity chamber. Goat anti-mouse secondary antibody conjugated to fluorescein iso-thiocyanate (Dako) was added at a dilution of 1:20 for 45 minutes. To determine the association of LRP with astrocytes, tissue sections were incubated with a second primary antibody, a polyclonal rabbit anti-human GFAP antibody (Dako) at a dilution of 1:500 at 37°C for 1 hour. A swine anti-rabbit secondary antibody conjugated to tetramethyl rhodamine iso-thiocyanate (Dako) was added at a dilution of 1:60 for 45 minutes. Tissue sections were mounted with Vectashield containing DAPI (4’, 6-diamidino-2-phenylindole) for nuclear staining. Images were captured on a Zeiss LSM 510 confocal microscope.

Quantitative and Qualitative Analyses

LRP immunolabeling was quantitatively graded by scanning slides with a light microscope at a magnification of ×1,000. Twenty images were captured from central to peripheral regions of each nerve section in a systematic, linear, nonoverlapping fashion, and analyzed with AnalySIS image software. The average immunopositive area for every slide and average ratio of specific immunolabeled area to total optic nerve area was recorded.

Slides immunohistochemically stained for NF were viewed under a light microscope at ×200 and ×1,000. The intensity of immunoreactivity for NF staining was evaluated qualitatively, and AD optic nerve slides were compared to controls.

RESULTS

Immunoperoxidase Localization of LRP in AD and Control Optic Nerves

Immunoperoxidase staining demonstrated that LRP was decreased in AD optic nerves, especially within the vasculature, as compared to that in controls (Fig. 1). We observed an increased perivasculare LRP staining within AD astrocytes in a punctate perinuclear pattern (Fig. 2 B, D). Our quantitative analysis using densitometry showed that total expression of LRP was significantly reduced in the AD group as compared to controls (Figs. 3, 4). The extent of LRP immunolabeling was 121.5 ± 13.3 μm² (mean ± standard error) in the control optic nerves and 18.9 ± 3.5 μm² in the AD optic nerves (P < 0.0001; Fig. 4). The 95% confidence interval of the mean quantity of LRP immunostaining was 91.4–151.6 μm² in controls vs 11.2–26.6 μm² in AD optic nerves (P < 0.0001).

Immunoperoxidase Labeling of NF in AD and Control Optic Nerves

Immunoperoxidase staining of NF, as a marker of axonal integrity, demonstrated clear degeneration of AD optic nerves compared to control tissues (Fig. 5). This example is representative of the study population. The majority of the AD optic nerves from the Alzheimer Disease Research Center came from patients with severe AD (Braak stage V-VI; Table 1) and were all severely affected as evidenced by greatly decreased NF staining.

Double-Immunofluorescence Labeling for LRP and Astrocytes

Double-immunofluorescence labeling revealed colocalization of LRP within GFAP-positive astrocytes of optic nerves in both age-matched controls (Fig. 2 A, C) and AD nerves (Fig. 2 B, D) but to a greater degree in the AD tissues.

DISCUSSION

We demonstrated a decrease in the expression of LRP in AD optic nerves compared to that in the age-matched controls; this corroborates with other studies showing decreased LRP in AD patients (24,30). We presented histochemical evidence of AD optic nerve degeneration by showing a large decrease in NF staining, which is interpreted as a large loss of axons. This is consistent with the previous reports identifying optic neuropathy in AD patients (3–7).

In humans and animal models, LRP has been shown to be responsible for clearing Aβ out of the CNS via transport across the BBB (19,29,30). Reduced LRP has been identified in the cerebral vasculature of AD patients and appears to be associated with the accumulation of Aβ in the brain, which is believed to initiate pathogenic cascades seen in AD (17). Furthermore, the accumulation of Aβ within cerebral blood vessels in AD, known as cerebral amyloid angiopathy (CAA), is associated with the cognitive decline of this disease. Decreased clearance of Aβ across the BBB may contribute to CAA and parenchymal Aβ deposits (17). This is supported by studies that have demonstrated that impairment in the clearance of CNS beta-amyloid may be fundamental to the pathophysiology of AD (41). These findings suggest that the decreased expression of LRP found in our study could, by reducing the efflux of Aβ out of the optic nerve, play an important role in the pathogenesis of AD optic neuropathy.

sLRP under normal conditions is the major endogenous Aβ chaperone protein in plasma, acting as a peripheral “sink” pulling Aβ from the brain to the blood, preventing Aβ entrance into the CNS and facilitating its clearance in the liver (29,34). However, there is decreased sLRP in AD,
most of which may become impaired by oxidation initiated by reactive oxygen species generated by the receptor for advanced glycation end products (RAGE) proinflammatory cascade (17). RAGE receptors in the BBB are responsible for the influx of Aβ into the CNS and have been shown to be upregulated in AD optic neuropathy (42). This suggests that the sLRP “peripheral sink” for Aβ is compromised in AD, leading to elevated free Aβ levels in plasma that exacerbate the increased Aβ levels in the CNS via RAGE-mediated transport across the BBB (29).

We also found a relative increase in LRP staining in AD astrocytes (Fig. 2). While quantification of the increased LRP staining in AD astrocytes was not performed, the example shown in Figure 2 is representative of the nerves.
sampled, as supported by other studies (35,43,44). We demonstrated colocalization of LRP within astrocytes in optic nerves, usually in a perinuclear fashion (Fig. 2), which is also supported by previous studies (44). The increased perivascular LRP staining observed in astrocytes in AD nerves likely represents astrocytic foot processes abutting against the vasculature (44). The expression of LRP in reactive astrocytes, coupled with the perinuclear Golgi network staining, suggests that these cells were actively manufacturing LRP. LRP production by these reactive astrocytes may have been a compensatory response for decreased LRP in the neighboring vasculature. This could also be part of a process of monocyte recruitment to the area of injury, as LRP binds ligands involved in cell migration in response to injury or infection such as C3 and uPA (16,45). Increasing LRP might also restore Aβ homeostasis and contribute to the development of neural networks (16,46,47).

Astrocytes are normally neuroprotective, functioning to monitor the surrounding tissue environment, supply nutrients, support BBB functions, and repair by way of gliosis (48). When chronically activated, they release neurotoxic cytokines and activate destructive pathways (49,50). Cellular LRP not only clears Aβ but also has the potential to produce Aβ. LRP can internalize amyloid precursor protein (APP) and deliver it to the endosomal compartment where it can undergo amyloidogenic processing by β-secretase. This is followed by γ-secretase action to produce Aβ. As a consequence of increased APP internalization, LRP can enhance Aβ secretion (31,51). However, LRP has been shown to modulate APP trafficking between the cell surface and the compartments of the endocytic pathway by

**FIG. 3.** Examples of micrograph sampling for densitometry analysis in age-matched control and AD optic nerves. Immunoperoxidase labeling for LRP can be observed in a control (A) and an AD (B) optic nerve. Note corresponding highlighted color for density of the LRP label in control (yellow) (C) and AD (red) (D) optic nerves, as seen in A and B, respectively (×1,000).

**FIG. 4.** The comparison of the mean area of density for LRP immunolabeling in control optic nerves (121.5 μm²) was greater than that in AD nerves (18.9 μm²) (P < 0.0001).
interacting with APP in the endoplasmic reticulum (ER) (52). By doing so, LRP has been shown to retain APP in the ER, reducing the levels of APP that reach the plasma membrane (53). Thus, LRP is intricately involved with cellular pathways that suppress Aβ generation but that can be altered to facilitate production (54). While we were able to show colocalization of LRP within astrocytes, future studies examining LRP immunolabeling with microglial markers and NF protein may further uncover the complicated role of LRP in the pathogenesis of AD optic neuropathy.

It should be noted that while the AD subjects were slightly older than the controls, this was not statistically significant \( P = 0.13 \). LRP has been shown to decrease with normal aging in rodents, non-human primates, and AD patients, but it has not been shown to decrease with age in normal humans (29).

A potential therapeutic approach to AD optic neuropathy might be to target the interruption of LRP-mediated internalization of APP, a necessary step for LRP-facilitated production of Aβ. LRP and APP must form a complex with the adaptor protein FE65 to internalize APP from the plasma membrane in order to process it into Aβ (55). Interrupting this process could harness the protective effects of LRP effluxing Aβ from the CNS without the downside of producing more Aβ. This is supported by studies that suggest that LRP can be protective against AD (56). Another potential avenue of treatment would be to develop a synthetic sLRP, which could be administered intravenously that would bind to Aβ with high affinity and minimal toxicity. This could shift the Aβ transport equilibrium toward the plasma (21). Furthermore, other studies have shown that administering recombinant LRP clusters can effectively sequester plasma Aβ in human AD plasma and in AD mice (18). In mice, sequestration resulted in reductions of Aβ accumulation in the brain parenchyma and vasculature. This resulted in improvements in memory, learning, and cerebral blood flow responses (57).

In conclusion, our findings demonstrate a significantly reduced expression of LRP in AD optic nerves as compared to that in age-matched controls. This result, along with the LRP expression in the AD microvasculature, is concordant with other investigators’ work and supports the hypothesis that decreased LRP may play a role in the underlying pathophysiology of AD optic neuropathy by reduced efflux of Aβ out of the optic nerve into the systemic circulation.

**ACKNOWLEDGMENTS**

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Unusual Presentation of Primary Orbital Microcystic Adnexal Carcinoma

Wen Ying Wu-Chen, MD, Christina Y. Weng, MD, K. D. A. Rajan, MD, Charles Eberhart, MD, PhD, Neil R. Miller, MD

Abstract: Microcystic adnexal carcinoma (MAC) is a rare and locally aggressive malignancy that occurs on the face, can invade deep tissue, and can rarely invade the orbit via perineural spread. It has been reported most often in the form of a cutaneous lesion. Although there have been 3 prior case reports of an orbital presentation of MAC, all have been from undiagnosed cutaneous or subcutaneous lesions. We report a rare case of a primary orbital MAC in a 39-year-old healthy woman who presented with progressive diplopia and enophthalmos without evidence of any cutaneous or subcutaneous lesions.

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A 39-year-old healthy woman presented initially with a history of an “odd feeling” over the left orbit and forehead, followed by painless diplopia and a dilated poorly reactive pupil. MRI showed changes consistent with an infiltrative process in the left orbit involving the extraocular muscles and fat. Additional workup included serologic studies for inflammatory processes, gallium scan, CT of the chest, and mammogram, none of which revealed any abnormalities. A biopsy of orbital fat via a transnasal endoscopic approach revealed only mild chronic inflammation.

At the initial visit to our institution, the patient had a visual acuity of 20/20 in the right eye, with normal color vision, and a superior arcuate field defect. The left eye had a visual acuity of 20/30, with normal color vision, and mild superior and inferior arcuate defects. There were bilateral optic disc drusen. The left pupil was dilated and poorly reactive to both light and near stimulations. On the left eye, there was a significant limitation of movement in all directions, a deep superior lid sulcus, and 1 mm of enophthalmos. Corneal and facial sensation were equal and normal bilaterally. A more extensive orbital biopsy was recommended, but the patient declined further evaluation.

Over the next 6 years, the patient developed worsening diplopia and increasing enophthalmos. Examination at that time demonstrated normal afferent visual function in both eyes except for bilateral arcuate visual field defects consistent with optic disc drusen. The left pupil remained dilated and nonreactive to both direct and consensual light stimulations, and eye movements on the left were limited in all directions of gaze. She had reduced left levator function, and exophthalmometry revealed 3 mm of left enophthalmos with moderate resistance to retropulsion (Fig. 1A, B). There was decreased left corneal sensation but normal corneal sensation on the right and normal sensation on both sides of the face. Slit-lamp biomicroscopy revealed diffuse punctate epithelial erosions of the left cornea. Both optic discs contained drusen associated with moderate peripapillary atrophy.

Orbital ultrasonography and a repeat MRI showed changes consistent with an infiltrative process in the left orbit.

**FIG. 2.** Left orbital biopsy specimen. **A.** Diffusely infiltrating epithelial process with deep invasion and associated dense desmoplasia (hematoxylin and eosin, ×20). **B.** Immunohistochemistry reveals expression of cytokeratins (dark areas) in tumor cells (cytokeratin AE1/AE3, ×100). **C.** The basaloid epithelial cells form nests and cords (arrows) surrounded by sclerotic stroma and are focally carcinoembryonic antigen immunoreactive (inset, brown areas) (hematoxylin and eosin, ×100; inset: monoclonal carcinoembryonic antigen). **D.** Ductule-like structures characteristic of MAC are also present (arrow) (hematoxylin and eosin, ×200).


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involving extraocular muscles and orbital fat (Fig. 1C, D). A positron emission tomography and a repeat mammogram revealed no abnormalities. The patient consented to orbital biopsy, at which time the orbital fat appeared somewhat gray and thickened. Microscopic examination revealed a low-grade infiltrating carcinoma composed of nests and strands of relatively bland epithelial cells that were immunopositive for cytokeratins AE1 and AE3, p53, and carcinoembryonic antigen (Fig. 2). Immunostains for CK7, CK20, CAM 5.2, CD34, and Bcl-2 were negative, with the latter suggesting that this was not a sclerosing basal cell carcinoma (sBCC). Estrogen receptor, progesterone receptor, and thyroid transcription factor 1 immunohistochemical stains were also negative, making an origin from breast, lung, or thyroid unlikely. The Ki67 proliferation index was low, and some of the tumor strands contained small “microcystic” ductules. The overall morphological and immunohistochemical profile was consistent with a microcystic adnexal carcinoma (MAC).

A consulting oncologist indicated that there was no role for radiation or chemotherapy and recommended orbital exenteration. The patient declined further surgery and is being followed with serial examinations and orbital imaging.

MAC is a rare, slow-growing, locally invasive skin tumor of eccrine and pilar origin first described in 1982 by Goldstein et al (1). It is also known as sclerosing sweat duct carcinoma (1), malignant syringoma (2), or sweat gland carcinoma with syringomatous features (3). Affected areas that have been reported include the face, scalp, neck, trunk, vulva (4), and eyelid (5–7). Orbital extension is usually through perineural spread from cutaneous lesions (7,8). Regional and isolated distant metastasis are rare (9–14). Associated risk factors include immunosuppression and previous radiotherapy; however, cases in immunocompetent patients have also been reported (15–19). Age, gender, and history of actinic damage have been implicated as risk factors for MAC, but these associations remain inconclusive (20).

MAC usually is misdiagnosed clinically and histologically because of its inconspicuous features. It can present as a slow-growing plaque or nodule on the eyelid or the central face area, commonly the upper lip and nasolabial folds, that can mimic a basal cell tumor or a chalazion (4,14). Pathologically, it can mimic a sBCC, trichoadenoma, syringoma, eccrine carcinoma, desmoplastic trichoepithelioma, or metastatic breast cancer (21–23). Late recognition is common and can be associated with local tissue destruction at the time of diagnosis.

The main histological features of MACs include eccrine and pilar components. The cell of origin is believed to be an adnexal keratinocyte capable of dual differentiation (23). Biopsy findings include cords and nests of uniform keratinocytes, keratin-containing cysts, and foci of ductal differentiation in a sclerotic desmoplastic stroma (7). The tumor cells express a distinctive pattern of staining for epithelial membrane antigen (24), carcinoembryonic antigen (24,25), cytokeratin AE1/AE3 (23,24), and focal expression of Bcl-2 that differentiate them from sBCCs and dTEs (22,26).

Treatment options for MACs include wide local excision, Mohs micrographic surgery (MMS), and exenteration when there is orbital involvement. Standardized surgical margins have not yet been defined. Radiation can be considered as an adjunctive therapy; however, this tumor has been shown to be fairly radioresistant (4,14). Reported recurrence rates range from 40% to 60% depending on the treatment modality, with lower rates after MMS (24,27,28); however, these statistics may be an overestimate as there is often misdiagnosis at the time of excision, and positive margins can sometimes be misread.

Secondary enophthalmos may be caused by a number of conditions, including bone growth arrest; trauma; orbital varix with secondary bone erosion; orbital fat atrophy from inflammation (e.g., lupus erythematosus profundus), infection, or radiation; wasting disorders (e.g., Parry-Romberg hemifacial atrophy, linear scleroderma); scirrhouss carcinoma, most commonly from breast metastasis; and silent sinus syndrome. To our knowledge, there are no reported cases of orbital MAC causing acquired enophthalmos.

We are aware of 3 reports of orbital involvement by MAC in the literature (7,8,25). Hoppenreijs et al (7) described 3 patients with lesions of the eyelid and medial canthal region, 2 of whom developed orbital invasion after local excision. Cooper and Mills (8) described a patient who developed a lesion on the left lip and left side of the nose that was resected but recurred about 2 years later at which time it involved the left orbit and the turbinates. A patient reported by Marshall et al (25) presented initially with a subcutaneous mass below the left medial canthal tendon that was excised; the patient later developed epiphora with diplopia and was found to have an orbital mass consistent with MAC.

Our case is unique compared with prior cases in its atypical clinical presentation—a pure orbital presentation with progressive diplopia and enophthalmos and a tonic pupil. The lack of any cutaneous or subcutaneous lesions on her external examination makes this patient very unusual and raises the question of the true origin of the tumor. One possibility is that the lesion arose from a small orbital dermoid cyst or other developmental malformation containing adnexal structures. Alternatively, the eccrine lachrymal gland or its ducts may have the capacity to give rise to a MAC, although if this is true, one might expect similar lesions in salivary glands. Finally, it may be that a small undiagnosed primary tumor arose from deep skin adnexae and extended into the orbit.

MAC is a diagnosis that should be considered in patients presenting with cutaneous or subcutaneous masses that extend into the orbit, particularly when the tumor has atypical histological features. In such cases, early diagnosis and treatment are critical in the prevention of extensive
tissue loss due to the aggressive and destructive nature of this disease. In addition, our case indicates that rare cases of MAC can present as an isolated infiltrative orbital process producing progressive enophthalmos, ophthalmoparesis, and other orbital signs.

REFERENCES

A Pigmented Optic Disc

Elaine Thung, MD, Rod Foroozan, MD

Abstract: This report describes the case of a 48-year-old white woman who was found to have an entirely pigmented optic disc in an otherwise normal eye. Pigmentation of the optic disc is an uncommon finding. The possible explanations of this physiologic variant are discussed.

