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Exceptions that Prove the Rules in Neuro-Ophthalmology

Franz M. Cruz, MD, Kathleen C. Oktavec, MD, MHS, Allison N. McCoy, MD, PhD, Neil R. Miller, MD

Although often misinterpreted in today’s vernacular, the idiom “the exception that proves the rule” should never be disregarded in medicine as it results in a correct, albeit unexpected, diagnosis. From the Latin “exceptio firmat regulam in casibus non exceptis,” the legal interpretation of the idiom emphasizes that the exception to a rule proves the existence of that rule (1). As clinical practice has become increasingly complex, this idiom is ever more important as it compels us to question our decisions and diagnoses when clinical evidence is not always straightforward.

We present 3 guiding principles in neuro-ophthalmology with an illustrative case that violates each principle. These exceptions prove that indeed these rules do exist.

Bitemporal Hemianopia Respecting the Vertical Midline Indicates an Optic Chiasmal Syndrome

Case 1: A 59-year-old hypertensive woman was referred to the neuro-ophthalmology clinic for evaluation of bitemporal visual field defects. On examination, visual acuity with myopic correction was 20/25 in the right eye and 20/20 in the left eye. Color vision using Hardy-Rand-Rittler (HRR) pseudochromatic plates was 10/10 bilaterally. Automated perimetry showed mild but definite bitemporal defects that obeyed the vertical midline (Fig. 1). Kinetic perimetry using a Goldmann perimeter confirmed bitemporal scotomatous field defects (Fig. 2). Pupils were normally reactive to light stimulation; there was no relative afferent pupillary defect in either eye. Slit-lamp biomicroscopy revealed minimal cataracts in both eyes, and intraocular pressures were normal. On opthalmoscopy, there were tilted optic discs with extensive peripapillary nasal and inferior chorioretinal atrophy (Fig. 3). Brain magnetic resonance imaging (MRI) showed a small enhancing lesion involving the left anterior clinoid process, most likely a meningioma, with no chiasmal compression. It also showed bilaterally elongated globes. The patient has been followed for more than 2 years with no changes in her clinical examination, no progression of visual field defects, and no change in the size or shape of the intracranial lesion.

Comment: Visual field defects that respect the vertical meridian usually indicate a neurological process. In the case of bitemporal hemianopia, one must suspect a process compressing or infiltrating the optic chiasm and proceed with neuroimaging (2). Sellar and suprasellar lesions, including pituitary adenoma, meningioma, craniohypophyseal, and aneurysms, are known to produce bitemporal hemianopia. Bitemporal hemianopia is also a finding in tilted disc syndrome, characterized by inferior or inferonasal tilting of the optic disc, segmental hypoplasia and ectasia of the choroid and retinal pigment epithelium, and situs inversus of the retinal vessels (3). The superotemporal visual field defects associated with tilted disc syndrome typically do not respect the vertical midline (4). However, Sowka and Luong (5) have reported a series of 5 patients with tilted disc syndrome and bitemporal field defects that seemingly respected the vertical midline on frequency doubling threshold perimetry. Similar to our patient, neuroimaging in these patients did not show any intrinsic or compressive lesion involving the optic chiasm. These authors suggested repeating the perimetric studies using an alternate device and test strategy that may be more sensitive in detecting neurological field defects. Indeed, manual kinetic
perimetry is superior to automated static perimetry in distinguishing bitemporal hemianopia due to an intracocular process from a neurological disorder (6). Even though a left anterior clinoid lesion was present in our patient, it was not responsible for her bilateral visual field defects; rather, the bitemporal hemianopia was a result of her tilted disc syndrome as opposed to a chiasmal process, making this case an exception that proves the rule.

**FIG. 1.** Case 1. Static perimetry, 24-2 threshold, Swedish Interactive Threshold Algorithm-Standard strategy, gray scale (above) and pattern deviation (below), shows what appears to be clear-cut bitemporal hemianopic defects respecting the vertical midline on the pattern deviation plots.

**FIG. 2.** Case 1. Kinetic perimetry shows bilateral temporal field defects that appear to respect the vertical midline.
Slowly Progressive Unilateral Visual Loss Associated With a Retrobulbar Optic Neuropathy Is Caused by a Compressive Lesion

Case 2: A 33-year-old woman complained of slowly progressive visual loss in her right eye over the previous 4 months. Her medical history was unremarkable, except that 1 year earlier, she had experienced a 3-week period of numbness of her left arm and leg that spontaneously resolved. On examination, her visual acuity was 20/70 in the right eye and 20/15 in the left eye. Color vision using HRR plates was 2/10 in the right eye and 10/10 in the left eye. Automated perimetry revealed a moderate reduction in sensitivity of the right visual field; the field of the left eye was full. There was a right relative afferent pupillary defect. Ocular motility was full, with smooth pursuit and accurate saccades. The patient was orthophoric at distance, near, and in the cardinal positions of gaze. Anterior segment findings and intraocular pressures were normal. The right optic disc was mildly pale; the left optic disc appeared normal. Optical coherence tomography of the peripapillary retinal nerve fiber layer (PRNFL) showed thinning in several sectors in the right fundus, with an average thickness of 84 μm. The thickness of the PRNFL on the left was normal in all but 1 sector, with an average thickness of 102 μm. Brain MRI revealed multiple, ovoid, periventricular white matter lesions on fluid-attenuated inversion recovery images, some of which enhanced after intravenous administration of gadolinium (Fig. 4). A subsequent evaluation that included lumbar puncture established a diagnosis of multiple sclerosis (MS).

Comment: Slowly progressive unilateral visual loss associated with evidence of a retrobulbar optic neuropathy almost always is due to a lesion that compresses the posterior orbital, canalicular, or intracranial portion of the optic nerve (7). A high-quality MRI of the brain and orbit with gadolinium is recommended in such cases. Chronic demyelinating optic neuritis can also cause slowly progressive, painless vision loss in 1 or both eyes in patients with established MS. Nevertheless, it is a diagnosis made only after exclusion of any compressive lesion to the anterior visual pathway and alternative MS mimics (8).

FIG. 3. Case 1. Fundus photographs show extreme tilting of both optic discs with inferonasal chorioretinal atrophy.

FIG. 4. Case 2. Axial (A) and sagittal (B) fluid-attenuated inversion recovery magnetic resonance imaging show multiple white matter lesions in the cerebral hemispheres and corpus callosum, consistent with demyelinating disease.
In rare cases, chronic demyelinating optic neuritis can be the presenting finding in a patient with an underlying neurological disorder (9,10), as was the case in our patient. This patient is an exception to the rule that slowly progressive monocular retrobulbar optic neuropathy is caused by a compressive lesion.

**A Complete Third Nerve Palsy With Sparing of the Pupil Is Never Caused by an Aneurysm**

Case 3: A 65-year-old hypertensive woman reported a 1-month history of complete ptosis of the right upper eyelid (this case has been previously reported [11]). She denied any headache or right orbital pain. On initial examination, the patient had a complete right third nerve palsy (TNP) (Fig. 5). The right eye had full abduction, and there was definite intorsion of the eye when the patient attempted to look down and to the right, indicating intact functions of the sixth and fourth cranial nerves, respectively. Both pupils measured 3 mm in light and 5 mm in darkness, and both constricted briskly to light stimulation. Results of the remainder of the ocular examination were normal. An edrophonium chloride (Tensilon) test resulted in no change in ocular motility, alignment, or ptosis. Topical 10% cocaine hydrochloride

**FIG. 5.** Case 3. External appearance of the patient shows a complete right oculomotor nerve palsy with sparing of the pupil.

**FIG. 6.** Case 3. Contrast-enhanced axial computed tomography (A) and lateral view of cerebral angiogram (B) demonstrate a large basilar tip aneurysm.
drops were placed in both eyes and produced equal dilation of both pupils. The erythrocyte sedimentation rate was normal, and a glucose tolerance test also gave normal results. A diagnosis of presumed ischemic TNP was made, and it was elected to observe the patient at regular intervals.

The patient returned 1 month later (2 months after the onset of ptosis), and repeat examination showed no change. The patient continued to deny headache, pain, or discomfort. Nevertheless, computed tomography was performed, which disclosed a large bilobed mass in the region of the junction of the basilar and posterior cerebral arteries (Fig. 6). A cerebral angiogram revealed an aneurysm measuring 25 mm in diameter originating from the tip of the basilar artery and projecting toward the right side (Fig. 6). The patient subsequently underwent clipping of the aneurysm, at which time, the oculomotor nerve was found to be compressed by the aneurysm. Unfortunately, the patient experienced a postoperative brainstem infarct that resulted in her ultimate demise.

Comment: According to the “rule of the pupil,” isolated complete TNP with pupil sparing in an elderly patient with vasculopathic risk factors is most likely from microvascular infarction of the peripheral nerve. Neuroimaging including angiography usually is not indicated unless there is no improvement in 2–3 months (12,13). However, TNP caused by intradural aneurysms is commonly associated with ipsilateral pupillary abnormality, that is, pupillary dilation and decreased velocity and extent of constriction (14). Although pupil-sparing third nerve palsies caused by aneurysmal compression occasionally occur, they are typically accompanied by incomplete ocular motility deficits. As ocular motility becomes maximally affected, the pupil invariably becomes involved (15,16). This patient violates the rule that intracranial aneurysms never cause a pupil-sparing complete TNP and, thus, is an exception that proves the rule.