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A 48-year-old white woman was referred after an evaluation for photorefractive keratectomy. She had been told 5 years previously that her right optic disc was abnormal in appearance because it was darker than the left one. She denied any change in vision over the past 5 years, and she had no prior medical problems.

Best-corrected visual acuity was 20/15 in both eyes. Color vision with Ishihara plates, Amsler grid testing, and automated perimetry were all normal. External examination was unremarkable without any nevi or other pigmented lesions near her eyelids or elsewhere on her face. Pupils were briskly reactive without an afferent pupillary defect, and extraocular motility was full. Anterior segment examination was normal, and no pigmented lesions were seen on the iris or conjunctiva. Intraocular pressure was 15 mg Hg bilaterally. There were no vitreous cells, and funduscopy revealed that the right optic disc was entirely pigmented and flat, measuring 1.8 mm vertically (Fig. 1). While the contour of the right optic disc was difficult to assess due to the dark pigmentation, the cup-to-disc ratio was estimated at 0.1. There were retinal pigment epithelial (RPE) changes temporal to the disc, and small spots of intraretinal pigment were noted around the optic disc. The left optic disc measured 2 mm vertically, was pink in color without any appreciable pigmentation, and had a cup-to-disc ratio of 0.3. Subtle RPE changes were noted temporal to the left disc but were less prominent than on the right disc (Fig. 1). Optical coherence tomography (OCT) of the retinal nerve fiber layer showed relative thinning superiorly on the right (Fig. 2). The appearance of each optic disc was unchanged from photographs obtained 5 years previously.

Pigmentation of the optic disc is an uncommon finding. It can be categorized as primary and secondary. Most patients in the primary group have other associated ocular abnormalities, including distended retinal vessels, iris transillumination defects, ptosis, and nystagmus (1,2). In reviewing reported cases, we were unable to find photographic documentation of benign pigmentation of the entire optic disc without other ocular abnormalities.

Secondary optic disc pigmentation may be due to pigmentation from melanocytoma, hemorrhage, and that associated with congenital anomalies of the optic disc, such as optic nerve hypoplasia. Our patient’s pigmented optic disc was slightly smaller than that of the fellow eye, with thinning of the retinal nerve fiber layer on OCT (Fig. 2). Her findings may represent a case of mild optic disc hypoplasia with pigmentation.
The etiology of primary optic disc pigmentation is unknown. Reese (3) noted that although the lamina cribrosa usually does not contain pigment cells, eyes with considerable pigmentation in the uveal tract may have chromatophores in the lamina cribrosa. He postulated that individuals with darker complexion would be more subject to such pigmentation. Our patient, however, had a light complexion. Another potential explanation for disc pigmentation is migration or extension of the RPE into the optic nerve head. Peripapillary disturbances, such as inflammation, may result in RPE proliferation causing hyperpigmentation (2). There was no evidence of this in our patient.

Secondary optic disc pigmentation may be due to pigment granules found between the nerve fiber bundles, resulting from hemolysis due to hemorrhage within the optic nerve, globe, or orbit. Iron salts within the optic disc, secondary to extensive siderosis of the globe, have also been described as a cause of optic disc pigmentation (3).

Sectoral pigmentation of the optic disc has been described in 3 of 16 Japanese women with nevus of Ota (4). These patients had good vision and no visual symptoms. Our patient did not have any other areas of pigmentation on her skin or conjunctiva, suggestive of nevus of Ota.

REFERENCES

Occult Temporal Arteritis in a 54-Year-Old Man

Flora Levin, MD, Hermann D. Schubert, MD, John C. Merriam, MD, Ralph S. Blume, MD, Jeffrey G. Odel, MD

Abstract: A 54-year-old white man with a remote history of pars planitis reported transient monocular visual loss (TMVL) in the left eye on standing. The following week he experienced multiple similar episodes. He denied associated systemic symptoms. Initial examination showed old peripheral retinal vascular sheathing and delayed retinal arterial filling time. Complete blood count, erythrocyte sedimentation rate, and MRI studies of the head and neck were normal. One week later, there were multiple cotton wool spots in the posterior pole, a relative afferent pupillary defect, and subtle visual field loss in the left eye. Evaluation for infectious, inflammatory, or embolic etiologies was nonrevealing. Biopsy of the prominent but nontender temporal arteries showed granulomatous inflammation, fragmentation, and duplication of the internal elastic lamina consistent with the temporal arteritis (TA). Radiography and MRI of the chest revealed dilation of the ascending aorta. The patient began treatment with high-dose oral steroids with resolution of his TMVL and retinal cotton wool spots and decrease in the size of the temporal arteries. Our case demonstrates the importance of considering TA in the setting of TMVL, visual loss, cotton wool spots, or dilated nontender temporal arteries in an otherwise asymptomatic patient even with normal inflammatory markers. Long-term follow-up is essential in unusual cases such as this one, given the high risk of ocular and systemic morbidity with TA.

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CASE REPORT

A 54-year-old white man reported transient left monocular visual loss lasting 2 minutes on standing. Five days later, while walking, suddenly his left eye “just saw gray with some sparing to the left side” for 3–5 minutes. He had a 3-decade history of pars planitis in the left eye requiring pars plana vitrectomy and cataract surgery with insertion of an intraocular lens. The patient denied systemic symptoms. He experienced 2 additional similar events, 1 with bending down.

Initial ophthalmologic examination was normal except for chronic retinal changes in the left eye from pars planitis. Laboratory testing revealed normal complete blood count (CBC) including platelet count of 339,000 per cubic millimeter and erythrocyte sedimentation rate (ESR) of 20 mm/h. Fluorescein angiography showed normal choroidal filling, delayed retinal filling at 28 seconds, enlarged foveal avascular zone with microaneurysms, and peripheral vascular staining with areas of peripheral nonperfusion in the left eye. MRI and MRA of the brain and neck were normal.

The patient continued to experience transient monocular visual loss (TMVL) in the left eye and underwent neuroophthalmic evaluation. He denied headache, jaw claudication, scalp or temporal tenderness, loss of appetite, weight loss, and fever or symptoms of polymyalgia rheumatica. Physical examination, including carotid auscultation and blood pressure measurement, was normal. Visual acuity was 20/15, right eye, and 20/25, left eye. There was a left relative afferent pupillary defect (RAPD) of 0.6 log units. Biomicroscopic examination was unremarkable and intraocular pressures were 14 mm Hg in both eyes with open angles on gonioscopy. Automated visual field testing was normal on the right, and there was an inferonasal defect on the left. Indirect ophthalmoscopy showed peripheral vascular sheathing. In the left eye, the optic disc was normal, there was pigment mottling in the fovea, multiple cotton wool spots in the posterior pole, and peripheral vascular sheathing.

Laboratory testing revealed a number of normal studies including CBC, platelet count, metabolic panel, hypercoagulable studies, fluorescent treponemal antibody absorption, Lyme and Bartonella antibodies, hepatitis panel, HIV, angiotensin-converting enzyme, antinuclear antibody, antineutrophil cytoplasmic antibody, and purified protein derivative skin testing. ESR was 6 mm/h, C-reactive protein...
The patient was treated with high-dose oral corticosteroids and had no further episodes of TMVL, and the cotton wool spots disappeared. The left RAPD and the visual field defect remained unchanged. The left optic disc became mildly pale. The temporal arteries became significantly smaller in size. The CBC, ESR, and CRP have remained normal, and the haptoglobin normalized after nearly 12 months of steroid therapy. To date, repeat imaging of the aorta has not been performed.

**DISCUSSION**

The most common identifiable cause of TMVL is atherosclerotic disease affecting the internal carotid arterial system. In patients with TA, transient visual symptoms may precede permanent blindness in 50%–64% by an average of 8.5 days. Visual loss results from optic nerve, retinal, or choriocapillaris ischemia and may be exacerbated by postural changes (2).

Elevated ESR and CRP are well-established aids in the diagnosis of TA. When combined, the 2 markers provide a sensitivity of up to 99.2% (3). Although normal ESR, CRP, or both are well documented in biopsy-proven TA, the exact prevalence is uncertain. Salvarani and Hunder (4) reported ESR less than 40 mm/h in 5.4% and less than 50 mm/h in 10.8% of 167 patients with active TA. Thrombocytosis over 400,000 per microliter may be another useful marker for positive temporal artery biopsy and make the diagnosis of TA 6 times more likely (5). Other markers may include fibrinogen, which is often elevated in TA but low in other conditions that raise the ESR; interleukin (IL)-6, which may be more sensitive than the ESR and comparable to the CRP; and other, less, well-studied reactants such as haptoglobin, IL-2, interferon-γ, IL-1β, platelet-derived growth factor, and vascular endothelial growth factor (5).

Thoracic and abdominal aortic structural damage is a well-documented complication of giant cell arteritis and occurs in a significant proportion of patients with TA, sometimes necessitating surgical repair. In a prospective study, Garcia-Martinez et al reported the development of aortic aneurysm or dilation in 22% of patients with biopsy-proven TA after a mean follow-up of 5.4 years. Interestingly, this finding was significantly more frequent among patients with weak inflammatory markers (6). MRI or positron emission tomography may be used in the detection of aortic involvement, to follow disease activity and response to therapy. Although we do not routinely screen patients with TA for the presence of thoracic aneurysm, the CXR finding led to further investigation in this case. While it cannot be said with complete certainty, it may be that the aortic dilation seen in this patient is the result of TA. Awareness of the possible presence of aortic aneurysm in TA may aid prompt recognition and therapy to avoid life-threatening complications.

As in our patient, occult TA (OTA) presents with local ischemic symptoms without the symptoms or signs of systemic inflammation (7). In a prospective study, Hayreh et al (8) reported 21.2% incidence of OTA in patients presenting with ocular involvement from TA. Amaurosis fugax was highly suggestive of TA, occurring in 33% of patients with occult disease. Interestingly, the ESR and CRP values were relatively lower in the group without systemic symptoms. Other studies (9,10) have found that lower ESR values and the absence of constitutional symptoms may be associated with an increased risk of irreversible cranial ischemic complications and visual loss.

It is important to consider the diagnosis of TA in patients presenting with TMVL, retrobulbar optic neuropathy, cotton wool spots, or dilated nontender temporal arteries in an otherwise asymptomatic relatively young patient even with normal inflammatory markers. Patient follow-up is mandatory to monitor their potential ocular and systemic morbidity.

**REFERENCES**

The Ocular Motor Features of Adult-Onset Alexander Disease: A Case and Review of the Literature

Gerald Pfeffer, MD, Mathias Abegg, MD, A. Talia Vertinsky, MD, Isabella Ceccherini, PhD, Francesco Caroli, Jason J. S. Barton, MD, PhD

Abstract: A 51-year-old Chinese man presented with gaze-evoked nystagmus, impaired smooth pursuit and vestibular ocular reflex cancellation, and saccadic dysmetria, along with a family history suggestive of late-onset autosomal dominant parkinsonism. MRI revealed abnormalities of the medulla and cervical spinal cord typical of adult-onset Alexander disease, and genetic testing showed homozygosity for the p.D295N polymorphic allele in the gene encoding the glial fibrillary acidic protein. A review of the literature shows that ocular signs are frequent in adult-onset Alexander disease, most commonly gaze-evoked nystagmus, pendular nystagmus, and/or oculopalatal myoclonus, and less commonly ptosis, miosis, and saccadic dysmetria. These signs are consistent with the propensity of adult-onset Alexander disease to cause medullary abnormalities on neuroimaging.

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Alexander disease is a rare leukoencephalopathy characterized pathologically by Rosenthal fibers and cytoplasmic inclusions that contain glial fibrillary acidic protein (GFAP). A variety of mutations in the GFAP gene have recently been described in many, but not all, patients with this disorder (1–3). Infantile, juvenile, and adult-onset variants are recognized. The classic pediatric variant presents with spasticity, mental retardation, megalencephaly, and seizures, accompanied by extensive frontal and posterior fossa white matter changes on MRI. In contrast, patients with the adult-onset variant have mainly bulbar dysfunction, ataxia, and/or spasticity, notably without cognitive impairment, optic atrophy, or megalencephaly (4). Their MRI shows minimal, if any, cerebral white matter changes; rather, there is an unusual atrophy and hyperintensity in the medulla and cervical cord that are virtually diagnostic of the condition (5).

Given the importance of medullary structures in ocular motor control, it is likely that abnormal eye movements will be found in a significant number of patients with adult-onset Alexander disease. We recently encountered a patient with the classic MRI features of this disorder, who presented with balance problems and visual symptoms. In this report, we describe his features and review the literature on the ocular motor signs of adult-onset Alexander disease.

CASE REPORT

A 51-year-old Chinese man reported mild imbalance for 2 years. For the past year he has also noted tingling in his neck, both hands and feet, left trunk and inner arm, and blurred vision momentarily after a saccade. He was not taking medication. His father, paternal aunt, and paternal grandfather had a parkinsonian syndrome that began in their 50s. Records indicated that the aunt’s condition was associated with dementia, vertical gaze palsy, pseudobulbar palsy with dysarthria, and diffuse muscle atrophy. Her CT at age 74 showed only cerebral atrophy, and nerve conduction studies were normal. All 3 had died without autopsy. The patient also has 2 younger brothers, 2 younger sisters, a daughter, and 2 sons, all well, but he declined to...
have them examined or imaged. There was no consanguinity or family history of ocular problems.

Visual acuity and fundoscopy were normal, without optic atrophy. He was orthotropic with full range of eye movements. There was a fine, left-beating, horizontal nystagmus in primary position, horizontal gaze-evoked nystagmus, and rebound nystagmus (Fig. 1) (see Video 1, Supplemental Digital Content 1, http://links.lww.com/WNO/A15). (Video 1 shows floccular signs in the patient. This begins with a demonstration of low-gain pursuit horizontally and then vertically. It then shows gaze-evoked nystagmus in right gaze, followed by subtle rebound nystagmus on return to primary [most evident in the left eye], and then gaze-evoked nystagmus in left gaze.) Saccades were dysmetric with occasional macrosaccadic oscillations, and his visual symptoms coincided with the occurrence of hypermetric saccades.

Pursuit and cancellation of the vestibulo-ocular reflex were impaired. There was mild gait ataxia but no parkinsonism, dysthria, or scoliosis.

These eye movements were documented, and saccades were analyzed with an Eyelink 1000 video-based system (SR Research; http://www.eyelinkinfo.com). Horizontal saccades to 20° targets had a mean hypermetria of 1.3 ± 2.1°, but the peak velocity/amplitude and duration/amplitude relationships of both the horizontal and vertical saccadic velocities were normal. Thus, horizontal saccades of 25–30° had a mean peak velocity of 558°/s (SE = 13) and a mean duration of 92 milliseconds (SE = 1), while vertical saccades of 15–25° had a mean peak velocity of 471°/s (SE = 17) and a mean duration of 81 milliseconds (SE = 3). These values are all within the normal range of published data (6).

The patient returned 1 year later. After being treated with systemic steroids, clindamycin, and ceftriaxone for facial cellulitis, he began having new bouts of spontaneous oscillopsia lasting 5–10 seconds. He still had subtle left-beating nystagmus in the primary position, which changed intermittently to right-beating horizontal nystagmus for 5–15 seconds, which was associated with the oscillopsia (see Video 2, Supplemental Digital Content 2, http://links.lww.com/WNO/A16). (The patient returns complaining of recurrent brief bouts of oscillopsia lasting minutes. The video captures him in the midst of a symptomatic spell, with right-beating nystagmus in the primary position that gradually subsides by the end of the video.) This occurred several times at irregular intervals during his examination. After several weeks, he reported that the oscillopsia had gradually abated and stopped.

Brain MRI (Figs. 2, 3) showed changes consistent with adult-onset Alexander disease. Nerve conduction studies revealed a mild left ulnar neuropathy but no generalized neuropathy or radiculopathy. Somatosensory potentials were delayed in the arms and legs. Auditory-evoked potentials had low amplitudes and prolonged latencies. Genetic testing for spinocerebellar ataxia types 1, 2, 3, 6, and 7 was negative. DNA sequencing showed that he was homozygous for the p.D295N polymorphic allele of the GFAP gene. The expected heterozygous state of the proband’s parents could not be confirmed so that the possibility of a hemizygous condition due to an interstitial deletion could not be ruled out.

**DISCUSSION**

The presentation of adult-onset Alexander disease in our patient was characterized by a predominance of ocular motility disturbances, which correlated well with the distribution of MRI signal abnormalities within the medulla. Poor tracking of moving objects, gaze-evoked nystagmus, and rebound nystagmus indicate impairment of ocular motor control circuits involving the flocculus and medullary structures, such as the medial vestibular nuclei and nuclei prepositus hypoglossi (7,8). The primary position nystagmus could indicate dysfunction in central vestibular...
pathways. His recurrent unprovoked episodes of right-beating nystagmus a year later are highly unusual. Although the patient attributed his several-week episode of oscillopsia and nystagmus to the use of steroids and antibiotics to treat his cellulitis, this may have been coincidental. Regardless, this period of episodic nystagmus also likely indicates a time of unstable central vestibular function. Saccadic dysmetria implicates circuits within the dorsal vermis and fastigial nuclei, some of which project to pontine structures (9) and others to the lateral medullary region (10,11). Abnormal auditory-evoked responses also support pontine involvement. Gait ataxia, sensory symptoms, and abnormal somatosensory potentials are consistent with structural changes in the medullary tegmentum or cervical cord.

Our patient presented with cerebellar findings and a family history of parkinsonism. This raises the diagnostic possibility of a spinocerebellar atrophy (SCA), such as SCA-2 or SCA-3 (12,13). Genetic testing ruled out the common forms of SCA and the neuroimaging findings proved diagnostic. Our patient had medullary and cervical cord atrophy consistent with adult-onset Alexander disease. Brain MRI showed no cerebellar abnormalities that would be seen in SCA (14).

Mutations in the \textit{GFAP} gene are found in approximately 95% of cases with infantile or adult-onset Alexander disease (2–4). Since normal GFAP can aggregate into Rosenthal fibers when overproduced (15), genetic abnormalities that affect normal GFAP expression may be responsible in patients carrying no mutation of the coding gene portion. The role of the p.D295N variant, regarded as a polymorphism and for which our patient was homozygous, is not clear. This polymorphism occurs in 3% of control subjects (16), and its protein product forms normal-appearing GFAP filaments (15). However, this polymorphism has been associated with other mutations of known pathogenicity, in a homozygous state in one patient with adult-onset

\textbf{FIG. 2.} Axial scans at level of the medulla demonstrate small olives (white arrows) just anterior to deep horizontal medullary clefts (black arrowheads). The cerebellum appears normal. T1 (A) and FLAIR (C) sequences show decreased signal within the olives and clefts, while T2 MRI (B) demonstrates hyperintense signal in these regions. On FLAIR (C), the medulla also demonstrates a brighter signal than the cerebellum.