In neuro-ophthalmology, as with most fields of medicine, one determines a diagnosis mostly by history and examination. Once evidence is gathered and is shuttled through the various clinical decision algorithms, appropriate ancillary tests are carried out and a final diagnosis is made. As there is no perfect process, clinical judgment remains of critical importance and much of it relies on certain tenets of neuro-ophthalmology.

REFERENCES
Venous Hypertension as the Cause of Intracranial Hypertension in Patients With Transverse Sinus Dural Arteriovenous Fistula

Rebekah M. Ahmed, MBBS(Hons), FRACP, Bryan Khoury, MBBCh, FRANZCR, Mark Wilkinson, MBChB, FRANZCR, Geoffrey D. Parker, MBBS, FRANZCR, G. Michael Halmagyi, MD, FRACP

Abstract: We describe 2 patients with transverse sinus dural arteriovenous fistulas (DAVFs) who presented with headache and papilledema due to intracranial hypertension. It has been proposed, but never proven, that venous hypertension causes the intracranial hypertension in DAVF. The data from our patients support this hypothesis. An additional factor leading to intracranial hypertension could be stenosis of the fellow transverse sinus.

CASE REPORTS

Case 1

A 51-year-old man presented with a 4-month history of left pulsatile tinnitus. He had an easily palpable left occipital artery, a bruit over the left mastoid, and moderately severe, bilateral papilledema. Visual acuity was 20/20 in each eye, and visual fields demonstrated enlarged blind spots without peripheral field constriction. MRA and magnetic resonance venogram (MRV) with auto-triggered elliptic centric ordered (ATECO) sequences (8) (Fig. 1A) showed occlusion of the left transverse and sigmoid sinuses, with an associated DAVF; the occipital artery was dilated and there was subtle cortical venous reflux (Cognard grade IIB) (9). Arteriography (Fig. 1B) confirmed a DAVF of the left transverse sinus with arterial supply from a large transmastoid occipital branch of the external carotid artery, the left middle meningeal artery, the left internal carotid artery via the meningo-hypophyseal trunk, and from both vertebral arteries via suboccipital branches. The left superior sigmoid sinus was severely attenuated with multiple venous channels, suggesting previous thrombosis. Venous sinus pressure measurements were recorded before and after embolization (Table 1).

The patient underwent 2 arterial embolization procedures with Onyx. After the second, a left carotid arteriogram demonstrated no reflux in to cortical veins (Cognard grade IIA).

Five months after embolization, the patient still had papilledema but no longer had tinnitus. Lumbar puncture showed an opening pressure of 350 mm H₂O with normal CSF contents. Arteriography showed no change in the DAVF. Venography demonstrated that the left transverse sinus was occluded, and there was a swollen arachnoid granulation in the right transverse sinus impairing venous flow.
(pressure gradient: 25 mm Hg). Anterior sagittal sinus pressure was elevated at 54 mm Hg.

Six months after arterial embolization, the DAVF was embolized via the right transverse sinus, with 11 hydrocoils placed in the stump of the left transverse sinus (Fig. 1C). Superior sagittal sinus and torcular pressure decreased to 29 mm Hg, and the pressure gradient across the arachnoid granulation of the right transverse sinus decreased to 5 mm Hg. The patient's papilledema resolved.

The most recent venogram documented that venous sinus pressure remained stable with a superior sagittal sinus pressure of 27 mm Hg and a pressure gradient across the right transverse sinus of 7 mm Hg (Table 1). The patient remains well without headache or papilledema.

**Case 2**

An 85-year-old woman with a long history of left pulsatile tinnitus was found to have papilledema. Her visual acuity was 20/30 in each eye, and visual fields showed enlarged blind spots but no peripheral constriction. MRV disclosed a DAVF draining into the left transverse sinus and distal occlusion of the left sigmoid sinus, with no filling of the left internal jugular vein.

Arteriography (Fig. 2A) demonstrated a DAVF involving the left transverse sinus with no cortical reflux, and drainage across the torcular into the right transverse sinus and right internal jugular vein (Cognard grade IIA). Arterial supply was predominantly via the left occipital and middle meningeal branches, with lesser supply via suboccipital and posterior

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**TABLE 1. Venous Sinus Pressures Recorded Before and After Embolization of DAVF of Transverse Sinus**

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Pre-embolization</th>
<th>Post-embolization</th>
<th>Case 2</th>
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<tr>
<td>Mid TS</td>
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<tr>
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<td>Sup. sig. sinus</td>
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<td>21</td>
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<td>14</td>
<td>12</td>
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</tr>
<tr>
<td>Internal jugular</td>
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<td>22</td>
<td>9</td>
<td>11</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Right atrium</td>
<td>17</td>
<td>17</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

*All pressure measurements are expressed in millimeters of mercury.

*Gradient across stenosis.

ASSS, anterior superior sagittal sinus; ATS, anterior transverse sinus; MSSS, mid-superior sagittal sinus; PSSS, posterior superior sagittal sinus; PVS, posterior transverse sinus; sup. sig. sinus, superior sigmoid sinus; inf. sig. sinus, inferior sigmoid sinus.
meningeal branches of the vertebral arteries and meningo-hypophyseal tentorial branches. There was no drainage into the left sigmoid sinus or left jugular vein. Venography demonstrated a narrowing of the right transverse sinus together with rapid inflow of unopacified blood via the fistula. The narrowing was felt to be due to a combination of swelling of an arachnoid granulation and elevated intracranial pressure. Superior sagittal sinus pressure measured 41 mm Hg (Fig. 2B, 2C; Table 1), with an abrupt drop to 15 mm Hg across the narrowed segment of the right transverse sinus (Fig. 2C).

The DAVF was embolized with Onyx via a transarterial approach. Superior sagittal sinus pressure decreased to 21 mm Hg, and the pressure gradient across the stenosis in the right transverse sinus resolved (Table 1). The patient developed a small intracerebral occipital hemorrhage but made a full recovery. Papilledema and pulsatile tinnitus resolved.

Four months later, venography showed normal venous sinus pressures (Table 1) and narrowing of the right transverse sinus had improved (Fig. 2D).

DISCUSSION
It has been proposed that intracranial hypertension in the setting of a transverse sinus DAVF is the result of a decreased pressure gradient in the right transverse sinus. The narrowing and increased intracranial pressure result in a decrease in venous outflow, leading to a higher blood flow and increased pressure in the venous sinuses. This increase in pressure leads to the development of papilledema and pulsatile tinnitus. The embolization of the DAVF resolved the pressure gradient and improved the patient’s symptoms.
CSF absorption secondary to venous hypertension (3,4,10). Our 2 cases support this concept. In our first patient, after embolization, venous pressure remained mildly elevated due to the ongoing arterial supply to the DAVF and narrowing of the right transverse sinus. Yet, treatment was sufficient to resolve the patient’s tinnitus and papilledema. In our second patient, embolization not only terminated flow in the DAVF but also lessened stenosis in the contralateral transverse sinus. Again, the patient’s symptoms resolved as did the papilledema and the venous hypertension.

It has been shown that the lack of even one functioning transverse sinus may lead to venous hypertension and intracranial hypertension (7,11). We propose that this also might be true in transverse sinus DAVFs causing intracranial hypertension, given the findings in our 2 patients.

Adding to the increase in venous pressures was the flow of arterialized blood into the transverse sinuses, leading to further venous hypertension and intracranial hypertension through decreased CSF absorption at the arachnoid villi. By embolizing the DAVFs, the venous hypertension improved, as did the intracranial hypertension and papilledema.

We propose that if a patient has a DAVF of one transverse sinus and the other transverse sinus is functioning, significant venous hypertension and subsequent intracranial hypertension will not develop. Cognard et al (3) in their review of DAVFs leading to intracranial hypertension reported that only 4 of 13 patients had normal venous sinuses. However, the authors did not look for stenosis of the contralateral sinus nor obtain pressure gradient measurements. It was reported that all patients had abnormal cerebral venous flow.

DAVFs with reflux into cortical veins (Cognard type IIB) pose great risk for hemorrhage and focal neurological damage (5). We believe that a DAVF with anterograde flow (Cognard type I) and reflux into the affected sinus (Cognard type IIA) are also not “benign” and may cause venous hypertension with papilledema and potential vision loss. Patients having arteriography for investigation of DAVFs should be considered for venography and manometry. In patients where venous hypertension is identified, especially in the setting of only one functioning transverse sinus, a full ophthalmic evaluation should be performed, including visual acuity, visual fields, and funduscopy. Embolization should be considered if there is any indication of risk of visual loss.

ACKNOWLEDGMENT
Dr Steve Reddel referred the second patient.

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Dural Puncture-Induced Intracranial Hypotension Causing Diplopia

Padmaja Sudhakar, MD, Jonathan D. Trobe, MD, Jeffrey Wesolowski, MD

Background: Diplopia that occurs after an epidural spinal catheter has been placed for pain control has been attributed to sixth nerve palsy nerve palsy induced by intracranial hypotension. There is sparse information about the factors that confound diagnosis in this setting.

Methods: Review of 6 cases examined over a period of 5 years at a single tertiary care medical center.

Results: Six confounders to diagnosis were identified: 1) lack of awareness that an epidural spinal catheter was or had been in place; 2) delayed reporting of diplopia; 3) mild or inapparent ductional deficits; 4) lack of postural headache; 5) clinical features that suggested an alternative diagnosis; 6) neuroimaging features that did not allow exclusion of pachymeningitis.

Conclusion: Clinicians should be aware of features that confound a diagnosis of dural puncture-induced intracranial hypotension as a cause of diplopia in the post-operative period when an epidural pain control system is or has been deployed. If these confounders are recognized and the correct diagnosis is reached, radiologists will be less likely to diagnose pachymeningitis and clinicians will be able to avoid lumbar puncture, which may exacerbate the condition.

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Indwelling spinal epidural catheters offer a generally safe and effective method of providing continuous intraoperative and postoperative analgesia. But considerable skill is involved in proper placement of the catheter. Even in skilled hands, accidental dural puncture may occur, estimated at a frequency of 0.19%–3.6% (1–4).

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The most common enduring complication of accidental dural puncture is “postdural puncture headache” (PDPH), reliably distinguished from other headache only by being more intense upon sitting or standing. Its incidence after dural puncture is estimated at 50%–80% (5,6), and higher when cutting or larger gauge needles are used (7). PDPH is attributed to intracranial hypotension (IH) owing to leakage of cerebrospinal fluid through the dural hole. Because the epidural needles are usually 18-gauge, wider than the 22-gauge needles recommended for lumbar puncture (7), PDPH is likely to be more common after accidental dural puncture than after lumbar puncture.

Brain imaging often displays one or more of the following signs of IH: subdural fluid collection, dural thickening and excessive contrast enhancement, engorged dural venous sinuses or change in sinus configuration, pituitary gland enlargement, and downward displacement of the brainstem (8–16).

The most common neurologic sign associated with PDPH is diplopia, usually caused by sixth nerve palsy, and estimated to occur in no more than 0.25% of dural punctures. The palsy is attributed to tension on the nerve as the brainstem sinks in IH (17). Because epidural pain control systems are used so commonly and IH is relatively rare in this setting, clinicians are apt to overlook IH as the cause of postoperative diplopia, particularly if the ophthalmologic findings are subtle or appear well after the epidural pain catheter has been removed, or if the patient fails to report the postural nature of the headache. If radiologists are not alerted that IH is a consideration, they may not look for its imaging features or incorrectly attribute these features to inflammation.

We describe 6 cases of sixth nerve palsy following presumed dural puncture in epidural pain control systems to highlight confounding features in the diagnosis of IH in this setting. Recognizing these confounders, clinicians and radiologists should be able to reject alternative diagnoses and avoid diagnostic lumbar puncture, which could exacerbate the condition.

METHODS

The January 2006 to December 2011 records of the Neuro-Ophthalmology and Ophthalmology Inpatient Consultation...
Services of the University of Michigan Medical System were searched for patients who had been diagnosed with sixth nerve palsy ultimately attributed to IH associated with an epidural pain control system. At least one characteristic magnetic resonance imaging (MRI) feature of IH had to be present.

Six patients met entry criteria and are the basis of this report. For the purposes of this study, their brain MRIs were re-reviewed by a single neuroradiologist (J.W.), who graded the presence of 4 brain imaging signs of IH: subdural fluid collection, excessively enhancing and thickened pachymeninges, enlarged pituitary gland, and downward displacement of the brainstem (9–16). Each sign was assigned a grade, as follows: 0 = absent, 1 = mild, and 2 = marked. We elected not to include measurement of the size of the dural sinuses because of great normal variability. Investigational review board permission was granted.

CASE REPORTS

Case 1
A 22-year-old man with refractory inflammatory bowel disease reported binocular horizontal diplopia but no headache 9 days after undergoing subtotal colectomy and ileostomy followed by gastrojejunostomy tube placement. Postoperatively, he received an epidural bupivacaine infusion catheter for pain management that was removed 4 days later. He had been treated chronically with prednisone and tacrolimus (Table 1).

He had no other relevant medical history and denied other neuro-ophthalmologic symptoms. Bedside examination disclosed normal visual function. The ocular adnexal examination was normal, but the conjunctiva was hyperemic in both eyes without discharge. There was mild limitation of abduction of the right eye with a slightly incomitant esodeviation. Other aspects of the neuro-ophthalmologic examination were normal.

In the setting of inflammatory bowel disease, the ophthalmologic findings raised a suspicion of orbital inflammatory disease. Brain and orbit MRI showed grade 2 pachymeningeal enhancement and thickening but no other signs of IH (Fig. 1). Because the interpreting neuroradiologist was not informed that an epidural pain catheter had previously been in place, the possibility of an inflammatory or neoplastic cause of the meningeal findings was considered. Following an unsuccessful bedside lumbar puncture, a fluoroscopically guided lumbar puncture yielded fluid at such a slow rate that an opening pressure could not be measured. The cerebrospinal constituents were normal.

Corticosteroid eyedrops were administered for presumed conjunctival inflammation. Within 2 weeks, the diplopia resolved and headache subsided within the next few weeks. Over the next 2 years, no new systemic or neuro-ophthalmologic abnormalities developed.

Case 2
A 38-year-old woman reported binocular horizontal diplopia 6 days after undergoing open biliary cystectomy and cholecystectomy for a recently diagnosed liver cyst. She also described postoperative headache and neck stiffness. As she was bed confined, she could not report whether the headache was postural. A pain management epidural catheter placed immediately after surgery was removed on the fifth postoperative day, and one day later she reported diplopia. In addition, the patient experienced night sweats and a 15-lb weight loss over the previous 6 months (Table 1).

Visual acuity and confrontation visual fields were normal, as were pupil size and reactivity. The left eye had limited abduction while other ductions were normal. The patient had a 20 prism-diopter esotropia in primary gaze, increasing to 30 prism diopeters in left gaze and decreasing to 14 prism-diopters in right gaze. All other aspects of the neuro-ophthalmologic examination were normal.

Brain MRI showed grade 1 pachymeningeal enhancement and grade 1 pituitary enlargement (Fig. 2). Grade 1 bilateral subdural fluid collections, overlooked initially, were detected on later review. In view of the reported weight loss and night sweats, the radiologist could not exclude infectious or neoplastic meningitis as the cause of the MRI findings.

Before lumbar puncture, as the patient became ambulatory, she reported that her headache was postural. With that information, clinicians thought of the epidural pain catheter, presumptively diagnosed IH, and canceled the lumbar puncture.

Two weeks later, her headache resolved, but the left abduction deficit was still present. Five weeks later, the deficit had improved, but she still had esotropia in primary and left gaze.

Case 3
A 21-year-old woman received epidural analgesia for parturition. On the first postpartum day, she developed a severe headache, seizures, and depressed consciousness (Table 1).

Brain computed tomography (CT) revealed a large right subdural hematoma with midline shift requiring emergent craniotomy. Several weeks later, she reported having binocular horizontal diplopia of an uncertain duration. All aspects of the neuro-ophthalmologic examination were normal except for a 14 prism-diopters esotropia in left gaze, consistent with a left sixth nerve palsy. Brain MRI showed grade 1 pachymeningeal enhancement and thickening, grade 2 pituitary gland enlargement, and grade 2 downward displacement of the brainstem consistent with IH (Fig. 3). The patient underwent epidural blood patching and the ocular motor findings gradually resolved.

Case 4
A 36-year-old man presented with horizontal binocular diplopia. Fourteen months earlier, he had undergone excision...
**TABLE 1.** Clinical and neuroimaging features of 6 patients with diplopia and intracranial hypotension

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age/sex</strong></td>
<td>22/M</td>
<td>38/F</td>
<td>21/F</td>
<td>36/M</td>
<td>71/F</td>
<td>35/F</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Colectomy for refractory inflammatory bowel disease</td>
<td>Biliary cystectomy for liver cyst</td>
<td>Normal parturition with epidural analgesia</td>
<td>Vertebrectomy for metastatic skin melanoma, Jackson-Pratt drain</td>
<td>Reduction pneumoplasty for severe emphysema</td>
<td>Ileocecal revision for Crohn disease</td>
</tr>
<tr>
<td><strong>Latency to reporting diplopia</strong></td>
<td>9 days after surgery</td>
<td>5 days after surgery</td>
<td>Uncertain because of clouded sensorium</td>
<td>10 days after surgery</td>
<td>14 days after surgery</td>
<td>6 days after surgery</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>No</td>
<td>Yes, later determined to be postural</td>
<td>Uncertain (clouded consciousness)</td>
<td>Yes, postural</td>
<td>No</td>
<td>Yes, postural</td>
</tr>
<tr>
<td><strong>Brain MRI</strong></td>
<td>Pachymeningeal enhancement and thickening</td>
<td>Subdural fluid collection (initially overlooked)</td>
<td>Pachymeningeal enhancement</td>
<td>Pachymeningeal enhancement and thickening</td>
<td>Pachymeningeal enhancement</td>
<td>Pachymeningeal enhancement and thickening</td>
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<tr>
<td></td>
<td>Pachymeningeal enhancement</td>
<td>Pituitary gland enlargement</td>
<td>Mild pituitary enlargement</td>
<td></td>
<td>Enlarged pituitary gland</td>
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<tr>
<td></td>
<td></td>
<td>Pituitary gland enlargement</td>
<td>Downward displacement of cerebellar tonsils</td>
<td>Mild downward displacement of brainstem</td>
<td>Mild downward displacement of brainstem</td>
<td></td>
</tr>
<tr>
<td><strong>Lumbar puncture</strong></td>
<td>Trickle</td>
<td>Not done</td>
<td>Not done</td>
<td>No fluid emerged (dry tap) from lumbar space; normal CSF from cervical puncture</td>
<td>No fluid obtained due to difficulty positioning patient (dry tap)</td>
<td>Not done</td>
</tr>
<tr>
<td><strong>Clinical confounders</strong></td>
<td>No headache</td>
<td>Diplopia reported 1 day after catheter removed</td>
<td>Following parturition, subdural hemorrhage requiring evacuation</td>
<td>Known metastatic melanoma</td>
<td>No headache</td>
<td>Diplopia reported 4 days after epidural catheter removed</td>
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<tr>
<td></td>
<td>Diplopia reported 5 days after catheter removed</td>
<td>Diplopia reported several weeks after delivery</td>
<td>Diplopia reported 10 days after surgery</td>
<td>Diplopia reported 14 days after surgery</td>
<td>Nearly comitant esodeviation attributed to fusion loss from pain medication</td>
<td>Normal ocular ductions with small comitant esotropia in side gaze</td>
</tr>
<tr>
<td></td>
<td>Red eyes in setting of inflammatory bowel disease suggested orbitopathy</td>
<td></td>
<td></td>
<td></td>
<td>Spinal MRI fluid collection suggested abscess</td>
<td></td>
</tr>
<tr>
<td><strong>Minimal ductional deficit</strong></td>
<td>—</td>
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</tbody>
</table>

MRI, magnetic resonance imaging.
of a malignant melanoma on his upper back. Right axillary lymph node dissection was positive (Table 1).