\textbf{FIG. 3.} Midline T2 sagittal MRI shows a lateral medullary cleft (white arrow) and decreased volume of the medulla and upper cervical spinal cord. Basis pontis and cerebellar folia are normal.
TABLE 1. Literature summary of ocular motor features of adult-onset Alexander disease (3,4,17–32)

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Number (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular motor symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>8</td>
</tr>
<tr>
<td>Oscillopsia</td>
<td>2</td>
</tr>
<tr>
<td><strong>Ocular motor signs</strong></td>
<td></td>
</tr>
<tr>
<td>Nystagmus</td>
<td>22</td>
</tr>
<tr>
<td>Undefined</td>
<td>8</td>
</tr>
<tr>
<td>Pendular</td>
<td>7</td>
</tr>
<tr>
<td>Gaze evoked</td>
<td>8</td>
</tr>
<tr>
<td>Rebound</td>
<td>2</td>
</tr>
<tr>
<td>Impaired pursuit/optokinetic response</td>
<td>9</td>
</tr>
<tr>
<td>Saccadic dysmetria</td>
<td>2</td>
</tr>
<tr>
<td>Internuclear ophthalmoparesis</td>
<td>1</td>
</tr>
<tr>
<td>Ptosis</td>
<td>3</td>
</tr>
<tr>
<td>Miosis</td>
<td>3</td>
</tr>
<tr>
<td>Oculopalatal myoclonus</td>
<td>2</td>
</tr>
<tr>
<td>Palatal myoclonus</td>
<td>14</td>
</tr>
<tr>
<td><strong>Other signs</strong></td>
<td></td>
</tr>
<tr>
<td>Dysarthria</td>
<td>32</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>20</td>
</tr>
<tr>
<td>Ataxia</td>
<td>29</td>
</tr>
<tr>
<td>Hyperreflexia/Babinski sign</td>
<td>29</td>
</tr>
<tr>
<td>Motor weakness</td>
<td>22</td>
</tr>
<tr>
<td>Spasticity</td>
<td>21</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>9</td>
</tr>
</tbody>
</table>

Alexander disease (2) and in a heterozygous state in another (1). Hence, it is possible that this polymorphism may play a modulatory role in the development of this disorder.

A review of 44 patients with adult-onset Alexander disease (3,4,17–32) showed that ocular symptoms are unusual at presentation, with only 3 patients noting diplopia and 2 oscillopsia (Table 1). Yet ocular motor signs commonly develop at some point in adult-onset Alexander disease, being present in 26 (59%) of the reported cases. The most frequent ocular finding is nystagmus, which was present in 22 patients (50%). Pendular nystagmus and gaze-evoked nystagmus were most common, and in at least some cases, the pendular form was part of oculopalatal myoclonus. Eight patients (18%) reported diplopia at some point in their course, but insufficient detail was given to determine if this was due to ocular motor nerve palsy or brainstem involvement. There is a single case reported with bilateral internuclear ophthalmoplegia (32).

In summary, ocular motor signs are common in adult-onset Alexander disease due to involvement of the medulla and upper cervical cord. This results in damage to vestibular pathways, structures important for gaze-holding, and olivary pathways required for gaze stabilization. In our case, there was also evidence of damage to circuits involving the cerebellar vermis that determines saccadic accuracy.

ACKNOWLEDGMENTS

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Update on Retinal Prosthetic Research: The Boston Retinal Implant Project

Joseph F. Rizzo III, MD

Abstract: The field of retinal prosthetic research, now more than 20 years old, has produced many high-quality technical options that have the potential to restore vision to patients with acquired disease of the outer retina. Five companies have performed Phase I clinical trials demonstrating that blind patients can reliably report basic elements of visual percepts induced by electrical stimulation. However, at present patients and observers generally do not consider the results to be useful enough in the performance of tasks of daily living to justify the risks of surgery and chronic implantation or the costs. Having developed a wireless device implanted in the subretinal space, the Boston Retinal Implant Project has focused its efforts on developing scalable technologies to create a hermetic device that can deliver individually controlled pulses of electrical stimulation to each of hundreds of electrodes. An advanced device with such attributes will be needed to justify the risks of implantation. An assessment of long-term biocompatibility for all devices remains to be done.

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A variety of biological and engineering advances now offer some hope for patients with blindness secondary to outer retinal disease, especially retinitis pigmentosa (RP) and age-related macular degeneration. The retinal implant is designed to stimulate nerve fibers that had been properly established during development and which survive the degeneration of more proximal neurons. This compelling theoretical opportunity to restore visual function, however, is inextricably linked to potential risks that are incurred by long-term implantation of a foreign device. Visual prostheses are being developed to interface with the visual pathway in the retina, optic nerve, lateral geniculate body, and the primary or higher visual cortical regions. Each approach has advantages and disadvantages. There is no clear benefit to one approach or the other.

The first attempt to build a visual prosthesis dates back to the 1970s (1). In the late 1980s, 2 research groups, one based at the Massachusetts Eye and Ear Infirmary/Harvard Medical School and the Massachusetts Institute of Technology and the other at the North Carolina State University and the Duke University, simultaneously began to investigate the development of a retinal prosthesis. The former consortium now includes the Boston Veterans Administration Hospital as an integral partner. The latter consortium moved to the Johns Hopkins Medical School and then to the University of Southern California and now forms a nucleus of activity that is tied to the Second Sight Medical Corporation. The field of retinal prosthetics now includes more than 15 research groups (5 of which are partners with corporate ventures) in 6 countries (2–7).

ENGINEERING CONSIDERATIONS

To provide vision to blind patients, a microelectronic retinal prosthesis in its most basic operational form must 1) capture visual images, 2) transform those images into a spatial pattern of controlled electrical pulses, and 3) deliver the controlled electrical pulses to the retina. Two basic approaches have been used to achieve these aims. The first approach is based on the implantation of a photodiode array that can convert the energy of light from the visual scene into electrical pulses that stimulate the retina (8–13). The second approach is based on the placement of the means for imaging the visual scene away from the retina, which requires the use of hard-wired connections to deliver the electrical pulses to stimulating electrodes that are implanted on the epiretinal or subretinal surface (14,15). The former approach is perhaps more elegant and reminiscent of how the eye actually works, but it requires implantation into the eye of more sophisticated electronics, which would increase the risk of failure of components that could not easily be fixed or replaced (14,15).
BOSTON RETINAL IMPLANT PROSTHESIS

Design

After nearly a decade of working on the epiretinal surface, the Boston Retinal Implant Project (BRIP) chose a sub-retinal approach to implant the electrode array (16). Our prosthetic designs have been motivated by the following principles:

1. Minimize disruption of the anatomy of the eye
2. Use a minimally invasive surgical method to implant the device
3. Minimize the amount and sophistication of the electronic components implanted into the eye and orbit
4. Use an ultrathin flexible substrate that can bend to match the contour of the ocular tissues
5. Use wireless technology to provide a functional connection between the external and the implanted components
6. Use means to individually control and to individually adjust the stimulation parameters to each electrode based on patient feedback.

The first 4 of these design principles should enhance the biocompatibility of our device. The third principle also should improve the reliability of our device by retaining much of the electronic functionality outside of the body. The use of wireless technology (the fifth principle) avoids the need for a connector cable, which is notoriously prone to failure. The sixth principle is founded on our belief that generation of useful visual images will be achieved only through iterative testing based on the feedback from each patient. Our first-generation device was developed for preliminary experiments in animals (Fig. 1), and the second-generation device is intended for use in humans (Fig. 2).

A frequent point of comparison among designs from different research groups or companies is the number of stimulating electrodes. Of those devices currently implanted in humans, the Second Sight device has 60 stimulating electrodes and the Retina Implant AG device has about 1,500 photodiode elements, which are not individually controllable. Our team is nearing completion of a device with more than 200 individually controlled stimulating electrodes. Many simulation studies with normally sighted subjects have offered predictions regarding how many

![First Generation Design](image1)

![Second Generation Design](image2)

FIG. 1. Images of the first-generation (left panels) and the second-generation (right panels) retinal prosthetic devices developed by the BRIP. The photograph of the first-generation device shows our custom-designed IC (yellow arrow, upper left panel), an upgraded version of which is housed within the hermetic environment of a titanium case in our second-generation device (white arrow, lower right panel). The ocular positioning of the first-generation device is shown in the lower left panel. The second-generation device, which we will be used for future human testing, includes a glasses-frame structure to support a small camera (red arrow, upper right panel) that collects visual images. The second-generation device also includes a radio frequency (RF) coil positioned around the limbus (yellow arrow, lower right panel), which receives wireless transmission of power and visual signal from a “primary” RF coil embedded within the glasses-frame. In both designs, the stimulating electrode array is the only component that has to be placed within the eye (red arrows, both lower images).
stimulating electrodes would be needed to perform tasks like navigation and reading (17–21), but the optimal number of electrodes to achieve a particular level of visual function will have to be reconciled through experimental studies with blind humans who have received a prosthesis. Meanwhile, plans for developing an ever-larger number of electrodes are fueled by the availability of sophisticated engineering methods and the belief that more electrodes will provide better vision.

Almost the entire BRIP device lies outside of the eye, which minimizes the potential for problems with bio-compatibility that are more likely to arise for components placed inside of the eye (Fig. 2). The external placement of the “stimulating chip” (our custom-designed integrated circuit [IC]) also allows us to provide hermetic encapsulation for the IC by using a titanium enclosure, which would be impractical for use inside of the eye. Titanium has been used reliably for decades to protect the electrical components of cardiac pacemakers, and we have modified this technology to create a miniaturized assembly. For the purpose of conducting animal studies, the BRIP made a 15-channel device that provides long-term tests of hermeticity (16). Each stimulating channel requires a hard-wired connection, called a “via,” that must emerge from the confines of the titanium enclosure. These exit points are vulnerable to leakage of water vapor and sodium ions, which even in minute quantities would destroy the transistors.

The plan to use hundreds of electrodes for our human-quality device is perhaps the greatest technical challenge that we face, and it has required the customization of an emerging technology to provide the larger number (and higher density) of feedthrough vials for our application. The need to develop hundreds of stimulation channels is a good example of how the demanding needs for a visual prosthesis are pushing the state-of-the-art for the development of other implantable microelectronic devices. By comparison, for instance, the highest number of channels for any other neural prosthetic device is 32, which is found in one embodiment of a cochlear prosthesis. Most deep brain devices, like those used to treat Parkinson disease, provide only 4 electrodes.

The most delicate engineering component in a retinal prosthesis is the part that contacts the retina. In the BRIP approach, only the stimulating electrode array is placed into the eye—into the subretinal space. This placement is achieved by passing the array through the sclera behind the eye (Fig. 3). The device that enters the eye is made of plastic (“polyimide”) of only 10 μm thickness. Because of its flexibility, it can bend to match the curvature of the delicate retina without generating a spring-like “restorative” force that might damage the host tissue. This device is made by using customized microfabrication technology to embed the microwires and form the stimulating electrodes (Fig. 4). Microfabricated devices like these can be designed to meet specifications for any reasonable number and density of electrodes, which can be shaped into practically any 2- or 3-dimensional geometry.
Surgical Implantation

The surgery to implant an electrode array on the epiretinal surface (22,23) is easier than that used to implant an array in the subretinal space (13,24–26), but the epiretinal approach creates a greater challenge to achieve a close and conformal alignment of the electrode array to the retinal surface (27). The most common method to affix an epiretinal implant uses a “tack”(23,28,29), which is prone to displacement and which tends to induce gliosis that potentially interposes a high resistive barrier to electrical stimulation. The risk of gliosis limits the number of tacks that can be used (typically only 1 or perhaps 2). Although a tack can effectively secure the electrode array near the retina at the site of insertion, the remainder of the array tends to vault away from the retina. Even minor elevation of the electrode array will cause a significant elevation in the stimulation thresholds (30,31), which increases the risk of damage to the retina and to the electrodes themselves. The epiretinal approach also becomes increasingly more challenging with attempts to use electrode arrays with larger areas (to provide more stimulating electrodes) because the mismatch between the 2-dimensional array and 3-dimensional retina accentuates at larger dimensions. (Although a similar geometrical mismatch is relevant for the subretinal approach, the pressure dynamics within the subretinal space enable a seemingly conformal alignment of our thin films over a relatively wide area, up to 5 mm in diameter.) These concerns contributed to our decision long ago to use a subretinal approach.

We developed a surgical method that required only a single slit in the back of the eye to introduce the electrode array. Once in place, it typically retains a tight apposition to the undersurface of the retina without the need for tacks or adhesives (Fig. 5). This stability is achieved in the absence of

FIG. 3. Microfabrication steps used by our team to produce polyimide arrays with iridium oxide–coated electrodes. Top: Upper left image shows the schematic layout of our first-generation device. Right image shows a 4” silicon wafer that contains numerous electrode arrays of varying shapes. Bottom: Left image shows a magnified view of the distal end of the electrode array with gold wire traces and 1 electrode coated with iridium oxide (large, round, brown object). Right image shows a magnified view of surface of electrode coated with iridium oxide 1 year after electrical pulsing in saline solution, which provides evidence of electrical stability.
significant fibrosis around the arrays, which has allowed us to safely and easily remove arrays that had been chronically implanted into the subretinal space of mini pigs (32). Our methods allowed implantation of a 5-mm-diameter electrode array, the largest surface area of an array safely implanted into a living eye (33). Our array should provide vision over roughly 14° of visual angle to assist in navigation through unfamiliar environments.

**Biocompatibility**

Biocompatibility includes the biological responses that occur secondary to the surgery, foreign materials, and effects of electrical stimulation. When we began our project, there was no evidence that foreign material could be safely implanted adjacent to the retina for long periods. We surveyed 6 materials as substrates for the electrode array (34). All caused some degree of damage or incited some degree of response to the foreign device, but none were severe enough to produce encapsulation of the implanted device, for instance. Other groups have also shown similarly favorable outcomes with foreign materials placed on the epiretinal surface.

**COLLECTIVE ACHIEVEMENTS IN THE VISUAL PROSTHETIC FIELD**

The basic goals of capturing visual information and delivering electrical stimulation to the retina have been

![Image 1](https://via.placeholder.com/150)

**FIG. 4.** Images of 2 different types of electrode arrays, manufactured by the Boston Retinal Implant Project. **A.** Fundus photograph of an electrode array 3 months after implantation in a rabbit retina. **B.** Optical coherence tomography of the same electrode array seen as a highly reflective (falsely colored) red line under the retina. The electrode array is tightly apposed to the retina over the length of the array. **C.** Ten-micrometer microfabricated polyimide array with 100 electrodes. **D.** Fundus photograph of the same array 3 months after implantation in a pig retina. This is the widest electrode array ever implanted into the subretinal space of an animal.

![Image 2](https://via.placeholder.com/150)

**FIG. 5.** Histology of pig retina 3 months after subretinal implantation of coated nonelectronic implants (seen as yellowish fairly flat structures under the retina). **A.** Relatively little anatomical alteration following implantation of Parylene. **B.** Two retinal pigment epithelial (RPE) cells (1 shown by arrow) have clumped over an implant made of polyimide, which is our favored substrate material. Both implants were 0.5 × 0.5 × 10 μm (hematoxylin and eosin, ×20).
achieved by numerous groups. Many different types of implanted devices are well tolerated even after prolonged implantation into the eye. These efforts have provided insights into how neurons respond to electrical stimulation and how these responses differ from those generated by the normal photic stimulation (30,35–44).

These achievements should not be construed to suggest that these areas of investigation are complete or that they will enable success in restoring vision to blind patients. There have been several problems associated with human implants, including multiple cases of extrusion of implanted devices through the conjunctiva, dislodging of retinal tacks, endophthalmitis, hypotony, and failure of hermetic protection of the implanted electronic components, which rendered the devices useless.

Five research groups have been involved in sustained efforts to develop a retinal implant (Table 1). A sixth group, Optobionics, Inc, put in a strong effort but declared bankruptcy after implantation of 20 patients with a subretinal prosthesis (45). The company concluded that its successes were not the result of electrically induced activation of neuronal responses that propagate to the brain. Rather, a “trophic” effect was identified, which although substantiated by careful scientific work (46–48), called into question the value of the device.

The most fundamental outcome of this collective work has been the reporting of the psychophysical threshold for electrical stimulation, that is, the amount of electrical charge required for patients to reliably report a visual sensation. The activation threshold is the most important single parameter to assess the potential safety of the long-term use of these devices and to design the power budget for a prosthetic system (49–51). The thresholds, which have been obtained in patients who were severely blind from RP, were initially found to be relatively high, perhaps too high for safe electrical stimulation with the platinum-type electrodes that were being used given the safety charge limits of these electrodes. More recently, measured thresholds have been substantially lower and more encouraging (in the range of a few microcoulombs per square centimeter or less). However, thresholds have varied considerably across patients, across electrodes within a single patient, and over time (49,52,53). The issue of long-term safety has yet to be reconciled.

Visual acuities have been reported to be as good as 20/1,000, which would provide a significant improvement over the baseline level of “light perception” in implanted patients (54). More recently, obtained with a 16-channel device, visual acuity without the benefits of visual scanning has been reported as equal to the physical spacing of the stimulating electrodes (55). This result has supported a belief that more electrodes would translate into higher quality spatial perception, but this outcome is far from certain. The uncertainty about the potential visual outcome for a given number of electrodes relates to the fact that the electrical fields emanate in complex ways from the electrodes, with patterns of constructive and destructive interference, like the ripples in water caused by the impact of a rock. This phenomenon creates uncertainty about the patterns of activation of neurons that govern the quality of perception.

Studies also demonstrated that implanted patients can localize the quadrant of a large stimulus, identify the direction of moving lines, and identify some common objects like forks and cups (29). The perception of brightness has been shown to correlate with the amount of electrical current used for stimulation, although considerable variability was found in 1 of the 2 subjects (56). Perhaps the most encouraging results have been reported by the Retina Implant AG company (Tubingen, Germany). After 1 week of implantation, a patient was judged to be capable of reading letters and words similar in size to those in newspaper headlines (57,58). If these results, derived by subretinal stimulation, are substantiated by further testing, the retinal prosthetic technology would have the potential to improve the quality of life for severely blind patients.