One year later he developed low back, left hip, anterior thigh, and knee pain. Brain MRI was normal, but MRI of the spine showed T1, T5, L2, and L5 vertebral body lesions suggestive of metastatic melanoma. He underwent L2 partial vertebrectomy, removal of an intraspinal mass, confirmed pathologically as melanoma, and L1-L3 posterior segmental fusion.

On the 10th postoperative day, he reported new binocular horizontal diplopia worse on left gaze and associated with headache exacerbated by sitting up. Neuro-ophthalmological examination was normal apart from mild limitation of abduction of the left eye. He had 6 prism-diopters of esophoria in the primary gaze position, increasing to 18 prism-diopters of esotropia on left gaze and 4 prism-diopters of esophoria on right gaze.

Brain MRI showed grade 2 pachymeningeal enhancement and thickening and grade 2 downward displacement of the brainstem (See Supplemental Digital Content, Figure 1, http://links.lww.com/WNO/A53). Given his history, these findings were interpreted as suggestive of meningeal spread of melanoma. Lumbar puncture yielded no cerebrospinal fluid but fluid was obtained with cervical puncture and had normal constituents. Chest, abdomen, and pelvis CT showed no metastatic lesions.

After these studies had been performed, it became apparent that a Jackson-Pratt drain had been left in the epidural space for 4 days postoperatively. Brain MRI findings were now reinterpreted as consistent with IH. One month later, the patient’s headache and neuro-ophthalmologic findings had resolved.

Case 5
A 71-year-old woman reported the sudden onset of horizontal binocular diplopia on the 14th day following bilateral reduction pneumoplasty for severe emphysema. An epidural pain-control catheter had been in place since the surgery. The patient denied headache, although she had been largely bed-confined. There were no other pertinent symptoms (Table 1).

Bedside neuro-ophthalmic examination disclosed an alert patient with no abnormalities apart from ocular motility and alignment. Ductions were full, but adducting saccades were slower than abducting saccades in both eyes. She described slightly wider separation of diplopic images on side gaze than in primary gaze, that appeared equal in right gaze and left gaze. Measurement of alignment indicated 8 prism-diopters of esotropia in primary gaze position and slightly greater esodeviation in right and left gaze. These findings were consistent with IH.

FIG. 1. Case 1. Postcontrast T1 axial magnetic resonance imaging demonstrates grade 2 pachymeningeal thickening and enhancement (arrows).

FIG. 2. Case 2. A. Postcontrast T1 coronal magnetic resonance imaging discloses grade 1 pachymeningeal enhancement (arrows) and grade 1 subdural effusions (arrowheads). B. Precontrast T1 sagittal image shows grade 1 prominence of the pituitary gland (arrow).
findings were attributed to a break in fusion because of narcotic medication.

Brain MRI showed grade 1 pachymeningeal enhancement but no other findings to suggest IH (See Supplemental Digital Content, Figure 2, http://links.lww.com/WNO/A53). A full spine MRI failed to disclose a cerebrospinal fluid leak. Lumbar puncture yielded normal spinal fluid but an opening pressure was not obtained owing to difficulty positioning the patient without causing discomfort. The epidural catheter was eventually removed. Follow-up examination 2 months later was normal.

Case 6
A 35-year-old woman with Crohn disease underwent ileocecal revision with placement of a mid-thoracic epidural catheter for pain control. On the first postoperative day, she complained of severe headache exacerbated by sitting up. An epidural catheter was removed on the second postoperative day, but the headache worsened and she developed neck discomfort, nausea, and vomiting. She was treated with narcotic analgesics. On the sixth postoperative day, she complained of intermittent diplopia (Table 1). Bedside examination disclosed normal visual acuity and confrontation visual fields, pupils, and funduscopy. She had full ocular ductions, but when fixating on a distant target, she noted diplopia in extremes of lateral gaze. On cover testing, the patient was orthotropic in primary position with 15 prism-diopters of esotropia in right and left gaze.

The patient reported worsening headache with pain extending down her back, together with chills, raising concern for spinal epidural hematoma or abscess. Brain MRI showed grade 2 pachymeningeal enhancement and thickening, grade 2 enlargement of the pituitary gland, and grade 1 downward displacement of the brainstem (See Supplemental Digital Content, Figure 3, http://links.lww.com/WNO/A53). Spine MRI showed an extrathecal fluid collection thought to represent a leak. Neurological examination disclosed no evidence of spinal cord or root compression. On the ninth postoperative day, she underwent a lumbar blood patch procedure. The following day, headache resolved but diplopia persisted.

Two weeks after surgery, the patient had full ocular ductions, with an 18 prism-diopter esotropia in primary and left gaze that increased to 25 prism-diopters on right gaze. Two months after the surgery, the diplopia had disappeared and ocular alignment was normal.

DISCUSSION
These 6 patients reported diplopia days to weeks after implantation of a spinal epidural catheter for postprocedural pain control (Cases 1, 2, 5, 6), postoperative fluid evacuation (Case 4), or following parturition (Case 3). Usually attributed to sixth nerve palsy, diplopia has been amply documented in IH (17–23). This report is distinctive in pointing out the confounding clinical features that delayed diagnosis for the following reasons:

1. Clinicians often did not realize that an epidural catheter had been in place. In some cases, the catheter had long been removed when the diplopia was first reported. When it was still in place, it often was not considered. Case 4 had a Jackson-Pratt epidural drain left in place postoperatively, a device about which clinicians caring for the patient were unfamiliar.

2. The diplopia was not reported immediately after the procedure. The delay ranged from 5 to 14 days, such that clinicians did not consider it a consequence of the procedure. In a comprehensive review of 95 cases of IH-associated sixth nerve palsy, the palsy was found to develop between 1 and 21 days after dural puncture, usually between 4 and 10 days (17).

3. The ocular motor findings were not obvious. The examination was usually at the bedside. Because they were uncomfortable as they were recovering from their procedures, patients could not always cooperate adequately with ocular motility and alignment testing. Ductional
Associated diplopia is nearly always caused by sixth nerve palsy, believed to arise from traction at the petroclival junction, where the sixth cranial nerve is tethered in Dorello canal. The palsy is usually unilateral (80%) (17,20,21,23). Patients range in age from 17 to 69 years and men and women are affected equally. Spontaneous recovery occurs in 90% of patients within 8 months, the majority recovering fully within 3 months. If the palsy is present after 8 months, it will be permanent (17). Epidural blood patch, effective in relieving PDPH, does not alter the recovery of sixth nerve palsy (17).

The consequences of not recognizing the connection between diplopia and IH are a fruitless and perhaps harmful diagnostic work-up that includes lumbar puncture, which in 2 of our patients (Cases 1, 5) led to “dry taps” and in 1 case (Case 4) to an unnecessary and risky cisternal puncture. In the experience of one of the authors (J.D.T.), repeated lumbar puncture in a patient with IH-associated diplopia may convert a partial into a total sixth nerve palsy without recovery. If an epidural pain control system has been used and one or more of the neuroimaging features of IH is present, a presumptive diagnosis of IH as the cause of diplopia can be justified without the need for lumbar puncture confirmation of low intracranial pressure.

REFERENCES


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Spontaneous Cerebrospinal Fluid Otorrhea and Rhinorrhea in Idiopathic Intracranial Hypertension Patients

Eldar Rosenfeld, MD, Gad Dotan, MD, Tali J. Kimchi, MD, Anat Kesler, MD

Background: Spontaneous cerebrospinal fluid (CSF) leakage may occur in patients with normal or increased intracranial pressure (ICP). We describe herein spontaneous CSF leakage as a result of chronic increased ICP in 4 patients with idiopathic intracranial hypertension (IIH). Although rhinorrhea previously has been described in IIH patients, to our knowledge this is the first report of otorrhea in these patients.

Methods: Four patients with spontaneous CSF leakage were examined between 2001 and 2011; 3 presented with rhinorrhea and 1 with otorrhea. Clinical settings and manifestations were analyzed.

Results: All patients were found to have IIH. Three had been diagnosed with IIH several years earlier and had been noncompliant with their medical treatment, whereas in 1 patient, CSF rhinorrhea was the presenting symptom of IIH.

Conclusion: CSF leak is a rare complication in IIH patients. We have shown that rhinorrhea can be the presenting sign in these patients and that rhinorrhea and otorrhea can be a late sign of the disease.

MATERIALS AND METHODS

Medical records, including patient history, examination findings, and neuroimaging results of four IIH patients who developed CSF leaks were reviewed. All patients were treated at the same medical institution and examined by the same neuroophthalmologist (AK). This study was performed in accordance with the principles set out in the Declaration of Helsinki.

CASE REPORTS

Case 1

A 48-year-old Caucasian woman with a body mass index (BMI) of 42 presented with headaches and transient visual obscurations of 2-month duration. Computed tomography (CT) of the brain was normal. For approximately 4 months, she noted a clear fluid discharge from the left nostril and occasionally, after an overnight sleep, her pillow was wet. Evaluation by an otolaryngologist was unremarkable.

Because of persistent headaches, she was sent to a neuroophthalmologist, who found bilateral papilledema on examination. Lumbar puncture (LP) revealed an opening pressure of 280 mm of water, with normal CSF composition. The patient was diagnosed with IIH and was treated with acetazolamide.

Fluid collected from her nostril was found to be positive for beta-2 transferrin. Magnetic resonance imaging (MRI) of the brain revealed an encephalocele descending from the cribriform plate (Fig. 1). The patient underwent an endonasal reconstruction of the bony defect with a nasoseptal flap.

Within 1 week, her symptoms and CSF rhinorrhea resolved. With weight loss (12 kg) and acetazolamide, there was gradual resolution of papilledema.

Case 2

A 35-year-old Caucasian woman with a BMI of 39 had been diagnosed 9 years earlier with IIH. Since then, she had...
been poorly compliant with treatment. She had a history of recurrent sinusitis, and 3 years previously, she experienced 2 episodes of tonic-clonic seizures. At that time, brain CT and computed tomographic venography (CTV) were unremarkable. She had normal visual function but bilateral papilledema.

During routine follow-up, the patient complained of exacerbation of headaches and the appearance of a watery discharge from her nose. CT revealed an eroded cribriform plate, with an encephalocele and CSF in the left nasal cavity. The nasal fluid was positive for beta-2 transferrin.

The patient underwent an endonasal closure of the eroded cribriform plate and was maintained on acetazolamide. CSF rhinorrhea and headache promptly resolved.

Case 3
A 42-year-old Caucasian woman with a BMI of 25 had been diagnosed 4 years earlier with IIH. At that time, she had normal neuroimaging, and on LP, the opening pressure was 270 mm of water. Because of allergic reactions to acetazolamide and topiramate, she was treated with furosemide.

On a follow-up visit, the patient reported a clear fluid discharge from her nose for the past 3 weeks. She had been examined by an otolaryngologist, who found no abnormality and recommended a decongestant nasal spray.

However, her neuro-ophthalmologist had the nasal fluid tested for beta-2 transferrin, and it was found to be present.

While brain CT was unremarkable, MRI revealed CSF leakage in the region of the left cribriform plate. The patient underwent lumboperitoneal shunt surgery, with prompt resolution of CSF rhinorrhea and headaches.

Case 4
A 44-year-old Caucasian woman with a BMI of 33 had undergone gastric bypass surgery 13 years previously. Two years later, she was diagnosed with IIH, following presentation with headaches and bilateral papilledema. At that time, MRI of the brain was normal, and opening pressure on LP was 370 mm of water, with normal CSF constituents. Treatment with acetazolamide was begun.

During follow-up, the patient was noncompliant, often discontinuing her medication and gaining weight. She occasionally complained of tinnitus and transient visual obscurations, but her visual function remained stable. Repeat LPs revealed opening pressures as high as 410 mm of water.

Eleven years after being diagnosed with IIH, the patient began complaining of fullness, pain, and autophonia in the left ear. MRI and magnetic resonance venography did not show any interval changes.

She was examined by an otolaryngologist and was treated with antibiotic drops for mild left otitis. Because of lack of improvement over the next 2 weeks, she was reexamined by the same otolaryngologist, who found fluid and air in her left middle ear, as well as pulsatile movement of the tympanic membrane. Additional neuroimaging studies confirmed a CSF leak into the left middle ear (Fig. 2). Fluid from the ear was collected and was found to contain beta-2 transferrin.

The patient underwent a lumboperitoneal shunt, with resolution of her headaches, autophonia, and the sensation of left ear fullness. During follow-up, she has remained stable.

DISCUSSION
Spontaneous CSF leakage occurs in patients without a history of head trauma, sinus surgery, or craniotomy (1). Such leaks occur with approximately equal frequency in the settings of normal and increased ICP (2).

FIG. 1. Case 1. Coronal T2 MRI shows an encephalocele (arrow) descending from the anterior cranial fossa through the cribriform plate.

FIG. 2. Case 4. A. Coronal T2 MRI demonstrates a small encephalocele (arrow) surrounded by cerebrospinal fluid (arrowhead). B. Coronal reconstructed computed tomography with bone settings reveals dehiscence of the floor of middle cranial fossa (white arrow) overlying the middle ear. The floor of the right middle cranial fossa (black arrow) is intact.
common causes of increased ICP are intracranial tumors, hydrocephalus, and IIH.

Table 1 summarizes previous reports of patients with IIH who developed a CSF leak. Many had received medical therapy, including weight loss, acetazolamide, diuretics, corticosteroids, multiple LPs, and some had undergone a CSF diversion procedure. Once identified, not all had resolution of their CSF leakage following initial surgery.

In addition, there are other reports of patients presenting with a CSF leak, yet the diagnosis of IIH had not been established. These patients had clinical features such as high BMI and neuroimaging abnormalities, including empty sella, making the diagnosis of IIH likely. Most patients experienced CSF rhinorrhea (11–14), a few experienced CSF otorrhea (15,16), some experienced both (17), and other studies did not mention the location of the leak (18,19).

The basic cause of CSF leak is disruption in the arachnoid and dura mater, coupled with an osseous defect, and a CSF pressure gradient that is continuously or intermittently greater than the tensile strength of the disrupted tissue (20). Disruption of the barrier between the sinonasal cavity and the anterior and middle cranial fossae can lead to the discharge of CSF into the nasal cavity. Otorrhea may be serous, serosanguineous, or purulent. Associated symptoms include ear pain, fever, vertigo, tinnitus, and hearing loss. The resulting communication within the central nervous system can lead to a multitude of infectious complications, with significant morbidity, potentially disastrous long-term neurologic deficits, and even death (21).

When serous discharge from the ear or nose is considered to be CSF, the initial diagnostic test is examination of the fluid for the presence of beta-2 transferrin. This is a carbohydrate-free isoform of transferrin produced by cerebral neuro-transaminase from beta-1 transferrin by desialization. This substance is present only in the CSF, perilymph, and vitreous of the eye (22,23).

Localization of the bony defect is the second diagnostic step. High-resolution CT is considered the method of choice for evaluating the bony integrity of the skull base (24). Arachnoid pits, secondary to bony impressions from the arachnoid villi at the base of the skull, are present in 63% of patients with spontaneous CSF leakage (25). The lateral recess of the sphenoid bone and the ethmoid roof are also common sites of skull base dehiscence (26,27).

The initial step in repairing a CSF leak is to lower the ICP, if possible before repair of the site of CSF leakage. Lumboperitoneal or ventriculoperitoneal shunt procedures are generally performed. In some patients, the fistula may not close completely after a shunt procedure, and the patient may be exposed to increased risk of infection because the pressure gradient across the fistula has been reversed. In cases of rhinorrhea where the fistula has not closed and the ICP is controlled by the shunt, surgical repair can be undertaken, either by intracranial and extracranial endoscopic approaches. Extracranial techniques carry reduced morbidity compared to intracranial repair (5,28).

In cases of CSF otorrhea, the tegmen mastoideum and tegmen tympani are the most common locations of middle fossa defects. A craniotomy gives maximum exposure to the entire floor of the middle cranial fossa, including defects adjacent to the zygomatic root and over the internal auditory canal. A transmastoid approach is appropriate for posterior fossa and tegmen mastoideum defects. Successful

<table>
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<tr>
<th>Reference</th>
<th>Patient/Age/Sex</th>
<th>Treatment</th>
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</tr>
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<tr>
<td>Brisman et al (3)</td>
<td>44/F</td>
<td>Craniotomy with bilateral cribriform plate repair</td>
<td>Resolved</td>
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<td>Eljamel and Foy (4)</td>
<td>Patient 1</td>
<td>Craniotomy</td>
<td>Resolved</td>
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<td>Patient 2</td>
<td>L-P shunt</td>
<td>Persistent rhinorrhea</td>
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<td>Tolley and Brookes (5)</td>
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<td>Intermittent CSF rhinorrhea</td>
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<td></td>
<td>34/F</td>
<td>Craniotomy</td>
<td>Resolved</td>
</tr>
<tr>
<td>Camras et al (7)</td>
<td>46/F</td>
<td>VP shunt and craniotomy</td>
<td>Resolved</td>
</tr>
<tr>
<td>Owler et al (8)</td>
<td>38/F</td>
<td>Craniotomy; L-P shunt; right transverse sinus stent</td>
<td>Resolved</td>
</tr>
<tr>
<td>Schlosser et al (9)</td>
<td>Eight patients</td>
<td>Extracranial repair of sinusoidal skull base defect</td>
<td>Resolved</td>
</tr>
<tr>
<td>Suryadevara et al (10)</td>
<td>45/F</td>
<td>Craniotomy, with repair of right cribriform plate</td>
<td>Resolved</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; IIH, intracranial hypertension; L-P, lumboperitoneal; NR, not reported; VP, ventriculoperitoneal.

TABLE 1. Reported cases of spontaneous CSF rhinorrhea in patients with IIH
repair is achieved in most cases using autologous materials and alloplastic bone cement (17).