**UNMET GOALS**

Several requirements for long-term success have yet to be met. There must be scientifically convincing evidence that the induced vision can improve quality of life for blind patients. There must be solid data on the safety of these devices, which will require surveillance of a large number of implanted patients. There must be further improvements in the engineering of these devices to provide a larger number of stimulating electrodes that can be interfaced more closely to the retinal neurons. Finally, there must be more knowledge of the neuroscience related to more effective stimulus paradigms, encoding of visual information from

**TABLE 1.** Retinal implant projects at or near the phase of human testing

<table>
<thead>
<tr>
<th>Company</th>
<th>Location</th>
<th>Position of Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Retinal Implant Group</td>
<td>Boston, MA</td>
<td>Subretinal</td>
</tr>
<tr>
<td>Second Sight</td>
<td>Sylmar, CA</td>
<td>Epiretinal</td>
</tr>
<tr>
<td>Retina Implant AG</td>
<td>Tubingen, Germany</td>
<td>Subretinal</td>
</tr>
<tr>
<td>Intelligent Medical Implants</td>
<td>Bonn, Germany</td>
<td>Epiretinal</td>
</tr>
<tr>
<td>Epi-Ret</td>
<td>Bonn, Germany</td>
<td>Epiretinal</td>
</tr>
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the retina to the brain, and plasticity of the visual cortex following blindness. There is still relatively little information about the physiology of degenerated retinas, but the need to understand these responses for the application of retinal prostheses has led to a very substantial increase in interest in this question (36,39,40).

CAN IMPROVED PSYCHOPHYSICAL RESULTS BE OBTAINED FROM BLIND HUMANS IMPLANTED WITH A RETINAL PROSTHESIS?

Vision is a complex and nuanced sensation compared to hearing, and it will undoubtedly be harder to create useful vision that it was to create useful hearing with cochlear prosthetic devices. There are several impediments to improving vision with such electrical implants. Electrical stimulation tends to activate retinal neuronal pathways indiscriminately, although we and others have discovered strategies to favorably bias the stimulation (30,44,59,60). Indiscriminate stimulation confounds any strategy to create useful vision. Loss of photoreceptors causes significant “reorganization” of the retina that will complicate the attempt to create predictable visual percepts (61,62). Visual cortical changes also occur following loss of retinal input (63,64). The extent to which these cortical changes might help or hinder the interpretation of the percepts generated by artificial electrical stimulation is unknown.

WHAT CAN PATIENTS BE TOLD?

The results of long-term testing of retinal implants in blind humans look promising. To properly consider the risk-to-benefit ratio, one would have to know as much detail about the complications as about the widely reported psychophysical outcomes. Such proper consideration cannot be carried out because the complications that have occurred have not been fully reported in public forums, mostly because the testing has been performed by companies that face the dilemma that reporting of untoward events might compromise the commercial potential of their product. At this stage of the investigation, there is not enough published evidence to offer comprehensive and unbiased advice to patients. Given this reality and the fact that the status of each group in the field is constantly changing, general recommendations of what advice might be given to interested patients are difficult to provide. Any serious consideration of becoming a recipient of a visual prosthesis must be grounded in reflection of the up-to-date outcomes from each group in the field. Representatives from the groups listed in Table 1 can discuss the status of their work and the relative merits of their approach. The interested reader also might access the Web site of each group, which provides descriptions of the current activities and contact information.

THE DIRECTION OF THE BRIP

Our group decided long ago not to begin chronic human implants until we had developed the technology to expand the number of stimulation channels to above 200, a number that might provide functionally “useful” vision to blind patients, like the ability to navigate safely in an unfamiliar environment. The technology needed to produce such a device includes the means to transmit sufficient power to support stimulation across the larger number of electrodes and the means of providing the hermeticity for the ICs and microwires that course through the ultrathin membrane that enters the eye. Such long-term development efforts are facilitated by the freedom to flexibly pursue technical solutions, the timetable of which is unpredictable. The value of retaining the independence to decide on an appropriate time to begin human implantation is the primary reason that our group has delayed a corporate strategy to develop this technology.

Having implanted wireless devices in laboratory animals for 2 years, we have begun to collect the necessary “preclinical” tests that are required by the Food and Drug Administration to obtain the Investigational Device Exemption that is needed before human testing can begin. Our initial human studies will be conducted with a device that will have more than 200 electrodes, which we anticipate will provide more useful vision for blind patients, although the primary intent of Phase I testing will be “safety.” The BRIP believes that our subretinal approach and that our means to discretely control stimulation across a large number of channels will prove to be advantageous in comparison to other approaches.

REFERENCES


Current Concepts in the Diagnosis, Pathogenesis, and Management of Nonarteritic Anterior Ischemic Optic Neuropathy

Neil R. Miller, MD

Anterior ischemic optic neuropathy (AION) is the second most common cause of optic nerve–related permanent visual loss in adults after glaucoma. There are 3 types of AION: nonarteritic, perioperative, and arteritic. In this editorial, I will consider only nonarteritic AION (NAION), the most common form, about which surprisingly little is known regarding pathogenesis or treatment.

Most cases of NAION occur in patients older than 55 years, with men and women being affected equally. Most have underlying systemic vascular disease, although this may be undiagnosed at the time of onset. The majority of cases of NAION are sporadic, but familial cases have also been reported (1). The prevalence of NAION in the United States has been reported to be between 3 and 10 per 100,000 (2).

NAION usually presents with painless unilateral loss of acuity, visual field, or both. Eye pain is unusual, and pain on eye movement is extremely rare (3). Visual acuity is variable, ranging from 20/15 to no light perception. Any visual field defect can be present, but the most common is an arcuate or altitudinal defect. A relative afferent pupillary defect is always present if the condition is unilateral, and there is no optic nerve or retinal disease in the fellow eye. The affected optic disc is typically swollen and hyperemic, with the hyperemia distinguishing it from the pale swelling that is typical of the arteritic form of AION. Peripapillary flame-shaped hemorrhages are almost always present.

Although there are exceptions (4), NAION occurs almost exclusively in patients with a typical morphology of the optic disc, that of a very small central cup (<0.3 cup-to-disc diameter), and may itself be smaller than normal (5). This appearance has been termed the “disc-at-risk.” In addition, patients almost always have systemic vascular risk factors, such as hypertension, hypercholesterolemia, diabetes mellitus, or a combination of these disorders (5,6). Other associations have been suggested or identified, including nocturnal hypotension, anemia, hyperhomocysteinemia, obstructive sleep apnea syndrome, and some coagulopathies (7). In addition, NAION may occur after various ocular and nonocular surgeries (6,8–10).

A number of medications have been associated with the development of individual cases of NAION. Some, such as pegylated interferon-alpha, appears to be related to the development of NAION in only a few isolated cases (11,12); however, more controversial is the relationship of NAION to the use of erectile dysfunction drugs (EDDs) and the cardiac medication amiodarone (13–16).

The current EDDs, sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra), are phosphodiesterase-5 inhibitors. Because they cause peripheral vasodilation and thus systemic hypotension, particularly in older individuals whose erectile dysfunction is related to systemic vascular disease or its treatment, it is reasonable to hypothesize that these drugs could induce NAION. Indeed, a number of cases of NAION have occurred that have been temporally related to the use of EDDs (17,18). In addition, several challenge cases have been reported; i.e., cases in which transient blurred vision occurred on several occasions following the ingestion of one of these drugs, eventually followed by permanent visual loss and clinical evidence of NAION. Nevertheless, fewer than 100 cases of NAION have been reported in patients taking an EDD compared with more than 50 million prescriptions having been written. I agree with those who recommend that any male patient who develops...
Apparent NAION be asked about the use of EDDs (in private!) and that any patient who asks about using EDDs have careful disc assessment and be told about the low but potential risk of NAION, particularly if he has a disc-at-risk (19).

Amiodarone was developed in the 1960s for treatment of angina but now is used as a first-line drug for atrial fibrillation in patients with left ventricular dysfunction and congestive heart failure. Although it has long been known that ocular symptoms, most frequently seeing blue-green rings or halos around lights, occur in 1%–11% of patients, it was not until 1987 that it was suggested that patients taking amiodarone had an increased risk of developing NAION compared with the normal population (20). Subsequently, numerous case reports, case series, and pathology reports have linked amiodarone to the development of NAION, which usually is insidious in onset and bilateral, with resolution of disc swelling slower than the typical NAION. On the other hand, the author of a large prospective study concluded that at commonly used clinical doses, amiodarone either never or infrequently causes bilateral visual loss from NAION. Although it may be that some patients taking amiodarone do not recognize that they have developed visual loss or that the ophthalmologists caring for them ascribe visual loss in these vasculopaths to other causes, such as cataracts or macular degeneration, it seems clear that if amiodarone causes an optic neuropathy, the visual loss in such cases is not particularly severe. In any event, I agree with the recommendation that any patient who develops NAION be asked if he or she is taking amiodarone, that anyone taking amiodarone who develops an anterior optic neuropathy be told of the possible association between the drug and NAION, and that the patient’s cardiologist and/or primary care provider be contacted and told of the possible association, at which point a decision to stop or continue drug can be made by the physician and patient (14).

Whatever its cause, NAION is characterized histologically by ischemia at the level of the prelaminar/laminar portions of optic nerve supplied by the circle of Zinn-Haller via short posterior ciliary arteries. Thus, this is not a disorder of large or medium-sized vessels but rather small-caliber vessels such as arterioles or capillaries (5).

About 40% of patients who develop NAION will experience a spontaneous improvement in visual function, with visual acuity being more likely to improve than visual field. As this occurs, the disc swelling resolves, and the disc becomes pale but not cupped as it does in arteritic NAION.

Patients in whom NAION occurs are at risk for subsequent cerebrovascular and cardiovascular events (e.g., transient ischemic attack, stroke, myocardial infarction) and their associated mortality. Many have an increased number of white matter lesions in the brain compared with age-matched controls (21). Thus, patients in whom the diagnosis is made should be told to undergo a complete physical examination, and their primary care provider should be notified of the occurrence of the condition and its systemic prognosis. Patients should be evaluated for systemic vascular disorders and treated appropriately. Because of the potential role of nocturnal hypotension in the development of NAION, patients with hypertension should be told to take their antihypertensive drug in the morning or during the day, not at night.

There is a small risk for recurrent NAION in the same eye (3%–5%) and a variable risk of NAION in the fellow eye (15%–25%) over the subsequent 5 years. It has been suggested that aspirin may reduce the risk of NAION in the fellow eye (22), but no controlled clinical trials have been performed testing this hypothesis, in large part because of the wide usage of aspirin and aspirin-containing products and the number of patients who would have to be followed over time to determine the efficacy of the drug.

The treatment of NAION is one of the most controversial and contentious issues surrounding the condition (23,24). At one time, it was suggested that optic nerve sheath fenestration (ONSF) was beneficial in patients experiencing progressive loss of visual function from NAION, but both retrospective series (25) and a controlled clinical trial to test this hypothesis failed to produce any evidence of such a benefit (26). The latter study actually found that patients treated with ONSF fared worse from a visual standpoint than those who were not treated.

The primary medications used for the treatment of NAION are corticosteroids, both as an intravitreal injection (27–29) and by systemic administration (29). While the results of these are controversial, many physicians now at least discuss this potential treatment with patients who experience acute NAION. Other drugs have been suggested to be potentially beneficial in small primarily non-randomized case series. These include intravitreally injected bevacizumab (28,30), even though use of this agent has been associated with the development of NAION in patients treated for wet macular degeneration (31). A particularly exciting new drug that was found to be associated with an improved visual outcome in a small but double-masked prospective study is erythropoietin. This drug appears to have neuroprotective properties apart from its effects on the hematopoietic system.

It seems clear that some patients develop a condition that looks ophthalmoscopically like typical NAION but is unassociated with any visual dysfunction (32–34). In these cases of “incipient NAION,” the disc swelling resolves spontaneously and never recurs in 50%, resolves and then recurs symptomatically in 25%, and progresses to symptomatic NAION in the remaining 25%.

The previous lack of an animal model of NAION has hampered efforts to determine the optimum treatment of the condition; however, there now exist both murine and primate models of the condition (35). Although the method used to create AION in these models may be quite different...
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Although relatively uncommon, indirect traumatic optic neuropathy (TON) often remains visually devastating (1). Numerous treatments have been suggested in the past, particularly surgical optic nerve decompression and high-dose systemic corticosteroids. However, more recent studies have suggested that no treatment might be better than potentially harmful therapeutic interventions, and the management of indirect TON remains highly controversial (1–3).

PRO—Steroids or surgery should be considered in patients with indirect traumatic optic neuropathy: Nicholas J. Volpe, MD

Opening statement
Despite 2 decades of ardent discussion, treatment attempts, clinical trial, and laboratory work, neuro-ophthalmologists have failed to develop a consensus opinion or to design an effective study to answer the question of whether any type of treatment benefits some patients with TON (1–3). This devastating optic neuropathy primarily affects young people in the prime of their lives and involves 5 of 100,000 population, a prevalence similar to that of optic neuritis and nonarteritic ischemic optic neuropathy. It is also a common injury encountered in the modern battlefield (4). Unfortunately, there is no class I evidence on the successful treatment of TON to date, and the spontaneous recovery rate from TON makes a comparison with proposed treatments difficult (2,3). There is however a substantial amount of retrospective data and anecdotal experience that favors treatment of these patients, in the absence of severe head trauma, with either steroids and or optic canal decompression. These treatments are relatively safe, have a scientific basis, and ultimately are driven by “what would I want if this happened to me?”

Background
TON can result from both direct and indirect trauma. For the purpose of this debate, we define indirect TON as due to trauma to the forehead, brow, or head producing an optic neuropathy as opposed to direct or penetrating ocular or orbital injury to the optic nerve. The latter develops after blows to the face and particularly the forehead and most commonly in the setting of motor vehicle accidents or falls (1). The presumed mechanism of injury involves contusion injury to the optic nerve in the optic canal. Optic canal fractures however are identified in only approximately one third of patients, and therefore identification of a fracture is not necessary for the diagnosis of posterior indirect TON (5). The condition can be associated with any level of visual dysfunction, but generally vision loss is severe. The diagnosis is generally not made when there is injury to the retina, intraocular hemorrhage, or external or initial ophthalmoscopic evidence of injury to the eye or the nerve (1). TON often accompanies severe head injury or
multisystem trauma, which at times can make establishing the diagnosis difficult and often precludes gathering meaningful clinical information necessary to study various treatments in a rigorous way.

Pathophysiologic observations that favor treatment

There are a number of reasons to believe that at least mechanistically this should be a treatable condition, recognizing that there is little evidence that any condition associated with any type of acute axonal injury (particularly the optic nerve) can be treated. Posterior indirect TON likely results from 2 factors: 1) the continued forward movement of the eye as the head suddenly decelerates and 2) from transmitted forces from the facial eminencies focally directed to the optic foramen. The combination of these factors leads to compression, stretching, shearing, and contusion of the optic nerve within the confines of the optic canal, where its dura is adherent to the bony walls. The axons may then swell in the tight bony optic canal, where there is no room for expansion (1,5). Therefore, delayed visual loss may result from further compression due to edema within the optic canal or from release of neurotoxic factors at the time of injury. An opportunity for treatment may exist based on a chance to 1) reduce swelling, 2) make more space for the swollen nerve, and 3) use neuroprotective agents of various types, which lessen the damage cascade that is set up at the moment of injury. The use of neuroprotective agents remains the main focus of treatment interventions for other optic neuropathies, including ischemic optic neuropathy and glaucoma.

Historical support for treatment

Several series have reported that between one quarter and one half of patients with untreated TON improve spontaneously (3,6). This high spontaneous recovery rate makes it particularly difficult to detect treatment effect and makes a “nontreater” comfortable and well grounded with his or her recommendation to manage expectantly.

There are 2 available options for treatment. One is the use of systemic corticosteroids and the other is the surgical decompression of the optic canal (7). Both target different aspects of the disease process. When used in combination, they may favor a better outcome compared to observation, as demonstrated by a meta-analysis of the available, albeit anecdotal medical literature (8). In injury conditions in which acute swelling and subsequent inflammatory reaction are undesirable, corticosteroids are well recognized to reduce swelling and inflammation. Indeed, retrospective studies have shown that steroids both in standard doses and in “megadoses” can increase to two thirds the fraction of patients who improve (9,10). Unfortunately, since these reports and the international TON treatment trial, there have been only a few meaningful attempts by neuro-ophthalmologists to report even their anecdotal and retrospective experiences. “Megadose” steroids gained popularity because of the results extrapolated from traumatic spinal cord injury studies. The National Acute Spinal Cord Injury Trial showed that “megadose” steroids (30 mg/kg of methylprednisolone load followed by 5.4 mg/kg/hour) reduced permanent deficits in patients with spinal cord injury (11). The mechanism was not believed to be related to glucocorticoid activity but theorized to be the result of reduction in free radical damage and prevention of lipid peroxidation, which is thought to be the final pathway in white matter injury. Steroids in these doses may also enhance blood flow. These studies investigated the treatment of spinal cord injury, not TON, and the most convincing (albeit not statistically significant) benefit was seen when steroids were given within 8 hours of injury (a treatment window that is often difficult to achieve with TON, since its recognition is often delayed outside of the acute injury period). In a post hoc analysis, there was also some evidence that those treated after the 8-hour period fared worse than placebo, but these data and conclusions are of questionable significance (11).

However, these data must be considered in the context of recent evidence that steroids (in “megadoses”) may be harmful to the optic nerve in a rat model of crush injury (12) and as well may be contraindicated in patients with severe head trauma because of reduced survival (12,13). The CRASH study (Corticosteroid Randomization After Significant Head Injury) reported that high-dose steroids were associated with reduced survival when given in the context of head injury (14). In this study, 10,008 patients with severe traumatic head injury were randomized, to either “megadose” steroid treatment (2 g of loading dose followed by 0.4 g/hour over 48 hours) or placebo. The mortality rate 2 weeks following the injury was 21.1% in the steroid group and 17.9% in the placebo group (P = 0.0001).