In conclusion, the clinician should be aware of CSF leak as a rare complication of IIH. Because most patients do not relate a clear fluid discharge from the nose or ear with their IIH, they usually do not provide this information. Initial patient evaluation includes analysis of the fluid discharge for the presence of beta-2 transferrin. Maxillofacial and brain neuro-imaging with CT or MRI is essential, carefully searching for a defect of the skull base. Optimal therapy includes lowering of ICP and surgical repair of the bony defect.

REFERENCES
Visual and Neurological Outcomes Following Endovascular Stenting for Pseudotumor Cerebri Associated With Transverse Sinus Stenosis

Martin G. Radvany, MD, David Solomon, MD, PhD, Satnam Nijjar, MD, Prem S. Subramanian, MD, PhD, Neil R. Miller, MD, Daniele Rigamonti, MD, Ari Blitz, MD, Philippe Gailloud, MD, Abhay Moghekar, MBBS

Background: Pseudotumor cerebri (PTC) is characterized by raised intracranial pressure (ICP) without an identifiable mass, evidence of hydrocephalus, or abnormal cerebrospinal fluid content. In the past, most cases of PTC appeared to have no identifiable etiology, and thus, they were classified as “idiopathic intracranial hypertension” (IIH). Recently, however, a subset of patients with presumed IIH has been found to have evidence of cerebral dural sinus stenoses, particularly involving one or both transverse sinuses (TS). The belief that the stenoses are the cause, rather than an effect of the increased ICP, has led investigators to recommend stenting of the stenosed sinus for the treatment of the condition. We describe detailed visual and neurological outcomes after stenting for PTC associated with hemodynamically significant dural sinus stenosis.

Methods: All patients with PTC had initial neurological, neuro-ophthalmological, and imaging assessments. Regardless of the findings, all were treated with medical therapy. If medical therapy failed and TS stenosis was detected on contrast-enhanced magnetic resonance or computed tomographic venography, catheter cerebral angiography with venous manometry was performed. If a mean pressure gradient (MPG) of 4 mm Hg or greater was present, unilateral transverse sinus stenting was performed.

Results: Twelve patients with PTC and TS stenosis associated with an MPG of ≥4 mm Hg who failed medical therapy were identified. TS stenting significantly decreased the pressure gradient in all cases. Unilateral stenting was sufficient to reduce pressure gradients even when the stenosis was bilateral. At a mean follow-up of 16 months (range, 9–36 months), tinnitus had improved in all patients, and 10 of 12 patients had improvement in visual function. Seven patients had significant improvement in headaches.

Conclusion: In this small series of patients with PTC associated with TS stenosis, endovascular stent placement was generally effective in treating visual dysfunction and tinnitus, although not headaches. The optimum gradient and vascular characteristics amenable for selection of patients for stenting needs further research.

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Pseudotumor cerebri (PTC) is defined as raised intracranial pressure (ICP) without clinical or imaging evidence of space-occupying intracranial pathology and with normal cerebrospinal fluid (CSF) analysis (1,2). A major morbidity of PTC is visual loss caused by prolonged papilledema with secondary optic nerve atrophy, occurring in 10%–20% of patients (2). Debilitating headache is the usual presenting symptom. Oral acetazolamide is the primary medical treatment; however, side effects, such as paresthesias, excessive fatigue, and kidney stones, limit its long-term use (3). Optic nerve sheath fenestration and CSF diversion procedure are potential surgical options (4).

Although some cases of PTC are associated with medication use or systemic inflammatory disorders, the majority of cases have no obvious etiology and are referred to as “idiopathic intracranial hypertension” (IIH). Recently, some patients with IIH have been found to have neuroimaging evidence of stenosis of one or both transverse sinuses (TS) (5). In some of these cases, the stenosis resolves if ICP is lowered and, thus, is thought to be caused by the elevated ICP. In others, the stenosis remains until the affected sinus is mechanically opened by stenting.
suggesting a role for venous outflow obstruction as an etiologic factor in these cases. It is unsettled if this group of patients should be called “idiopathic” or intracranial hypertension secondary to venous sinus stenoses.

To date, most reports of intracranial venous sinus stenting for PTC have documented visual and headache outcomes qualitatively rather than quantitatively (6–11). We report results of stenting in 12 patients with PTC associated with TS stenosis, with quantitative assessment of several aspects of visual and neurological function.

**METHODS**

Institutional Review Board approval was obtained for this study. Between January 2008 and June 2011, a total of 88 adult patients with IIH were screened. All patients satisfied modified Dandy criteria for IIH, were not pregnant, and were not on medications or had medical conditions associated with intracranial hypertension. None of these patients had undergone shunt or bariatric surgery. We evaluated 14 of these patients with evidence of unilateral or bilateral TS stenosis who had failed medical therapy; 12 subsequently underwent stent placement. Medical treatment failure was defined as allergy to acetazolamide, intolerance to escalating doses of this medication, or worsening of papilledema, despite treatment of up to 3,000 mg of acetazolamide daily. Detailed neurological and neuro-ophthalmological evaluations were obtained before and after the treatment. Neurological assessment included a detailed headache history and examination to exclude other causes of PTC and lumbar puncture. Opening pressure was measured with the patient in the left lateral decubitus position with hips and knees extended and head neutral. Neuro-ophthalmological assessment included measurement of visual acuity, color vision using Hardy-Rand-Rittler pseudoisochromatic plates, automated visual field testing, and funduscopic examination with grading of papilledema according to the Frisén classification (12). For the purpose of analysis, visual acuity results were converted to logarithm of the minimal angle of resolution units. Headache intensity was assessed using the Headache Impact Test-6 (HIT-6) score (13). Improvement in headache was defined as a decrease in the HIT-6 score of 1 standard deviation (10 points).

After review by a multidisciplinary team, including neurologists, neurosurgeons, neuro-ophtalmologists, and interventional neuroradiologists, these patients were offered optic nerve sheath fenestration, a CSF diversion procedure, or TS stent on an off-label basis. Informed consent was obtained from all patients.

All patients had magnetic resonance imaging of the brain and magnetic resonance venography (MRV) with contrast. The neuroradiologist reviewed the raw data in multiple planes and performed 3-dimensional rendering (Webspace; Siemens, Erlangen, Germany).

Once the patient chose stent placement, the diagnosis of TS stenosis was confirmed with computed tomographic venography (CTV) using a 320 detector computed tomographic scanner (Aquilion; Toshiba, Tustin, CA). CTV was chosen to confirm the diagnosis because of our experience of overestimating stenosis with MRV (unpublished data, Gailloud 2012). In 6 of the 12 patients, CTV was performed immediately after the reduction of CSF pressure to <15 cm of water by lumbar puncture. If CTV demonstrated unilateral TS stenosis (Fig. 1), bilateral stenoses, or stenosis of a single dominant TS (contralateral TS, aplastic or absent) that did not resolve with normalization of ICP, the patient was scheduled for cerebral catheter angiography, endovenous pressure measurements, and possible stent placement (Fig. 2A).

Endovascular stent placement was performed when a pressure gradient of at least 4 mm Hg was documented. In the case of bilateral stenoses, the side with the larger gradient was targeted (Fig. 2B). Endovenous pressure measurements were repeated after stenting. Clopidogrel and aspirin, which were initiated 4 days before angiography, were continued for 6 months.

All patients had follow-up appointments for neurological and neuro-ophthalmological evaluations at 6 weeks, 3 months,
6 months, and then every 6 months. Stent patency was evaluated with CTV at 6 months (Fig. 1B) or earlier if a patient had recurrent symptoms. Acetazolamide was continued for 3–6 months after the surgery in those taking it prior to the surgery, and the dose was tapered gradually after assessing response to stenting.

RESULTS

There were 11 female patients and 1 male patient ranging in age from 21 to 55 years (mean age, 39 years) with a mean body mass index of 32.6 kg/m² (range, 27.3–45.7 kg/m²). All patients had headaches and had papilledema. All but 1 had subjective pulsatile tinnitus. A recent lumbar puncture in all patients demonstrated elevated CSF pressures ranging from 29 to 55 cm of water.

Stent insertion was followed by a significant reduction in the trans-stenotic gradient in all 12 patients (Table 1). There were no serious complications after stent placement; however, in 1 patient, the procedure was interrupted after stagnation of contrast was observed in the venous sinus wall that raised concerns for dissection. The patient was discharged after overnight observation and subsequently treated successfully. Two additional patients who underwent catheter venography had no pressure gradient, despite apparent TS stenosis on CTV, and were not stented.