Transcranial and extracranial (transethmoidal, transantral-ethmoidal) surgical decompression of the optic canal have been reported in uncontrolled and retrospective studies to result in up to 70% improvement in patients with TON (6,15). However, there is no class I evidence that demonstrates that this is an unequivocally successful treatment (2). Benefits of optic canal decompression have also been reported in the pediatric population (16). With the increasing availability and training of endoscopic surgeons familiar with the extracranial approach, the complication rate is very low and most centers that use the procedure do so in conjunction with steroid therapy (7,17–19).

Conclusion

Currently, there is no standard of care for the treatment of TON. The International Optic Nerve Trauma Study compared observation to both steroids and canal decompression and found no clear benefit for either modality (6). Vision improved by at least 3 Snellen lines in 57% of the untreated group, 32% of the surgery group, and 52% of the steroid...
CON—No treatment should be offered to patients with indirect traumatic optic neuropathy: Leonard A. Levin, MD, PhD

Opening statement

Neuro-ophthalmologists are uncomfortably familiar with the use of therapies that subsequently turn out to be ineffective (or worse, harmful) when tested in randomized clinical trials. The poster trial for this effect is the Ischemic Optic Nerve Decompression Trial, which showed that fenestration of the optic nerve sheath did not help nonprogressive nonarteritic anterior ischemic optic neuropathy (NAION) (20). The results from this study stopped the use of optic nerve sheath fenestration in NAION. Similarly, the frequent use of standard-dose oral corticosteroids for optic neuritis was virtually halted after the Optic Neuritis Treatment Trial suggested a higher recurrence rate in patients treated in that way when compared to high-dose intravenous corticosteroids or placebo (21). Similar trials have demonstrated ineffective treatment results using brimonidine for NAION (22) and Leber hereditary optic neuropathy (23).

Given this experience, on what basis could an experienced and ethical physician advocate treating patients with indirect TON, a disease for which not only is there minimal data for efficacy from nonrandomized trials (24) but also the most commonly used treatment (corticosteroids) is actually harmful (12,14,24,25)? Treatment of this disorder is complicated by several factors: its natural history includes both dramatic improvement and worsening, its incidence is relatively low, and it is difficult to obtain accurate baseline data regarding vision of 10 patients with recent head trauma. Clearly, only a randomized clinical trial would inform us of how to treat TON, but such a trial would likely be difficult to carry out if change in visual function was the primary end point. Some disease-therapy combinations are simply resistant to study (26).

A solution to this conundrum may come as our ability to correlate structural and functional measures of optic neuropathy improves. At present, visual function is the end point or hematoma impinging on the optic nerve. Surgery should be offered in patients with severe vision loss when surgery is being done to repair other facial fractures or in cases of continued visual deterioration with or without steroid treatment. In any patient in whom there is diagnostic uncertainty, such as those with simultaneous globe injury or those with severe head injuries, which make it difficult to assess visual function, we discourage any treatment beyond moderate doses of steroids. In the future, the likely treatment for TON will be a neuroprotective agent. Until then, this will remain an important topic to debate, and more systematic attempts at data collection and treatment studies should again be considered by those experts in this field.

Rebuttal: Nicholas J. Volpe, MD

Dr. Levin is one of the world’s experts in the field of neuroprotection and has spent more time than most of us studying TON, both from the standpoint of the best approach to designing experiments and compounds for neuroprotection and the best approach to treatment. Once again I would highlight that we are in agreement that there is simply no class I evidence to support the treatment of TON patients with corticosteroids. I also agree and strongly endorse his conclusions that ultimately we will have a much better understanding on how to treat all types of optic nerve disorders when we can perfect our structural measurements of the optic nerve and tie them tightly to visual function. This will eliminate the inaccuracies associated with subjective vision testing and all the limitations that have been discussed regarding the difficulty in examining and qualifying visual deficits in patients with TON. Ultimately, the answer to how to best treat this condition will come from studies in which testing modalities are able to assess the viability and function of optic nerve axons at presentation and during follow-up with different treatments.

Dr. Levin accurately points out, as did I, that a number of treatments have been abandoned in neuro-ophthalmic practice as a result of prospective randomized clinical trials. His implication is that only with laboratory or clinical evidence should any therapy be used. This argument would fall short in other clinical situations in neuro-ophthalmology in which our individual and collective experiences, based on the clinical management of patients, dominate our decision making. One such example is in the management of idiopathic intracranial hypertension. Most experts would consider acetazolamide as the treatment of choice in patients with early and moderate vision loss. The use of this treatment, based on a sound physiologic principle, has never been rigorously tested but is now the subject of a recently initiated prospective randomized treatment trial. While I acknowledge that the argument for neuroprotection from “megadoses” of steroids is not substantiated by any laboratory or clinical trial evidence, I would offer that in this situation, conventional doses of steroids may well be helping reduce tissue edema in the tight confines of the optic canal regardless of whether they have any neuroprotective effect. Similarly, this may be the mechanism by which optic canal decompression may also be helpful.

Frankly, I feel that the argument that steroids are harmful falls short in some ways. In each of the examples cited, it was their effect on laboratory rats, their use in other diseases, or their use in a group of patients with severe head trauma that found steroids to be harmful. As clinicians dealing with isolated TON, we are certainly not dealing with laboratory animals and in many situations not dealing with patients who also have severe head injuries. However, I do agree that based on the CRASH data, steroids should be contraindicated in the setting of severe head injury.

I believe Dr. Levin and I agree that we are a long way from having an ideal and clearly effective treatment. There is no sound clinical trial evidence to support the treatment of TON, and the clinical course is highly variable making it difficult to test such a treatment. We both agree that structural measurements of optic nerve function will aid us in the future design of clinical trials to test possible treatments. Where our opinions differ is largely based on whether in patients with isolated TON and the absence of severe head injury, we can safely use moderate doses of steroids and optic canal decompression in an effort to lessen the damage to the optic nerve. Lacking class 1 evidence, I believe this decision on personal experience and non-rigorous retrospective data is reasonable at this time.

Rebuttal: Leonard A. Levin, MD, PhD

Dr. Volpe cogently and accurately summarizes the critical literature describing the presentation, pathophysiology, and treatment of indirect TON. I have no disagreement with what he writes, and more specifically, I agree with him that there is no evidence based on prospective randomized studies to support a choice of any specific therapy vs observation. He is correct that in a meta-analysis that my colleagues and I performed 15 years ago (8), we concluded that surgery or corticosteroids were superior to observation. However, the results of the International Optic Nerve Trauma Study (6) published 3 years later reached the opposite conclusion in a concurrent (albeit nonrandomized) observational study.

I contend that his recommendation for treatment with corticosteroids and/or surgery is based less on scientific evidence than the fact that he is an ethical and caring physician who desires the best for his patients, and as he writes, “what would I want if this happened to me?” But the critical question is not what would the physician want if the situation were reversed, but what would the patient want. An equally ethical and caring position is that without laboratory or clinical evidence of efficacy with a therapy, withholding these therapies (observation alone) is indicated. Given that laboratory evidence and the CRASH study demonstrate significant potential risks of high-dose corticosteroids, one can strongly justify recommending no therapy.

Dr. Volpe correctly states that “there is little evidence that any condition associated with any type of acute axonal injury (particularly the optic nerve) can be treated.” This
statement is supported by level 1 clinical evidence for memantine in Alzheimer disease (3), riluzole in amyotrophic lateral sclerosis (4), and most recently, brimonidine in normal-tension glaucoma (5). On the other hand, there are dozens of animal studies demonstrating neuroprotective effects of drugs and other therapies on optic nerve crush and transection, which are preclinical models of TON.

This discrepancy between results in the clinic and the laboratory has 2 sources. First, most animal studies examine the effects of the treatment on survival of the cell soma (the retinal ganglion cell), but the survival of the axon is equally important (6). The development of axoprotective drugs is a lacunae in our therapeutic armamentarium, and without attending to the axon, there is unlikely to be visual improvement in most optic neuropathies. Second, therapies that work in cell culture or animal models frequently fail in human trials. This disconnect arises from a variety of reasons inherent to translational research that we have called the “Lost in Translation” problem (6). In other words, there may be a good reason why it has been difficult to find effective therapies for indirect TON and provides further justification for pilot studies using a structural end point, such as retinal nerve fiber layer thickness.

In summary, there is inadequate evidence from clinical trials to support any specific treatment for indirect TON, and animal and clinical studies suggest that one such treatment, high-dose corticosteroids, may even be harmful. On the other hand, laboratory research continues to entice us with the possibility of using neuroprotective and axoprotective therapies. The best approach is to focus our efforts on finding more efficient ways of testing treatments in clinical trials using novel end points and trial designs, and thereby increase our chances of having an effective therapy to offer our patients.

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

Once again, the lack of class I evidence makes it difficult for expert neuro-ophthalmologists to agree on the treatment of a well-recognized entity, such as indirect TON. This controversy emphasizes the importance of randomized clinical trials, without which the debate will continue.

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Papilledema: The Vexing Issues

Jonathan D. Trobe, MD

Abstract: Papilledema has long been recognized as a valuable sign of increased intracranial pressure (ICP). But because papilledema is based on interruption of the energy-dependent process of axoplasmic flow, it appears late after a rise in ICP. Papilledema is usually present in chronically high ICP but sometimes asymmetrically in the 2 eyes and rarely in 1 eye only. Distinguishing it from other optic neuropathies that produce elevated optic discs is challenging, especially in the chronic phase, when visual function may be impaired. Papilledema is often an unrecognized cause of optic disc edema in inflammatory and compressive meningeal disorders that interfere with cerebrospinal fluid (CSF) passage through the arachnoid granulations. Its detection is particularly critical in patients with noncompliant ventricles or extraventricular blockage of cerebrospinal flow because imaging may fail to disclose conventional signs of high ICP. Therefore, patients with indwelling CSF shunts, tuberous sclerosis, chronic granulomatous meningitis, or meningiomatosis should be periodically examined for papilledema so that timely ICP-lowering measures can be instituted to preserve vision.

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fluid (CSF) into the optic chiasm and thence into the optic nerves, leakage of vessels within the optic discs from vasomotor instability, and a toxic substance within the CSF.

In 1910 (3) and 1911 (4), Leslie Paton, an ophthalmologist, and Gordon Holmes, a neurologist, reported the results of the first definitive light microscopic study of papilledema. It came from 50 eyes and optic nerves of 39 patients who had died of brain tumors at the National Hospital for the Paralysed and Epileptic in London (now known as the National Hospital for Neurology and Neurosurgery, Queen Square).

In this landmark publication, the authors made 3 important observations: 1) the optic discs and the retrolaminar and distal retrobulbar nerves contained excessive edema, which they assumed was extra-axonal, 2) the prelaminar axons were “varicose” and “fragmented” where they were most deviated by the optic disc swelling, and 3) the central retinal vein was dilated in the retrolaminar and prelaminar optic nerve but flattened in the subarachnoid space around the optic nerve (Fig. 1). From these observations, they concluded that papilledema came from compression of the subarachnoid portion of the central retinal vein by high ICP. This mechanical process, they believed, led to dilation of the vein’s optic disc segment. Leakage from this dilated vein and its feeding capillaries caused prelaminar optic disc swelling and bending of axons, which sometimes led to their fracture.

The Paton-Holmes venous compression doctrine held sway for most of the 20th century. However, critics asked why retinal edema, hemorrhages, and cotton wool spots—features associated with occlusion of the central retinal vein—were not usually evident with the papilledema. Moreover, optic disc edema is known to be an unimpressive finding even in severe central retinal vein occlusion (2).

**FIG. 1.** The Paton-Holmes light microscopic study of the eyes of 39 patients who had died of brain tumors. A. Cross section of representative swollen optic disc. Prelaminar optic disc edema; the authors assumed it was extra-axonal. B. Prelaminar swollen and fragmented axon (arrow). C. Postlaminar dilated central retinal vein (arrow). D. Collapsed central retinal vein (arrow) in the subarachnoid space behind the eye. The authors posited that the high ICP caused the retrobulbar vein to collapse, leading to dilation of the perilaminar vein, its leakage, and secondary optic disc swelling. They believed that the swelling induced extreme bending of the axons and their breakage. (Modified from Paton and Holmes (4).)
In 1948 came the discovery that organelles normally flow back and forth between cell bodies and their synaptic terminals in an energy-dependent process called axoplasmic transport (5). In 1976 and 1977, a flurry of publications reported electron microscopic studies on the anatomy and physiology of optic nerve axons and axoplasmic transport in acute glaucoma, ocular hypotony, and increased ICP (6–9). In all 3 conditions, electron microscopy showed edema of the optic disc that was mostly intra-axonal. Studies of axoplasmic flow within the optic nerve, as measured by the progress of tritiated leucine injected into the vitreous cavity and incorporated into retinal ganglion cells, showed that axoplasm was arrested in the region of the lamina cribrosa (Fig. 2). Considering that these 3 conditions share a high pressure gradient across the lamina cribrosa—albeit in opposite directions in acute glaucoma and ocular hypotony/increased ICP—investigators reasoned that this abnormal pressure gradient caused or contributed to the axoplasmic pileup.

As an explanation for papilledema, the doctrine of venous hypertension gave way to the doctrine of axoplasmic stasis. But still unanswered was the question of how high ICP caused this axoplasmic stasis. Was it by direct compression of axons (mechanical theory) or by reduced perfusion of axons (ischemic theory) (1,2,10–13) (Fig. 3)? Although the mechanical theory has generally been favored, there is compelling support for the ischemic theory. For example, experimental occlusion of the ciliary arteries leads to axoplasmic stasis and axonal swelling (14,15). Fluorescein angiography in patients with papilledema shows delayed filling of the optic disc and peripapillary choroidal vessels (11). Patients with arteriosclerosis seem to be especially prone to optic neuropathy in the setting of chronic idiopathic intracranial hypertension (IIH) (16).

There are some tantalizing similarities between the optic neuropathy of papilledema and the optic neuropathy of acute systemic hypotension. First, there is a shared proclivity to affect the inferior arcuate nerve fiber bundles and to spare the maculopapillary bundles. Second, just as papilledema may be the only important neurologic finding in chronic high ICP, so ischemic optic neuropathy may be the only important neurologic finding in acute systemic hypotension (17). These phenomena converge on the ciliary arterial circle, which might be the site of acute hypoperfusion in systemic hypotension and chronic hypoperfusion in sustained high ICP (Fig. 3).

Why might the ciliary arterial circle be so vulnerable to low blood pressure and high ICP? Because it competes with the choroidal circulation, which draws off a voluminous flow to furnish oxygen to the highly metabolic visual transduction process and to dissipate the heat that transduction generates. Under normal circumstances, there is enough arterial blood flow to go around. But if systemic blood pressure falls or subarachnoid pressure rises, the optic nerve might suffer from “choroidal steal.” Notably, one postulate as to how optic nerve sheath fenestration protects the optic nerve in papilledema is that it forms a scar around the nerve that isolates the ciliary arterial circle from transmission of high subarachnoid pressure (12).

The issue about whether axons lose function from compression or ischemia also applies to primary open-angle glaucoma (POAG), where it remains unresolved. Papilledema and POAG share a pressure gradient across the lamina cribrosa and visual field loss that affects principally the arcuate bundles in the nasal field with sparing of visual acuity. But there is a profound difference between papilledema and POAG: the optic neuropathy of chronic papilledema does not include excavation of the neuroretinal rim tissue. Thus, there must be something else besides chronic ischemia to the pathogenetic mechanism for POAG (18).

The relationship between axoplasmic stasis and optic nerve dysfunction is uncertain. The optic nerve is evidently

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**FIG. 2.** The Tso-Hayreh electronic microscopic studies of papilledema in rhesus monkeys whose intracranial pressure had been elevated by implantation of an intracranial balloon. **A.** Prelaminar optic disc shows some very distended axons (asterisks). (Modified from Tso and Hayreh (7), Arch Ophthalmol. 1977;95:1448–1457, copyright © 1977 American Medical Association. All rights reserved.) **B.** Autoradiograph of optic nerve from a rhesus monkey eye enucleated 6 hours after intravitreal injection of tritiated leucine. Silver grains (arrows) have accumulated in perilaminar region as compared to control eyes (not shown). (Modified from Tso and Hayreh (8), Arch Ophthalmol. 1977;95:1458–1462, copyright © 1977 American Medical Association. All rights reserved.)

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able to conduct visual signals adequately as long as the stasis is not severe, given that visual function is relatively preserved in papilledema in the early stages—even when there is considerable optic disc elevation.

Axoplasmic stasis is not unique to papilledema, having been found or surmised in many other optic neuropathies (19). But in papilledema, the axoplasm presumably accumulates more slowly as optic nerve dysfunction usually takes a longer time to develop.

THE VEXING ISSUES

Is papilledema a reliable clinical indicator of a recent rise in intracranial pressure?

No—at least not in humans. In one monkey experiment, ICP elevation induced by subarachnoid balloon inflation led to the development of papilledema in 30% within 24 hours and in 90% within 120 hours. The faster the balloon was inflated and the higher the ICP, the greater the likelihood and degree of papilledema (20). But in humans, papilledema lags. Among 37 patients who had documented high ICP from acute intracranial hemorrhage in trauma or ruptured aneurysm and who were examined for several days in an intensive care unit, only 1 patient had papilledema. Five patients had peripapillary hemorrhages, a phenomenon known as Terson syndrome (21). Other studies have affirmed that fewer than 20% of patients examined within a few days of sustaining head trauma (22) or ruptured aneurysm (23) have papilledema. The shortcoming in the evidence about the prevalence of papilledema in acutely high ICP is that authors do not consistently report how long they continued performing ophthalmoscopy in these patients.

The delay in the appearance of papilledema in acutely elevated ICP is consistent with the idea that papilledema is not based on dilated veins, as is the case in Terson syndrome, but rather on interruption of the metabolic process that mediates axoplasmic flow. Based on examination of patients in a neurointensive care unit for several decades, I believe that Terson syndrome is more common than papilledema within the first few days of a sudden rise in ICP. I have also found papilledema to be generally absent in hydrocephalic children who sustain acute shunt failure, a topic that requires further study.

Is papilledema a reliable indicator of chronically high ICP?

Yes, but there are no published studies that correlate papilledema with ICP. Older studies found that papilledema occurred in 50%–80% of brain tumors (1). That range is now probably an overestimate as modern brain imaging detects tumors before ICP has risen enough to cause papilledema.

flow to the choroid. The optic nerve axons are distended (a) as chronic ischemia interferes with the metabolic process of axoplasmic flow. CSF, cerebrospinal fluid.
In a study of 252 brain tumors, Paton (1) found that papilledema appears more rapidly in cerebellar tumors than cerebral tumors. That observation fits with my experience, namely that a very large amount of supratentorial mass effect is necessary to cause papilledema, whereas a relatively inconspicuous tumor may cause elevated ICP and papilledema if it blocks convexity arachnoid granulations (24), ventricular CSF egress (25,26), or dural venous sinuses (27).

The papilledema of chronically high ICP may be of different severity in the 2 eyes. It may be entirely absent from 1 eye, but rarely from both eyes. The frequency of strictly unilateral papilledema has never been adequately documented, but in my experience, it occurs in fewer than 5% of cases. This phenomenon is attributed to anatomic variations that impede transmission of ICP through the optic canal to the distal optic nerve.

How often is papilledema completely absent in chronically high ICP? Studies of IIH indicate that about 6% of such patients lack papilledema (IIH without papilledema or IIHWOP) (28). The weakness of this evidence is that without papilledema as an anchor, the diagnosis of IIH depends on the accuracy of the lumbar puncture opening.

**FIG. 4.** Postdecompression optic neuropathy. **A.** Optic discs show a mixture of swelling and pallor. **B.** Precontrast T1 sagittal MRI discloses hydrocephalus from a suprasellar ganglioglioma (arrow). **C.** Following surgery, optic discs eventually became flat and pale and vision did not recover (right eye: finger counting, left eye: no light perception).
pressure measurement, which is egregiously error-ridden (29). Are these patients suffering from chronic migraine or tension headache and generating falsely high opening pressures because of poorly performed lumbar punctures? Reversal of headache with ICP-lowering treatment in IIHWOP, often used as support for the diagnosis, is not convincing.

Can patients develop optic neuropathy from chronically high ICP if they do not have papilledema?

No. In a series of 20 patients with IIHWOP (28), many had constricted visual fields, but all were judged to be “nonphysiologic,” that is, faked. Apparently, optic neuropathy will not occur unless the optic disc swells to the point of being visible on ophthalmoscopy. Thus, IIHWOP remains an issue of headache, not vision loss.

Can a sudden rise in ICP cause vision loss from optic neuropathy without first causing papilledema?

Such a phenomenon has never been properly documented, but there are hints that it may rarely occur. In a study of the long-term visual outcome in 30 patients with Terson syndrome (30), 2 patients developed optic disc pallor and markedly impaired vision. In those patients, papilledema was not described but may have been hidden behind peripapillary retinal hemorrhages. Although persistent visual loss in Terson syndrome in that series was attributed mostly to epiretinal membrane, cystic maculopathy, or macular hole, a contribution from optic neuropathy may have been overlooked.

I have encountered a patient who developed severe vision loss and optic disc pallor after postpartum dural sinus thrombosis. A retinal specialist had examined the patient several times during the first 14 days after the thrombosis and found no papilledema! I urge my colleagues to look out for this phenomenon and to report it if they come upon it.

Can papilledema linger after ICP has normalized?

Yes. Because papilledema is based on axoplasmic stasis, which is a failure of an energy-dependent metabolic process, it lags not only on the way up but also on the way down.

**FIG. 5.** Nonpapilledematous optic disc swelling in malignant hypertension. A. Bilateral hemorrhagic optic disc edema is evident in these photographs performed with a hand-held camera at presentation in a 14-year-old boy with acute glomerulonephritis. Ophthalmoscopy also disclosed serous retinal detachments and cotton wool spots and Elschng spots. B. Six months after successful treatment, standard fundus photographs show normal-appearing optic discs and small scattered retinal pigment epithelial defects (arrows). Visual fields were normal. (Modified from Besirli et al (47), with permission.)
The attendant visual deficit may linger as well. As a consequence, errors in patient management may occur, and I have made them.

For example, a young man developed transient obscurations of vision in the left eye and had asymmetric optic disc elevation and nerve fiber bundle visual field loss worse in the symptomatic eye. MRI showed triventriculomegaly from aqueductal stenosis owing to a presumed low-grade tectal astrocytoma. The patient underwent third ventriculostomy. Three weeks after the procedure, the visual obscurations had ceased, but the papilledema was unchanged and the visual fields had only slightly improved. I suggested that the ventriculostomy had failed and recommended ICP monitoring. It was normal. Eight weeks later, the papilledema and visual fields had finally recovered. The correct diagnosis, which had eluded me, was prompt resolution of high ICP and delayed resolution of papilledema.

In many cases, papilledema never goes away—even months after ICP has normalized. A 40-year-old woman shunted for hydrocephalus in infancy had undergone several shunt revisions for recurrent headache. She came under my care for a new headache with features similar to those that had triggered previous shunt revisions. Visual acuity was normal, visual fields were unreliable, and optic discs showed mild elevation. A thorough evaluation showed no new ventricular enlargement, a functioning shunt reservoir, and a normal opening pressure and normal CSF formula on lumbar puncture. Six weeks later, the optic discs were unchanged and visual function remained normal. The diagnosis was residual optic disc elevation, perhaps related to surface gliosis but not to high ICP. She was treated symptomatically for headache and improved.

Can vision loss from optic neuropathy develop after ICP has normalized in patients who previously had papilledema?

Yes. Vision loss from optic neuropathy can develop immediately after ICP has been normalized or months to years later, long after papilledema has disappeared.

The immediate type of visual loss has been amply documented in patients who undergo surgery for brain tumor or CSF diversion for high ICP. Such patients have always had a mixture of optic disc elevation and pallor, together with optic nerve dysfunction, before the decompressive procedure occurred (31). I encountered this sad phenomenon in a 10-year-old boy with hydrocephalus from a suprasellar ganglioglioma who presented with slowly progressive binocular visual loss and best-corrected visual acuities of 20/400 in the right eye and finger counting in the left eye. Visual fields were severely compromised, and optic discs displayed a mixture of elevation and pallor. One day after ventriculoperitoneal shunting and partial tumor removal, visual acuities fell to finger counting in the right eye and no light perception in the left eye. Months later, visual acuity was unchanged and optic discs had flattened and become profoundly pale (Fig. 4).

The explanation for this “postdecompression optic neuropathy” is uncertain. Perhaps tumor decompression and restoration of normal ICP disturb compensatory blood flow to the optic nerve. To prevent this phenomenon, preoperative administration of ICP-lowering medication has been advocated, but its efficacy is unproven (31).

Optic nerve dysfunction can also occur progressively or develop suddenly months to years after decompression, even when ICP is normal (32). For example, an 18-year-old girl...
with chronic optic disc edema and severely compromised visual fields from IIH underwent ventriculoperitoneal shunting under my care. Visual function improved after the shunt and remained stable until 18 months later, when she suddenly lost all vision in 1 eye. Both optic discs were profoundly pale. ICP monitoring was normal, as performed with an intraparenchymal Codman ICP Monitoring System (33). In this delayed form of postdecompression optic neuropathy, I presume that damaged axons are prone to die, much as muscles are in the postpolio syndrome. I know of no effective way to guard against this tragic phenomenon, but I recommend measures to avoid systemic hypotension.

Can we reliably predict who is at risk for irreversible optic neuropathy from papilledema?

No. In one IIH study, the amount of papilledema appeared to be an independent risk factor, as judged by the fact that the eye with the greater amount of papilledema had the worse visual field. But there was poor correlation between the amount of papilledema and the visual field loss (34). Other putative risk factors in IIH, not necessarily independent of each other, are the amount of preexisting optic nerve dysfunction (35), superimposed optic disc atrophic features (35), narrowed retinal arterioles (35), sustained systemic hypertension (16), weight gain, anemia (36), and African American race (37). Transient obscurations of vision and the height of the lumbar puncture opening pressure, which are intuitive risk factor candidates, have not been adequately dispelled as contributory (38).

We lack reliable data on the prevalence of clinically meaningful visual loss in papilledema. Data on this point come entirely from the studies of IIH in referral centers. Reviews of these data affirm that on automated static perimetry, nearly all patients with IIH have visual field defects initially affecting the inferior nasal visual field (39,40). But how often is the visual loss disabling? One

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**FIG. 7.** Detection of papilledema may be critical: decompensated hydrocephalus. A. Axial FLAIR MRI. It shows periependymal capping (arrows) and multiple cavernomas (white arrowheads). Because ventricles were not larger than on MRI performed 1 year earlier, the patient’s symptoms were attributed to mental illness and the ventriculomegaly was considered “compensated.” B. Vision loss became more severe, and ophthalmologic examination showed papilledema. ICP monitoring showed very high ICP. After placement of a ventriculoperitoneal shunt, the patient returned to baseline neurologic and vision status. C. Postoperative MRI shows smaller ventricles. D. Resolution of papilledema. (Modified from Mizrachi et al (50), with permission.)
In common with other studies, I have found that most patients with severe visual loss from papilledema already have advanced visual loss when the papilledema is first detected. Shunts or optic nerve sheath decompressions performed on my patients have nearly always occurred within hours to days of the first clinical encounter!

Among my patients, I have found that severe visual loss from papilledema occurs in 3 groups: 1) Group 1: young women with IIH who have florid and/or atrophic papilledema and severe optic neuropathy at diagnosis, 2) Group 2: children with long-standing obstructive hydrocephalus from aqueductal stenosis or brain tumors who have atrophic papilledema and severe optic neuropathy at diagnosis, and 3) Group 3: children or adults shunted for hydrocephalus in infancy who have not been regularly monitored by ophthalmologists and who eventually appear for consultation when vision fails from chronically high ICP owing to shunt malfunction. Ophthalmoscopy typically discloses atrophic papilledema. In this third group, brain imaging usually does not show ventriculomegaly because shunted hydrocephalus is associated with stiff ventricular walls (43).

Patients in all 3 groups present late because the visual loss of chronic papilledema proceeds silently and because chronic high ICP often causes no headache. Symptoms are ignored by children, dismissed by their parents, or attributed to other causes by their physicians. I recommend intensified instruction in ophthalmoscopy to pediatricians and internists and periodic ophthalmologic examination of patients at high risk for papilledema, such as those with indwelling shunts, tuberous sclerosis (proclivity for obstructing giant cell astrocytomas), and neurofibromatosis (proclivity for meninigiomas).

Can papilledema be reliably distinguished ophthalmoscopically from congenitally elevated optic discs?

No. Although there are reasonable ophthalmoscopic clues to congenitally anomalous optic disc elevation (drusen, dome-shaped elevation, anomalous surface vessels, and clear peripapillary nerve fiber layer), there are many cases in which one simply cannot tell if the optic disc elevation is congenital or acquired. Such diagnostic difficulty should not be surprising, given that anomalous optic discs contain axons that are crowded into small scleral canals (44). Although congenitally elevated optic discs associated with buried drusen can be readily identified by ultrasound or CT, the confusing cases I encounter have minimal optic disc elevation without drusen. Fluorescein angiography and optical coherence tomography probably cannot reliably distinguish minimal papilledema from a congenitally anomalous elevated optic disc (45). If I find no visual field loss or manifestations of a neurologic illness, I perform fundus photography, defer brain imaging, and re-examine for optic disc changes after several months. With this approach, I do not believe that I have overlooked high ICP.
Can papilledema be distinguished from other acquired optic neuropathies?

Not always. Yes, there are some ophthalmoscopic signs that allow a presumptive diagnosis of other types of optic neuropathy, such as segmental and pallid edema in ischemic optic neuropathy, peripapillary telangiectasia in Leber hereditary optic neuropathy, and optociliary shunt vessels in juxtapapillary optic nerve sheath meningioma. But unless these signs are present, an ophthalmoscopic diagnosis of papilledema is difficult. After all, the optic disc edema of all acquired optic neuropathies arises from axoplasmic stasis (19).

Therefore, distinguishing papilledema from other optic neuropathies with optic disc edema is typically based on 2 nonophthalmoscopic criteria: 1) binocular involvement and 2) relatively preserved visual function for the amount of nonatrophic optic disc edema. But these criteria will often fail to make a clear distinction. Papilledema can be monocular. Binocular optic disc edema can occur in inflammatory, ischemic, diabetic, neoplastic, and hypertensive optic neuropathies. Relative preservation of visual function may occur in those conditions. As papilledema becomes chronic, visual dysfunction develops. These facts create clinical errors as follows.

A 30-year-old mildly overweight woman developed blurred vision in both eyes. Both optic discs were mildly swollen, and visual fields showed mild inferior nasal nerve fiber bundle defects. Brain MRI was interpreted as normal. Lumbar puncture showed an opening pressure of 35 cm H2O and a normal cerebrospinal formula. A diagnosis of IIH was made elsewhere, and the patient was treated with acetazolamide. When vision continued to worsen, I examined her and made the same observations, but an orbit-centered MRI showed enhancement of both optic nerves, and a chest CT showed hilar adenopathy. Bronchoscopic biopsy disclosed granulomas. The diagnosis was changed to sarcoidosis, the patient was treated with corticosteroid, and vision gradually recovered. The mistake was interpreting bilateral chronic optic disc elevation as papilledema when it was likely due to inflammation.

The opposite scenario can also occur.

A 20-year-old man with acquired immunodeficiency syndrome developed cryptococcal meningitis, but no opening pressure had been performed on lumbar puncture. He complained of diminished vision in both eyes. Brain imaging showed enhancement of the optic nerves and meninges; there was no ventriculomegaly. On ophthalmoscopy, the optic discs were elevated. The explanation for the visual loss was cryptococcal infiltration of the optic nerves. When vision declined precipitously, he underwent another lumbar puncture that showed a markedly elevated opening pressure. Ventriculoperitoneal shunting improved headache and vision, but as papilledema turned into optic disc pallor, he was left with considerable optic nerve dysfunction. The error was in attributing vision loss entirely to optic nerve infiltration and in not recognizing papilledema as an important contributor.

This last case exemplifies a common situation, namely that optic disc edema may be the result of a mixed mechanism—inflammation of the optic nerve and increased ICP. Such a mixed mechanism often occurs in meningitis, where the optic nerves may be directly attacked and the arachnoid granulations blocked to cause high ICP. In viral meningitis, the high ICP is usually well tolerated, but in bacterial, fungal, protozoal, or neoplastic meningitis, it may be vision threatening, CSF diversion is critical.

Does papilledema occur in malignant hypertension or in hypertensive encephalopathy?

No. This is a common misconception. Optic disc edema certainly occurs in malignant hypertension, but it represents leakage of serum from incompetent optic disc arterioles owing to protective vasoconstriction followed by autoregulatory breakthrough vasodilation (46) (Fig. 5). Vascular leakage from excessive autoregulation underlies hypertensive retinopathy (cotton wool spots, surface hemorrhages, and hard exudates), which is always present if the optic disc is swollen in malignant hypertension (46). The vasogenic edema of malignant hypertension is not enough to cause very high ICP, which occurs only when the brain becomes massively infarcted, a rare phenomenon now that there is earlier intervention with powerful blood pressure-lowering regimens (48,49). But the vasogenic edema may be enough to cause a mild elevation of the opening pressure. Unless the vasogenic edema of malignant hypertension turns into infarction in the optic disc, visual function will be relatively preserved, a feature that will tempt a mistaken impression of papilledema, particularly if the opening pressure is elevated (48).

I have encountered patients who have undergone lumbar puncture prompted by the finding of bilateral optic disc edema in the setting of malignant hypertension. The lumbar puncture has shown an elevated opening pressure and led to ill-advised placement of a ventriculoperitoneal shunt. I suggest that the optic disc edema of malignant hypertension be interpreted as a manifestation of high blood pressure rather than of high ICP. The appropriate intervention is gradual lowering of blood pressure, not CSF diversion or optic nerve sheath fenestration.

Can papilledema be present even if brain imaging shows no clear signs of high ICP?

Yes. The signs that radiologists look for in diagnosing high ICP—enlarged or enlarging ventricles, periependymal signal alteration, sulcal or cisternal obliteration—are not very sensitive to high ICP. First, patients with shunted hydrocephalus typically have stiff ventricular walls that do not expand with pressure (43). Second, patients whose obstruction to CSF outflow is in the arachnoid granulations or dural venous sinuses usually do not develop ventriculomegaly because there is no pressure gradient between the intraventricular and extraventricular spaces (27). Third,
patients with parenchymal edema from head trauma or encephalitis or tight skulls from syndromic craniosynostosis may lack obvious radiologic signs of high ICP. Here is an example of how this issue plays out in clinical practice.

A 39-year-old man who had undergone ventriculoperitoneal shunting at age 12 for hydrocephalus developed new headache and vision loss 27 years later. Although papilledema was noted, shunt malfunction was initially dismissed as a diagnosis because MRI did not show definite signs of high ICP. The shunt was eventually revised, at which time ventricular pressure was very high. Following the revision, papilledema resolved to pallor but the patient had lost a substantial amount of vision (43) (Fig. 6).

Brain ventricles may be dilated yet the ICP is normal, a condition called “compensated hydrocephalus.” If there are no other compelling imaging signs of high ICP, radiologists typically look for an enlargement of ventricular size over time before suspecting high ICP. Here is an example of how imaging can be misleading, and the finding of papilledema can be critical.

A 54-year-old woman developed a confusional state, but her symptoms were disregarded because she carried an earlier diagnosis of bipolar disorder (50). She had undergone brain imaging a year earlier in follow-up of a known diagnosis of Osler-Weber-Rendu disease producing multiple brain cavernomas. Brain MRI showed ventriculomegaly but no change in the ventricular size as compared to an MRI performed a year earlier. The ventriculomegaly was considered compensated. But months later, she became incoherent, complained of blurred vision, and was found to have papilledema. ICP monitoring showed very high ICP. Ventriculoperitoneal shunting restored baseline mental status and normal vision and eliminated papilledema (Fig. 7).

The search for papilledema is especially important in patients who are prone to high ICP because they have an indwelling CSF shunt, a subependymal giant cell astrocytoma in tuberous sclerosis (Fig. 8), chronic granulomatous meningitis, or meningiomatosis. Such patients may be unaware of progressive visual loss from high ICP. Their imaging may be insensitive to high ICP, and their tests of shunt function may be unreliable. Finding papilledema may be vision saving and excluding it may spare them ICP monitoring or needless shunt revision (24–26,43).

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Background: The intensity of downbeat nystagmus (DBN) decreases during the daytime when the head is in upright position.