All patients experienced retro-orbital pain ipsilateral to the stent placement immediately after the procedure, which resolved in all cases over a few days. When examined between 6 and 12 weeks following stent placement, 11 of the 12 patients showed improvement in visual function or stable visual function and decreased papilledema. Visual acuity was stable or improved in 22 of 24 eyes, and color vision was stable or improved in 21 of 24 eyes (Table 2). Visual fields improved or remained stable in 19 of 24 eyes, as measured by mean deviation, and there

---

**TABLE 1.** Patient demographics and treatment summary

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)/Sex</th>
<th>Body Mass Index (kg/m²)</th>
<th>Opening Pressure (cm of Water)</th>
<th>Treatment Failure</th>
<th>TS Stented</th>
<th>Gradient (mm Hg)</th>
<th>Gradient After Stent (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37/F</td>
<td>28.1</td>
<td>43</td>
<td>Shunt infected × 2</td>
<td>Right</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>42/F</td>
<td>35.5</td>
<td>35</td>
<td>Intolerant to acetazolamide</td>
<td>Right</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>37/M</td>
<td>35.7</td>
<td>42</td>
<td>Nephrolithiasis</td>
<td>Left</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>36/F</td>
<td>27.3</td>
<td>31</td>
<td>Intolerant to acetazolamide</td>
<td>Right</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>48/F</td>
<td>27.4</td>
<td>44</td>
<td>Intolerant to acetazolamide</td>
<td>Right</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>55/F</td>
<td>32.3</td>
<td>29</td>
<td>Medical treatment failed</td>
<td>Right</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>21/F</td>
<td>29</td>
<td>42</td>
<td>Medical treatment failed</td>
<td>Right</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>33/F</td>
<td>45.7</td>
<td>55</td>
<td>Medical treatment failed</td>
<td>Right</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>44/F</td>
<td>40.2</td>
<td>32</td>
<td>Nephrolithiasis; medical treatment failed</td>
<td>Left</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>51/F</td>
<td>30.3</td>
<td>32</td>
<td>Medical treatment failed</td>
<td>Right</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>34/F</td>
<td>30.9</td>
<td>55</td>
<td>Medical treatment failed</td>
<td>Right</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>25/F</td>
<td>29.2</td>
<td>33</td>
<td>Medical treatment failed</td>
<td>Right</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

*Patients 8 and 11 developed stenosis proximal to the stent.*

F, female; M, male; TS, transverse sinuses.
was resolution of papilledema in 11 of the 12 patients (Table 3).

Only patient 12 had worsening of visual parameters and persistent papilledema following stenting. Patients 8 and 11 developed recurrent papilledema and worsening headaches at 6 months. In both cases, CTV demonstrated a widely patent TS when stented without thrombus formation. However, a new TS stenosis was noted proximal to the stent (Fig. 3). Both patients underwent repeat stenting and had initial resolution of symptoms and signs. Patient 11 had an 8-mm Hg gradient across her right transverse sinus stenosis, and following stenting, she had improvement in visual acuity, visual field, and papilledema. However, at 6-month follow-up, her color vision and visual fields had worsened, although papilledema had resolved. CTV confirmed a patent stent but showed TS stenosis proximal to the stent. The patient underwent ventriculoperitoneal shunt surgery that stabilized her visual function and eliminated her headaches.

Following stenting, headaches resolved completely in 2 patients and improved in 5 but persisted in the remaining 5 patients. On the HIT-6 assessment, 36 is the lowest score obtainable (Table 4). Between 6 and 12 months after TS stenting, all 5 patients with persistent severe headache underwent a lumbar puncture or continuous spinal fluid pressure monitoring, 4 of whom were found to have normal ICP. The fifth patient (patient 8) had a mean pressure of 20 mm Hg (approximately 26 cm of water) for 68 minutes of the 490 minutes that she was monitored.

Tinnitus improved on the stented side in all 11 of the patients in whom it had been present (Table 4), whereas 4 of 7 patients with bilateral tinnitus experienced improvement on both sides.

**DISCUSSION**

Although Johnston and Paterson (14) first proposed venous hypertension as a potential cause of intracranial hypertension in 1974, it was not until 1995 that King et al (15) documented elevated sagittal and proximal transverse sinus pressures in patients with presumed IIH. In 2003, Higgins et al (7) reported a series of 12 patients with IIH associated with dural sinus stenosis, in whom stenting produced variable resolution of papilledema and headache. Although similar results have been reported (6,8–11), there is a lack of uniformity in methods and outcomes in these studies. We undertook a quantitative analysis of neurological and visual function in patients with PTC associated with venous sinus stenosis and a pressure gradient of >4 mm Hg who underwent stenting following unsuccessful medical therapy.

Regarding neurologic findings, headache usually is the presenting symptom in patients with increased ICP. However, all headaches in this setting may not be caused by increased pressure and not resolve despite lowering it to a normal range (16). Our patients who continued to have
headaches despite stenting and normalization of ICP had many features associated with migraine. Of 5 patients in this series who continued to have headaches despite normalization of CSF pressure after stenting, 4 responded to migraine prophylactic medications.

Transient ipsilateral headaches were present immediately after stent placement in all patients. This is not an unexpected finding considering the innervation of the meninges in this location. The intracranial branch of the ophthalmic division of the fifth nerve (tentorial nerve of Arnold) supplies the tentorium, superior surface of the transverse and straight venous sinuses, and the inferior two thirds of the falx cerebri (17).

Pulsatile tinnitus is a common symptom in PTC. In patients with transverse sinus stenosis, it is likely secondary to turbulent flow across the stenotic region, located in proximity to the inner ear. Tinnitus resolved in all our patients on the side ipsilateral to TS stenting. Possibly, the reduction of flow across the contralateral stenotic side also resulted in improved tinnitus in 4 of the 7 patients who presented with bilateral TS stenosis.

The normal gradual drop in intrasinus pressure from the superior sagittal sinus to the internal jugular bulb is 0–3 mm Hg (15), and a threshold of 4 mm Hg gradient has been proposed for stenting (11). Reduction in the TS gradient was achieved in all our patients with a gradient of 4 mm Hg or greater. Two patients developed a new stenosis proximal to the stent, an observation previously described (6,18). We postulate that continued expansion of the sinus by the stent may have caused stenosis adjacent to the treated segment, possibly as a result of the uneven force exerted by the stent on the noncylindrical sinus. Alternatively, with

| TABLE 3. Visual outcomes after transverse sinus stenting: visual fields and papilledema |

<table>
<thead>
<tr>
<th>Patient</th>
<th>MD—Right Eye Pre</th>
<th>MD—Left Eye Pre</th>
<th>Papilledema Grade, Right Eye Pre</th>
<th>Papilledema Grade, Left Eye Pre</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−2.63</td>
<td>−2.19</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>−28.03</td>
<td>0.15</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>−1.75</td>
<td>−1.37</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>−2.35</td>
<td>−2.29</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>−0.83</td>
<td>−0.17</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0.01</td>
<td>−0.51</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>−7.40</td>
<td>−4.33</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>−2.34</td>
<td>−1.70</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>−4.67</td>
<td>−0.57</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>−3.24</td>
<td>−1.18</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>−15.01</td>
<td>−13.04</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>−2.48</td>
<td>−13.24</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

MD, mean deviation; pre, before stenting; post, after stenting; VA, visual acuity.

| TABLE 4. Outcomes of headache and tinnitus following transverse sinus stenting |

<table>
<thead>
<tr>
<th>HiT-6 Score</th>
<th>Tinnitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt</td>
<td>Pre</td>
</tr>
<tr>
<td>1</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
</tr>
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<td>6</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>78</td>
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<tr>
<td>8</td>
<td>69</td>
</tr>
<tr>
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<td>10</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td>64</td>
</tr>
<tr>
<td>12</td>
<td>67</td>
</tr>
</tbody>
</table>

HIT-6 = Headache Impact Test-6; pre, before stenting; post, after stenting.
increased blood flow through the stented transverse sinus, flow may be diverted from the contralateral side leading to lowered intraluminal pressure within the transverse sinus causing it to collapse in the region not supported by the stent (Bernoulli effect) (19).

Rohr et al (20) theorized that there were 2 types of venous sinus stenoses: stenoses caused by elevated ICP narrowing the sinus extrinsically and fixed stenoses in which reduction of CSF pressure would not affect the diameter of the sinus. In 6 patients, we normalized ICP before performing CTV and did not observe resolution of stenosis. One of these patients (patient 11) developed a new stenosis proximal to the stent, and her trans-stenotic gradient was 8 mm Hg. Some patients with lower gradients (patients 2 and 10) responded to stenting. The explanation that these venous sinus stenoses were secondary to extrinsic compression from raised ICP appears unlikely. The dispute about extrinsic venous stenoses caused by intracranial hypertension vs intrinsic stenosis has been extensively debated without clear resolution (21).

We recognize the limitations of our study. Treatment was not standardized or randomized, and the number of patients was small. In addition, only a carefully screened subset of patients who had failed medical therapy was considered for the procedure. Further studies are needed to evaluate patient selection parameters, the long-term efficacy of this technique, and its effectiveness vs CSF diversion procedures.

REFERENCES

Distinguishing Optic Neuritis in Neuromyelitis Optica Spectrum Disease From Multiple Sclerosis: A Novel Magnetic Resonance Imaging Scoring System

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Background: The management of acute optic neuritis differs according to the underlying etiology and techniques which may help with early differential diagnosis are therefore of considerable value.

Objective: We wanted to determine if multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) could be differentiated on the basis of neuroimaging abnormalities of the anterior visual pathways following an episode of optic neuritis.

Methods: Magnetic resonance imaging (MRI) findings of 27 patients diagnosed with MS (n = 15) or NMOSD (n = 12), who presented with acute isolated optic neuritis over a 3-year period, were reviewed retrospectively. The extent and location of inflammation along the anterior visual pathways were analyzed. A novel scoring system was devised, based upon the number of anatomical segments involved.

Results: Patients with NMOSD had a relative risk of 7.5 (confidence interval: 0.3–17.3) of having a score of 4 or more. Only NMOSD patients were found to have a score of 6 or higher. A trend for more posterior involvement of the anterior visual pathways was noted in the NMOSD group.

Conclusion: This pilot study suggests that the MRI-based scoring system described here may aid in distinguishing patients with optic neuritis who have MS vs NMOSD. Visual pathway inflammation in NMOSD patients appears to be more extensive than in MS, mirroring the longitudinally extensive spinal cord lesions found in neuromyelitis optica.