Objective: This prospective study investigated whether resting in different head positions (upright, supine, prone) modulates the intensity of DBN after resting.

Methods: Eye movements of 9 patients with DBN due to cerebellar (n = 2) or unknown etiology (n = 7) were recorded with video-oculography. Mean slow-phase velocities (SPV) of DBN were determined in the upright position before resting at 9 AM and then after 2 hours (11 AM) and after 4 hours (1 PM) of resting. Whole-body positions during resting were upright, supine, or prone. The effects of all the 3 resting positions were assessed on 3 separate days in each patient.

Results: Before resting (9 AM), the average SPV ranged from 3.05°/s to 3.6°/s on the separate days of measurement. After resting in an upright position, the average SPV at 11 AM and 1 PM was 0.65°/s, which was less (P < 0.05) than after resting in supine (2.1°/s) or prone (2.22°/sec) position.

Conclusion: DBN measured during the daytime in an upright position becomes minimal after the patient has rested upright. The spontaneous decrease of DBN is less pronounced when patients lie down to rest. This indicates a modulation by otolithic input. We recommend that patients with DBN rest in an upright position during the daytime.

Classification of Evidence: This study provides Class II evidence that for patients with DBN, 2 hours of rest in the upright position decreases nystagmus more than 2 hours of rest in the supine or prone positions (relative improvement, 79% upright, 33% supine, and 38% prone; P < 0.05).

The authors measured slow-phase velocity (SPV) of downbeat nystagmus (DBN) before and after 2 hours of resting in the supine, prone, and upright positions. The SPV improved by about 30%–40% after resting in prone and supine positions and by about 80% after resting in the upright position. They did not find a difference between resting in the light or in the dark while upright.

This could be a practical pearl for patients with DBN. They could dramatically improve their DBN by resting in the upright position. I would also ask patients to consider even sleeping in the upright position overnight to see if it resulted in better or longer improvement in nystagmus.

I am disappointed that the authors did not grade subjective patient responses to corroborate their eye movement recordings. Without this data, it is difficult to know how beneficial this truly is.

—Michael S. Lee, MD

This is an interesting finding from the eye movement laboratory. However, I don’t think it translates into useful information for our clinical world. The authors’ suggestion “. . . to advise patients with DBN to rest in an upright position during the day in order to alleviate distressing oscillopsia . . . ” seems premature. First, they don’t report if any patients perceived a symptomatic improvement. Second, we don’t know if the benefit of 4 hours of rest in the upright position persists for any length of time. So, if the patient then gets up and walks 10 feet, is he/she back to baseline? How practical is it to sit upright without moving for hours for a brief benefit? If this truly works, I think some observant patients (e.g., sitting for hours watching a football game on TV) would have figured it out for themselves and would have told us. Let’s consider this as interesting laboratory information that may be a first step toward a strategy for improvement in these patients.

—Mark L. Moster, MD


Objective: Sports-related concussion has received increasing attention as a cause of short- and long-term neurologic symptoms among athletes. The King-Devick (K-D) test is based on the measurement of the speed of rapid number naming (reading aloud single-digit numbers from 3 test cards) and captures impairment of eye movements, attention, language, and other correlates of suboptimal brain function. We investigated the K-D test as a potential rapid sideline screening for concussion in a cohort of boxers and mixed martial arts fighters.

Methods: The K-D test was administered prefight and postfight. The Military Acute Concussion Evaluation
Postfight K-D scores (n = 39 participants) were significantly higher (worse) for those with head trauma during the match (59.1 ± 7.4 vs 41.0 ± 6.7 seconds; P < 0.0001, Wilcoxon rank sum test). Those with loss of consciousness showed the greatest worsening from prefight to postfight. Worse postfight K-D scores (r(s) = −0.79; P = 0.0001) and greater worsening of scores (r(s) = 0.90; P < 0.0001) correlated well with postfight MACE scores. Worsening of K-D scores by ≥5 seconds was a distinguishing characteristic noted only among participants with head trauma. High levels of test-retest reliability were observed (intraclass correlation coefficient, 0.97 [95% confidence interval, 0.90–1.0]).

**Conclusion:** The K-D test is an accurate and reliable method for identifying athletes with head trauma and is a strong candidate rapid sideline screening test for concussion.

The King-Devick (K-D) test is a set of 3 cards filled with numbers that are separated by variable spacing. The test measures how rapidly a person can read all of numbers accurately. The authors measured boxers and mixed martial arts fighters prefight and postfight. Those without head trauma read the cards faster after fight. Fighters with head trauma slowed down by 5 or more seconds on the postfight evaluation. The authors suggest that the K-D test could represent a rapid screening test for concussion.

I see some huge advantages here: 1) The test is easy to take. I believe a 6-year-old athlete could take this test without difficulty. 2) It does not require a lot of training to administer. Many youth sports do not have a neurologist or sports medicine doctor on the sidelines. Lay people could easily administer the K-D test. 3) The outcome is very easy to interpret. Athletes who take more than 5 seconds over the baseline to complete the test require further evaluation. 4) It takes less than 2 minutes to administer, which means an unaffected athlete can get back into the game quickly. However, I see one potential issue with the K-D test. I could envision an athlete in a contact sport purposely slowing down the pregame K-D test time. For instance, let’s suppose a football player slows down his baseline test to 60 seconds. He sustains a head on collision during the game and his second test takes 58 seconds. He passes the K-D test and may not be identified. It might be worth establishing age-matched normal to avoid this.

—Michael S. Lee, MD

In recent years, the awareness of the dangers of sports concussions has grown rapidly. This is beginning to overcome the prior pressures of keeping the athlete in the game at all cost. Professional sports, school organizations, states, and others are developing guidelines for sports injuries, which will translate into better neurologic outcomes for athletes. Having a simple, rapid, and reliable test for concussion, as demonstrated for the K-D test in this article, will make it easier to achieve the task of keeping our athletes safe.

—Mark L. Moster, MD


**Background:** The American Academy of Ophthalmology recommendations for screening of chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy were published in 2002, but improved screening tools and new knowledge about the prevalence of toxicity have appeared in the ensuing years. No treatment exists as yet for this disorder, so it is imperative that patients and their physicians be aware of the best practices for minimizing toxic damage.

**Risk of Toxicity:** New data have shown that the risk of toxicity increases sharply toward 1% after 5 to 7 years of use, or a cumulative dose of 1,000 g, of HCQ. The risk increases further with continued use of the drug.

**Dosage:** The prior recommendation emphasized dosing by weight. However, most patients are routinely given 400 mg of HCQ daily (or 250 mg CQ). This dose is now considered acceptable, except for individuals of short stature, for whom the dose should be determined on the basis of ideal body weight to avoid overdosage.

**Screening Schedule:** A baseline examination is advised for patients starting these drugs to serve as a reference point and to rule out maculopathy, which might be a contraindication to their use. Annual screening should begin after 5 years (or sooner if there are unusual risk factors).

**Screening Tests:** Newer objective tests, such as multifocal electroretinogram (mfERG), spectral-domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF), can be more sensitive than visual fields. It is now recommended that along with 10-2 automated fields, at least one of these procedures be used for routine screening where available. When fields are performed independently, even the most subtle 10-2 field changes should be taken seriously and are an indication for the evaluation by objective testing. Because mfERG testing is an objective test that evaluates function, it may be used in place of visual fields. Amsler grid testing is no longer recommended. Fundus examinations are advised for documentation, but visible bull’s-eye maculopathy is a late change, and the goal of screening is to recognize toxicity at an earlier stage.

**Counseling:** Patients should be aware of the risk of toxicity and the rationale for screening (to detect early changes and minimize visual loss not necessarily to prevent it). The drugs should be stopped if possible when toxicity is recognized or strongly suspected, but this is a decision to be made in conjunction with patients and their medical physicians.

In 2002, the American Academy of Ophthalmology (AAO) published Preferred Practice Patterns to screen for hydroxychloroquine and chloroquine retinal toxicity. In this...
article, the AAO updates these recommendations. While many neuro-ophthalmologists do not spend their time screening for these toxicities, we have all seen patients with unexplained symptoms from hydroxychloroquine retinopathy and I think this represents useful reading.

This evidence-based article notes that Amsler grid, color vision testing, fluorescein angiography, full-field ERG, EOG, and time-domain OCT are NOT helpful because either their yield is low or it catches these patients too late. The authors recommend as the best screening test an automated visual field 10-2 with a white stimulus. Any abnormality at all on the 10-2 is worth reinvestigating for repeatability. Because of the subjective nature of perimetry, the recommendations describe benefits of objective retinal testing. Multifocal ERG (mERG), spectral-domain OCT (SD-OCT), and fundus autofluorescence (FAF) can show evidence of toxicity prior to the onset of visual field loss or in the setting of unreliable field testing.

We as neuro-ophthalmologists should consider these objective tests to help rule in or rule out subtle retinal toxicity, despite a referral from the retinal specialist. The mERG shows paracentral depression of P1 amplitudes with an intact foveal amplitude. SD-OCT shows loss of the inner segment/outer segment junction of the outer retinal layers. Finally, FAF shows an increased autofluorescence in the parfoveal macula.

—Michael S. Lee, MD

This article from the AAO makes a few important points. First, it refers to many patients who have the nonspecific VF changes on the central 10-2 program ignored by the ophthalmologist. Most of the patients who I’ve diagnosed with hydroxychloroquine retinopathy have been conscientiously followed with VFs that have clear progressive “nonspecific defects.”

The second point of importance is that finding a “bull’s-eye maculopathy” on funduscopy is really too late. Two of the 3 last cases I’ve seen were followed by retina specialists who did not make the diagnosis because fundus examination (and in one case time-domain OCT) was normal.

The third point is that patients don’t need screening every 6 months in the beginning when they start the medication. It is okay to wait up to 5 years after the baseline examination.

Having sensitive tests, such as SD-OCT, mERG and FAF, is great. I do have a concern that on further study, mERG may turn out to be too sensitive and would cause us to discontinue the medication in patients who otherwise might benefit and never lose vision from retinal toxicity.

—Mark L. Moster, MD

I would agree with you on your last point. I just saw a patient with a central depression on mERG who is low-risk by all the criteria in this article. She has a couple of nonspecific changes on her visual field, is this an over-call on the toxicity based on mERG or is this the earliest findings of the toxicity?

—Michael S. Lee, MD


Background: Oculopharyngodistal myopathy (OPDM) has been reported as a rare, adult-onset hereditary muscle disease with putative autosomal dominant and autosomal recessive inheritance. Patients with OPDM present with progressive ocular, pharyngeal, and distal limb muscle involvement. The genetic defect causing OPDM has not been elucidated.

Methods: Clinical and genetic findings of 47 patients from 9 unrelated Turkish families diagnosed with OPDM at the Department of Neurology, Istanbul Faculty of Medicine, between 1982 and 2009 were evaluated.

Results: The mean age at the onset was around 22 years. Both autosomal dominant and autosomal recessive traits were observed, without any clear difference in clinical phenotype or severity. The most common initial symptom was ptosis, followed by oropharyngeal symptoms and distal weakness, which started after the fifth disease year. Intrafamilial variability of disease phenotype and severity was notable in the largest autosomal dominant family. Atypical presentations, such as absence of limb weakness in long-term follow-up in 9, proximal predominant weakness in 4, and asymmetric ptosis in 3 patients, were observed. Swallowing difficulty was due to oropharyngeal dysphagia with myopathic origin. Serum creatine kinase levels were slightly increased, and EMG revealed myopathic pattern with occasional myotonic discharges. Myopathologic findings included rimmed and autophagic vacuoles and chronic myopathic changes. Importantly, a considerable proportion of patients developed respiratory muscle weakness while still ambulant. Linkage to the genetic loci for all known muscular dystrophies, and for distal and myofibrillar myopathies, was excluded in the largest autosomal dominant and autosomal recessive OPDM families.

Conclusion: We suggest that OPDM is a clinically and genetically distinct myopathy.

The report by Durmus et al on oculopharyngodistal myopathy (OPDM) is the largest to date and almost triples the world literature on this rare disorder. They characterize 47 patients with this disorder from 9 families. There is phenotypic overlap with oculopharyngeal dystrophy (OPMD), as well as EMG (but not clinical) features of myotonia in these patients, so it is good that the authors have done genetic testing to exclude OPMD, myotonic dystrophy, and most other known muscular dystrophies in these families. The inheritance pattern is either autosomal dominant or autosomal recessive, but in some families, the pattern is not well defined.
With some variability, the following are the important clinical features for the practicing neuro-ophthalmologist:

1. Onset: Most often in 20s and 30s, Men 1.8 as women.
2. First 5 years characterized by ptosis, followed by ophthalmoparesis.
3. After 5 years distal/proximal extremity weakness progresses.
4. Prominent features after 5 years also include severe facial weakness, dysphagia, dyspnea. and vocal cord changes.
5. Limited long-term follow-up revealed 6 disease-related deaths at an average age of 40.

Creatine kinase ranged from normal to 8 times normal. EMG reveals myogenic potentials with myotonia in around half the patients studied. Muscle biopsy reveals myopathic changes with rimmed vacuoles.

For the clinician, distinguishing features from OPMD include earlier onset and progression, prominent ophthalmoparesis, facial weakness, and distal weakness, as well as the lack of autosomal dominant inheritance in some cases.

—Mark L. Moster, MD

I found it interesting that the ophthalmoparesis affected lateral gaze first and more severely in this group with OPDM. Unfortunately, this is a clinical diagnosis and a diagnosis of exclusion—you have to exclude OPMD, myotonic dystrophy 1, and facioscapulohumeral dystrophy via genetic testing. Muscle biopsy possesses no unique characteristic to seal the diagnosis.

—Michael S. Lee, MD


Leber hereditary optic neuropathy, the most frequent mitochondrial disease due to mitochondrial DNA point mutations in complex I, is characterized by the selective degeneration of retinal ganglion cells, leading to optic atrophy and loss of central vision prevalently in young men. The current study investigated the reasons for the higher prevalence of Leber hereditary optic neuropathy in men, exploring the potential compensatory effects of estrogens on mutant cell metabolism. Control and Leber hereditary optic neuropathy osteosarcoma-derived cybrids (11778/ND4, 3460/ND1, and 14484/ND6) were grown in glucose or glucose-free galactose-supplemented medium. After having shown the nuclear and mitochondrial localization of estrogen receptors in cybrids, experiments were carried out by adding 100 nM of 17β-estradiol. In a set of experiments, cells were preincubated with the estrogen receptor antagonist ICI 182780. Leber hereditary optic neuropathy cybrids in galactose medium presented overproduction of reactive oxygen species, which led to decrease in mitochondrial membrane potential, increased apoptotic rate, loss of cell viability, and hyperfragmented mitochondrial morphology compared with control cybrids. Treatment with 17β-estradiol significantly rescued these pathological features and led to the activation of the antioxidant enzyme superoxide dismutase 2. In addition, 17β-estradiol induced the general activation of mitochondrial biogenesis and a small, although significant, improvement in energetic competence. All these effects were estrogen receptor mediated. Finally, we showed that the estrogen receptor β localizes to the mitochondrial network of human retinal ganglion cells. Our results strongly support a metabolic basis for the unexplained male prevalence in Leber hereditary optic neuropathy and hold promises for a therapeutic use for estrogen-like molecules.

LHON has been a baffling illness from many aspects, mainly the explanation of the sudden and sequential onset and the predominant male prevalence. Prior reports have suggested that there may be an X-linked modifying gene that may play a role in the gender prevalence (1). The current study provides evidence for a completely different mechanism for the gender difference, namely, metabolic protection by estrogen.

The study demonstrates the presence of estrogen-beta receptors on mitochondria in retinal ganglion cells. In this study, osteosarcoma-derived cybrids were used. A cybrid is a hybrid cell that combines the nuclear genome from one source with the mitochondrial genome from another source, allowing a dissociation of the contribution of the 2 sources of DNA.

Cybrids bearing the LHON mutation showed overproduction of reactive oxygen species, which led to decreased mitochondrial membrane potential, increased apoptotic rate, loss of cell viability and hyperfragmented mitochondrial morphology. Treatment with 17β estradiol diminished these pathologic features and led to activation of superoxide dismutase 2, an antioxidant enzyme, as well as induced activation of mitochondrial biogenesis and a small improvement in energetic competence. Pretreatment with an estrogen receptor antagonist abolished the beneficial effects of the estradiol.

This is an exciting line of research, which may explain a mysterious difference in sexual prevalence of LHON, but more importantly may give rise to a different treatment strategy, hormonal treatments that may preserve vision in LHON patients at risk.

—Mark L. Moster, MD

This is a very cool study that sets the groundwork for looking at estrogen-like molecules to improve visual prognosis in patients with LHON. The questions that arise include...
which estrogens to use, when and how long to try the estrogen, how to give it, and what kinds of side effects may occur?

—Michael S. Lee, MD


Background: Photophobia is an abnormal sensitivity to light experienced by migraineurs during attacks. The pathophysiology of photophobia is poorly understood. Nevertheless, 2 facts appear to have a link with photophobia: visual cortex hyperexcitability on the one hand and interactions between visual pathway and trigeminal nociception on the other.

Methods: We used H(2)(15)O PET to study photophobia induced by continuous luminous stimulation covering the whole visual field in 8 migraineurs during spontaneous migraine attacks, after headache relief by sumatriptan, and during attack-free interval. The intensity of the luminous stimulation provoking photophobia with subsequent headache enhancement was specifically determined for each patient.

Results: We found that low luminous stimulation (median of 240 Cd/m^2) activated the visual cortex during migraine attacks and after headache relief but not during the attack-free interval. The visual cortex activation was statistically stronger during migraine headache than after pain relief.

Conclusion: These findings suggest that ictal photophobia is linked with a visual cortex hyperexcitability. The mechanism of this cortical hyperexcitability could not be explained only by trigeminal nociception because it persisted after headache relief. We hypothesize that modulation of cortical excitability during migraine attack could be under brainstem nuclei control.

This study used ^15O PET to study the response of the occipital cortex to a light stimulus and showed an increase in blood flow during an attack of migraine without aura. After finding the light intensity required to induce an increase in pain, they used the same intensity to measure blood flow. The findings included that there was an increase in CBF during the migraine as well as 100% decrease in CBF after relief of headache with sumatriptan. This increase occurred even though there was no photophobia or pain after sumatriptan treatment.

The authors deduce that although pain may stimulate the increase in CBF, it cannot be the only cause, since it occurs when the patient became pain free. They also speculate that the findings reflect abnormal brainstem modulation of cortical excitability. However, this is only one plausible explanation.

As the accompanying editorial by Brennan (1) suggests, this study confirms that migraine without aura is a cortical disease not just a brainstem disease. He suggests that prophylaxis is more important than mere pain relief since migraine “is so much more than pain.”

Demonstration of cortical excitability in these patients may help in future treatments in migraine. It would be reasonable to study cortical responses to light stimuli in other populations with photophobia, including those who seem to have nonorganic disease. We may be surprised to find some organic changes in the occipital cortex in these patients.

—Mark L. Moster, MD

I don’t know that this study promotes greater interest in prophylaxis. The authors waited only 10 minutes after pain subsided before performing the PET scan again. Who knows? It may be that the increased CBF is only present for 15–20 minutes after migraine pain resolves. Additionally, I am not aware that the postictal increase in CBF in the occipital lobes is harmful and warrants greater motivation to treat prophylactically.

The brainstem modulation consideration is based on previous work. These same authors (2) published a similar study in which they studied 7 patients with a history of migraine and 7 healthy nonheadache controls. The controls showed no increased in CBF to light stimulation, but if given a painful stimulus in V1 (increased the temperature of a probe until it hurt), then the CBF increased in the primary and secondary visual cortex. The response was exaggerated in migraineurs. This suggests that pain in V1 somehow activates the visual cortex, but it may not be unique to migraine patients.

—Michael S. Lee, MD

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In Memoriam

Joel S. Glaser, MD (1938–2011)

On February 10, 2011, Joel S. Glaser, MD, died at home in Miami after a long illness. The neuro-ophthalmology community had lost one of its most esteemed members.

Dr. Glaser was born in Brooklyn, New York, where his father Benjamin practiced as an eye, ear, nose, and throat medical specialist. His grandparents were Jews who had emigrated half a century earlier from Ukraine and Latvia. During World War II, his father was stationed in an army camp in north Florida, and when the war ended, the family moved to Orlando. The young Glaser first became attracted to medicine as he watched and admired his father, who was largely self-taught in ophthalmology. In an interview for this journal in 2006, he recalled that in the early postwar period, his father was offended by the treatment of black patients, who could not be seated in the same waiting room as white patients. In most medical practices, black patients would wait outside in the hot sun. He defied conventional attitudes by building a comfortable, air-conditioned waiting room for them.

After graduating from high school in 1955, Glaser attended Duke University in Durham, North Carolina. During that time, he majored in Biology and minored in English, deepening an interest in literature as he read Sartre, Baudelaire, and St. Exupery in the original French. He then attended Duke University Medical School. At first he wanted to pursue cardiology, but when that elective was full, he signed up for a rotation with “Red” Smith (aka J. Lawton Smith, MD), a young ophthalmology faculty member who cruised the wards dazzling medical students and residents with his clinical legerdemain. Before starting with Smith, Glaser decided to explore a rotation at the medical school of the University of California-San Francisco (UCSF). He was directed to the office of William F. Hoyt, MD, who, upon hearing that Glaser was about to take an elective with Smith, instantly invited him to spend time with him at the UCSF. Glaser often reflected that his career in neuro-ophthalmology was set in motion by an unavailable cardiology elective and the sporting rivalry of Smith and Hoyt.

Before the elective with Smith was to begin, Smith had accepted a faculty position at the Bascom Palmer Eye Institute (BPEI), University of Miami, and Glaser followed him there. Exposure to the finesse of Smith and other prominent neuro-ophthalmologists in the BPEI faculty, Noble David, MD, and Edward Norton, MD, set him on the path of that subspecialty. He completed his ophthalmology residency at the BPEI and a neuro-ophthalmology fellowship with Hoyt.

The year with Hoyt shaped Glaser. In the 2006 interview, Glaser shared this story:

This was where I learned that it is not what you know, but when you know it. We would make ward rounds on the inpatients . . . Hoyt would ask a question of the group. He would go around the circle, prodding stomachs with an enormously long British direct ophthalmoscope. We stopped to discuss a pale middle-aged man who had visual loss in both eyes. Hoyt asked the trembling assembly: “what is the first test you would do on this man?” The dreaded ophthalmoscope pointed around like the (moving) hands of a clock, and no one seemed to come up with the right answer. Exasperated, Hoyt finally turned to the little medical student—me . . . I had just experienced pituitary tumors with (Lawton) Smith, so I suggested doing “a peripheral field examination”.

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Hoyt beamed! The youngest, least experienced member of the circle had gotten it right. And with the next patient, no one recognized the third nerve misdirection but me. I was made.

Glaser returned in 1970 to the BPEI as a faculty member to begin a distinguished 40-year academic career at a time when that single institution boasted 7 of the most famous neuro-ophthalmologists in the world. He became the chief author of the highly acclaimed textbook *Neuro-Ophthalmology*. The book eventually went into 3 editions. He coauthored more than 120 journal articles, trained more than 50 neuro-ophthalmology fellows, and delivered countless named lectures.

Glaser met his wife Irena in 1977. He became the father of 4 wonderful children, Owen, Larah, Benjamin, and Jacob, and a grandfather to Mayan. In his later years, he found great pleasure in playing the cello in an amateur orchestra.

His fellows—I was one of them—remember him for the breadth of his knowledge, astounding insights, and acerbic wit. His legendary friendship with Norman J. Schatz, MD, with whom he practiced neuro-ophthalmology in Miami for the past 2 decades, sustained him after Irena died. Schatz was with him every day during the months before his death. Together they reminisced about the great medical stories and experiences that made them such terrific doctors and allowed them to have so much fun together.

Joel Glaser brought a profound intellect and an enduring scholarship to the field of neuro-ophthalmology. He infused his professional life with a sweeping knowledge of history and culture. He was a brilliant teacher, a fascinating colleague, and a devoted father. He leaves a lasting legacy.

Jonathan D. Trobe, MD
Magnetic Resonance Findings in the Pregeniculate Visual Pathways in Leber Hereditary Optic Neuropathy

I enjoyed reading the article by van Westen et al entitled “Magnetic resonance findings in the pregeniculate visual pathways in Leber hereditary optic neuropathy” (1). However, I was perplexed by the discussion when the authors indicated that they referenced reports regarding optic nerve MRI abnormalities yet failed to cite 3 articles specifically written to address orbital MRI findings in Leber hereditary optic neuropathy (LHON). One was the first reported case of optic nerve enhancement on orbital MRI in LHON (2), another was a follow-up MRI report of the same patient 4 years later (3), and the third article documented 3 patients with optic nerve and/or chiasmal enhancement in LHON (4). The patients reported by van Westen et al may have had optic nerve enhancement on contrast-enhanced orbital fat-suppressed MRI if they were imaged at presentation instead of 1 month later, as in case 1, or 6 months later, as in case 2. This report by van Westen et al continues to expand the spectrum of neuroimaging findings in patients with LHON.

Michael S. Vaphiades, DO
Departments of Ophthalmology, Neurology and Neurosurgery
University of Alabama, Birmingham, Alabama
vaph@uab.edu

REFERENCES

Reply

We appreciate the comments by Dr. Vaphiades but wish to emphasize that our primary focus was on optic tract changes on MRI in patients with LHON. We also look forward to new MRI findings in this patient population, which will hopefully provide greater insight into this disorder.

Danielle van Westen, MD
Department of Neuroradiology
Center for Medical Imaging and Physiology
Skåne University Hospital
Lund, Sweden

Choroidal Infarction or Cilioretinal Artery Occlusion in the Setting of Elevated Intracranial Pressure Due To Fulminant Idiopathic Intracranial Hypertension?

Lamirel and colleagues (1) recently described a 20-year-old white woman with fulminant idiopathic intracranial hypertension (IIH) and a paracentral scotoma. Color fundus photographs and fluorescein and indocyanine green (ICG) angiography images are shown in the article. An area of whitened retina that also appears as a dark area on the ICG angiogram in the inferior macula is interpreted to be a choroidal filling defect from choroidal infarction responsible for the scotoma.

Careful review shows that the interpretation of the images, and the resultant diagnosis, is likely incorrect. First, the color fundus photograph demonstrates an area of stark retinal whitening. This is most consistent with inner retinal infarction; outer retinal infarction from choroidal ischemia usually has a less dramatically white appearance and is often cream colored. Second, the infarction follows a retinal arteriole emanating from the optic nerve head. This arteriole is most likely responsible for the retinal infarction. The area of noninfarcted retina immediately adjacent and inferior to this artery is not perfused by this vessel and thus not infarcted. On the other hand, the branches from this vessel that project toward the median raphe are surrounded by infarcted retina. The area of whitening corresponds to the area that these vessels perfuse. Third, the hypofluorescence on the ICG corresponds exactly to the area of opacified retina, but does not seem to correlate with any visible (or known) choroidal circulation pattern in this area. Thus, this hypofluorescence is most likely a relative blocking defect. It should also be noted that there is a relative blocking defect from the edematous retina surrounding the optic nerve. The arteriole responsible for the infarction is most likely a cilioretinal artery. A fairly large vessel perfusing part of the macula in this location, with a normal arcade vessel nearby, commonly is a cilioretinal artery. In the fluorescein
angiogram laminar flow phase image, the vessel in question appears to fluoresce more brightly than the other retinal vessels, suggesting that it was perfused earlier in the angiogram, a characteristic of cilioretinal arteries. The ICG angiogram image does not show a definite connection of the artery adjacent to the infarcted retina to the central retinal artery, further suggesting that this is a cilioretinal artery.

The pathophysiology of the cilioretinal artery occlusion in the setting of IIH may be similar to that in the setting of central retinal vein occlusion (CRVO). Hayreh et al (2) postulates that cilioretinal artery occlusion occurs due to increased intraluminal retinal capillary bed pressure resulting from the CRVO. It is possible that in this case presented by Lamirel et al (1), the abnormality is due to a similar pathophysiology, however, initiated by the IIH, due to optic nerve head congestion. Nonetheless, a case of cilioretinal artery occlusion in the setting of fulminant IIH has not been reported before in the literature.

Colin A. McCannel, MD
Department of Ophthalmology, Jules Stein Eye Institute
UCLA Geffen School of Medicine, Los Angeles, California
ccmccannel@sei.ucla.edu

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REFERENCES

Reply

It is indeed possible that the funduscopic appearance observed in our patient with severe papilledema from idiopathic intracranial hypertension might have been related to a cilioretinal artery occlusion rather than choroidal infarction. The distinction between these two entities can be difficult and was raised by our retina specialists when the patient was initially evaluated. However, it was concluded that choroidal infarction was more likely based on careful review of the retinal fluorescein and ICG video angiographies. The retinal arteriole seen on fundus photographs was normally perfused acutely. Nevertheless, as mentioned by Dr. McCannel, the pathophysiology of a cilioretinal artery occlusion would be similar to that of a choroidal infarction in the setting of severe papilledema and would have similar consequences for visual function.

Valérie Biouss, MD
Nancy J. Newman, MD
Emory University School of Medicine
Atlanta, Georgia
vbiouss@emory.edu

Lupus Erythematosus Profundus and Enophthalmos

I read the recent case report of lupus erythematosus profundus (LEP) by Kao et al (1) with a great interest. Kao et al concluded that “LEP should be considered in patients with a characteristic rash and orbital inflammation and may cause acquired enophthalmos.” Indeed, in LEP, lobular lymphocytic infiltration and destruction of subcutaneous fat tissue are common and can occur in any part of body (2). Although ocular involvement in systemic lupus erythematosus is uncommon, Davies and Rao (3) suggested that “aggressive systemic therapy is often needed to control the disease.” This clearly applies to LEP as well since the inflammatory reaction can lead to enophthalmos, as presented in this case.

Viroj Wiwanitkit, MD
Wiwanitkit House, Bangkhae, Bangkok, Thailand
wviroj@yahoo.com

REFERENCES

Reply

We appreciate Dr. Wiwanitkit’s interest in our report. We agree wholeheartedly with his assertion that orbital involvement in lupus profundus may be accompanied by serious consequences but is, fortunately, an uncommon phenomenon. It should be treated in a timely manner and as aggressively as necessary to achieve control of the disease.

Thomas Hwang, MD, PhD
Department of Ophthalmology, Kaiser Permanente
Redwood City, California
Emergencies in Neuro-Ophthalmology: A Case Based Approach

Andrew G. Lee, MD,
Paul W. Brazis, MD,
Mansoor Mughal, MD,
Fabiana Policeni, MD
2010, 184 pp, Hard cover, 18 chapters
ISBN-10: 9814295019
Price: $66.00

Referenced

Intended audience: Ophthalmologists, neurologists, neuro-ophthalmologists, residents, and fellows.

This case-based textbook provides the reader a concise, easy-to-read, and practical resource in the evaluation and treatment of vision-threatening conditions. The case vignettes are compiled from real clinical cases, but the clinical details of each patient have been modified for teaching purposes.

Chapters cover a variety of acute disorders of the afferent and efferent visual system, including painful ptosis, complete ophthalmoplegia with a red eye, homonymous hemianopia, bilateral optic disc edema, isolated sixth nerve palsy, pupil-involved third nerve palsy, and optic disc edema with a macular star figure.

Printed on high-quality paper, there are multiple color photographs of fundus and ocular motility abnormalities, as well as other diagnostic testing included.

Radiology of the Orbit and Visual Pathways

Jonathan J. Dutton, MD, PhD, FACS
2010, 408 pp, Hard cover, 6 chapters
ISBN: 978-1-4377-1151-6
Price: $189.00

Referenced

Intended audience: Radiologists, neurologists, neurosurgeons, neuro-ophthalmologists, residents and fellows.

In this very clinically applicable text, the author, a leader in orbital surgery, offers his expertise regarding CT and MRI imaging of the orbit. From abscess to varices and systemic diseases, this book covers the imaging findings of nearly 130 disorders, most of which involve the anterior visual pathways. Chapters include computed tomography, magnetic resonance imaging, anatomy of the orbit, anatomy of the intracranial visual pathways, radiologic anatomy of the orbit and visual pathways, CT, and MR imaging of visual system lesions.

This atlas-style publication has over 1,100 figures and scans with accompanying text formatted in a concise fashion.

Online access to the contents of this book, including illustrations, can be found at expertconsult.com along with Medline links to references.

Vision Rehabilitation: Multidisciplinary Care of the Patient Following Brain Injury

Penelope S. Suter, OD,
Lisa H. Harvey, OD
2011, 514 pp, Hard cover, 14 chapters
ISBN: 9781439836552
ISBN-10: 1439836558
Price: $89.95

Referenced

Intended audience: Neurologists, neurosurgeons, neuro-ophthalmologists, physical medicine, and rehabilitation specialists.

This multi-authored multidisciplinary in-depth text outlines the clinical and scientific evidence supporting the current diagnostic and treatment strategies in adult brain injury vision rehabilitation.

Chapters cover a variety of disorders, including the approach to vision rehabilitation following brain injury, the use of lenses to improve the quality of life following brain injury, photophobia, light, and color in acquired brain injury, the vestibular system, visual information processing deficits, incorporating vision rehabilitation into the primary care practice, and advocating for your patient in the legal system.

With a 12-page middle section of color illustrations and multiple black-and-white line drawings throughout, this book is an easy and enjoyable read.
The North American Neuro-Ophthalmology Society (NANOS) held its 37th annual meeting at the Fairmount Hotel in downtown Vancouver, British Columbia, Canada. This was the first time in the history of NANOS that the meeting was held in a city rather than in a resort, and the meeting was superbly organized by Janel Fick and Tami Page. The beautiful venue and the wide variety of restaurants and activities drew 368 attendees from 19 countries outside of North America.

We started the Walsh Session on Sunday hosted by the St Louis neuro-ophthalmologists Sophia Chung, MD (Saint Louis University), and Greg VanStavern, MD (Washington University). The invited commentary by the neuroradiologist Aseem Sharma, MD, and neuropathologist Joseph Corbo, MD, PhD, both from Washington University, energized the discussions of interesting cases. Clare Fraser, MD, received the best Walsh Paper award for “Bad Eyes, Bad Walking and Bad Judgment.”

This year’s symposia highlighted motion vision along with facial recognition and amblyopia, current understanding of demyelinating disease, evidence-based neuro-ophthalmic practice, and retinal mimics of optic nerve disease. The hot topics covered included current status of rehabilitation for patients with visual field defects, radiation treatment of skull-based tumors, stem cell research in neuro-ophthalmology, and update on research dealing with retinal prosthetics and artificial vision.

The platform presentations, poster sessions, and poster discussion reflected the exciting research being done by our members, as well as our fellows, residents and students. The following awards were given:

1. Best student presentation by Joyce Ho: “In Vivo Imaging of Murine Experimental Anterior Ischemic Optic Neuropathy.”
2. Best resident presentation by Patrick Yu-Wai Man, MD, PhD: “Efficacy and Safety of Idebenone in Patients With Leber’s Hereditary Optic Neuropathy.”

The optional afternoon sessions highlighted “Getting Your Manuscript Published” by Lanning Kline, MD, and Walter Jay, MD; improving neuro-ophthalmology practice at Skip’s Tips by Richard “Skip” Legge, MD; and increasing effectiveness by using mobile applications, Google sites, Endnote bibliography training, and the NOVEL collection by Nancy Lombardo, Jeanne LeBer, and Ed Fitzgibbon, MD.

The Carlow Young Investigator Award was presented to Y. Joyce Liao, MD, PhD, for “Laser-Assisted Transplantation of Stem Cells into the Adult Eye.”

The 2011 Jacobson lecture featured Kathleen Digre, MD, discussing “Neuro-ophthalmologic Disorders in Pregnancy.”

NANOS honored John Keltner, MD, University of California, Davis, with the Distinguished Service Award—NANOS’ highest honor. Dr. Sadun highlighted Dr. Keltner’s many contributions to NANOS and neuro-ophthalmology (Fig. 1), including his research dealing with visual fields, establishment of a visual field reading center, and accreditation with neuro-ophthalmology fellowships through the Association of University Professors of Ophthalmology.

Kathleen B. Digre, MD
Departments of Ophthalmology and Neurology
University of Utah, Salt Lake City, Utah

Fig. 1. Alfredo Sadun presents John Keltner with the NANOS Distinguished Service Award.

Digre: J Neuro-Ophthalmol 2011; 31: 197

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