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Acute isolated optic neuritis may be the first manifestation of both multiple sclerosis (MS) and neuromyelitis optica (NMO). The discovery of the aquaporin 4 autoantibody (AQP4-Ab) has provided serological markers to distinguish NMO from MS and led to the description of neuromyelitis optica spectrum disorder (NMOSD) (1,2) (Table 1).

Patients with NMO may experience a long temporal delay after acute optic neuritis before a relapse in the form of transverse myelitis occurs (2). In such cases, an episode of optic neuritis caused by NMO may be indistinguishable clinically from optic neuritis caused by MS. Comparison of brain magnetic resonance imaging (MRI) findings may be limited as Matsushita et al (3) have shown in patients who are seropositive for AQP4-Ab and those with typical MS. However, would MRI of the anterior visual pathways be more useful in distinguishing patients with NMO from MS?

Khanna et al (4) have reported a trend for more posterior lesions within the anterior visual pathways in patients with NMO and chiasmatic involvement occurring only in NMO. They found no significant difference in the length of the inflammatory lesion between the 2 groups.

In this pilot study, we compared the MRI appearance of the anterior visual pathways in acute optic neuritis in NMOSD to MS. We devised a simple scoring system to evaluate 2 aspects of the MR abnormalities: the linear location and thickness of the cross-sectional area (CSA).
METHODS

This was a retrospective pilot study in which the MRI results of 27 patients were studied. Fifteen patients had confirmed MS and 12 patients had NMOSD. All patients presented over a 3-year period with acute isolated optic neuritis and were scanned using a 1.5-tesla or 3.0-tesla scanner during the acute phase (all within 6 weeks of symptom onset). Patients with coexisting neurological or systemic illness causing other visual pathway or brain lesions were excluded.

A diagnosis of NMOSD was given to patients who met established diagnostic criteria (2) (Table 1). Multiple sclerosis was diagnosed according to the revised McDonald criteria (5). All patients were tested for AQP4-Ab. Testing was carried out at the Wetherall Institute of Molecular Medicine, University of Oxford, by a method using the fluorescence immunoprecipitation assay technique described elsewhere (6). Multiple sclerosis patients were all seronegative for AQP4-Ab.

Neuroimaging

The majority of patients had MRI of the anterior visual pathways using standardized clinical protocols, performed on a General Electric Discovery MR450 1.5-tesla MRI unit (GE Healthcare, Waukesha, WI) or Siemens Trio 3-tesla MRI unit (Siemens AG, Erlangen, Germany). As data was collected over several years, some examinations were acquired with other scanners with minor variations in acquisition protocols. All MRIs included coronal T2 fat-suppressed and T1 images of the anterior visual pathways in addition to imaging of the brain and/or spine. Intravenous contrast was used in selected cases.

Imaging parameters for the coronal T2 fat-suppressed sequences were 1) General Electric Discovery MR450 1.5-tesla MRI: fat saturation, echo delay time (TE) 102.0, repetition time (TR) 4983.0, sample averaging (NEX) 3, base resolution 384, field of view (FoV) 18.0, slice thickness 3.0 mm and 2) Siemens Trio 3-tesla MRI: fat saturation, TE 84.0, TR 5020.0, averages 3, base resolution 384, FoV 18.0, slice thickness 2.0 mm.

Imaging parameters for the coronal T1 sequences were 1) General Electric Discovery MR450 1.5-tesla MRI: TE 8.0, TR 597.0, NEX 4, base resolution 256, FoV 18.0, slice thickness 3.0 mm and 2) Siemens Trio 3-tesla MRI: fat saturation, TE 8.2, TR 500.0, averages 2, base resolution 256, FoV 18.0, slice thickness 2.0 mm.

Magnetic resonance images were assessed independently by 2 neuroradiologists (I.D. and M.R.), who were blinded to the patients’ history and diagnosis. A consensus decision was reached in case of disagreement.

Protocol for the Presence of Inflammation

Contrast-enhanced MRI has been reported as the gold standard for the detection of inflammation in the visual pathways (7). In accordance with local hospital protocol, gadolinium was not used in the majority of our cases. Increase in the thickness or CSA of the affected part of the anterior visual pathways occurring during acute optic neuritis was used as an absolute marker for inflammation (8). The presence of optic nerve T2 signal hyperintensity supported the presence of inflammation; it was not considered an absolute marker for inflammation as its persistence following the resolution of acute optic neuritis has been reported (8).

TABLE 1. Features of neuromyelitis optica spectrum disorder

<table>
<thead>
<tr>
<th>NMO</th>
<th>Limited forms of NMO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord lesion detected on MRI)</td>
</tr>
<tr>
<td></td>
<td>Optic neuritis: recurrent or simultaneous bilateral</td>
</tr>
<tr>
<td>Asian optic–spinal MS</td>
<td></td>
</tr>
<tr>
<td>Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease</td>
<td></td>
</tr>
<tr>
<td>Optic neuritis or myelitis associated with brain lesions typical of NMO (hypothalamic, corpus callosal, periventricular, or brainstem)</td>
<td></td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; MS, multiple sclerosis; NMO, neuromyelitis optica.

Adapted from Wingerchuk et al (2).

FIG. 1. Schematic representation of the anterior visual pathways divided into 10 segments.
**Image Analysis**

Anterior visual pathways were divided into 10 segments: orbital, canalicular, and intracranial segments of the left and right optic nerves, the left and right halves of the optic chiasm, and the left and right optic tracts (Fig. 1). T2 fat-suppressed and corresponding T1 sequences were used to assess CSA and T2 signal hyperintensity.

The number of anatomical segments affected by an increase in CSA at any point on the segment was noted in each case. A score of +1 was given for each affected segment, such that...

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**FIG. 2.** Pattern of visual pathway involvement in the neuromyelitis spectrum disease (NMOSD) group (n = 12). Each affected segment is represented by a solid line, and unaffected segments are represented by a dotted line.

**FIG. 3.** Pattern of visual pathway involvement in the multiple sclerosis (MS) group (n = 15). Each affected segment is represented by a solid line, and unaffected segments are represented by a dotted line.
a patient with the involvement of all segments would be given a score of 10. A segment was not required to be thickened along its entire length in order for it to be given a score of +1. The entire anatomical extent of the lesion did not need to be continuous along the extent of positive scoring.

**Statistical Analysis**

Lesion extent scores were compared between MS and NMOSD groups using the Mann–Whitney rank sum test. A *P* value of 5% was used to define statistical significance. The relative risk (RR) of higher scoring was calculated for the 2 groups.

The involvement of each segment was compared between the 2 groups using the 2-tailed Fisher exact test. A *P* value of 5% was used to define statistical significance. The RR of the involvement of each segment for the 2 groups was calculated.

**RESULTS**

Twelve patients were diagnosed with NMOSD and 15 patients with MS. The female to male ratio was 10:2 in the NMOSD group and 11:4 in the MS group. The mean age of patients was 39 years (range 27–51) and 34 years (range 26–42) in the NMOSD group and MS group, respectively. Caucasians comprised 69% of the MS patients and 17% of those with NMOSD. Figures 2 and 3 are schematic illustrations demonstrating the pattern of visual pathway involvement in the NMOSD and MS groups.

**Lesion Extent**

Figure 4 shows the lesion extent scores in optic neuritis patients with NMOSD and MS. Patients with MS demonstrated a mean score of 2.2 (range, 1–5) compared with a mean score of 4.0 (range, 2–7) in NMOSD patients. The difference between the means was statistically significant (*P* = 0.007). The RR of having a lesion extent score 4 in NMOSD vs MS was 7.5 (95% confidence interval: 0.33–17.3). A score of greater than 6 was seen only in patients with NMOSD.

**Lesion Site**

Table 2 shows the frequency of involvement of each site and the RR for NMOSD over MS at each site across the patients within each group. A trend for anterior involvement was seen in MS patients. The RR of segment involvement within the NMOSD group increased with a more posterior location (RR for optic tract involvement = 3.13 vs RR for intracanalicular involvement = 1.25). The number of NMOSD patients with chiasmal involvement was significantly greater than the number of MS patients (*P* = 0.021). Both MS (n = 2) and NMOSD (n = 5) patients displayed bilateral optic chiasmal involvement.

**DISCUSSION**

Our study demonstrates that a novel MRI-based scoring system may help differentiate optic neuritis in patients with NMOSD vs MS. A lesion extent score ≥4 is highly suggestive of NMOSD. Anterior visual pathway inflammation in optic neuritis secondary to NMOSD may mirror the longitudinally extensive spinal cord lesions found in NMO. While lesion distribution was not demonstrably different between NMO and MS patients, predilection was found for...
more posterior segments in NMOSD patients and for more anterior segments in MS. This is consistent with previous reports (4,9). Chiasmal inflammation was more frequent in patients with NMOSD than MS. This is in contrast to the findings of Khanna et al (4), where chiasmal involvement was found exclusively in NMO patients. In that study, the use of smaller sample sizes (NMO: n = 6; MS: n = 11) and differing imaging techniques (exclusive use of 1.5-tesla magnet) may explain these differences.

Our study has a number of limitations including small number of patients and the lack of use of intravenous contrast. The presence of increased CSA as the criterion for assessing the presence of inflammation along the visual pathway may have excluded patients with prior optic atrophy. As this was a pilot study, there was no standard protocol for the time interval between onset of optic neuritis and the time of scanning or examination of visual parameters. Although a trend for more extensive visual pathway inflammation was observed in NMOSD, the degree of inflammation may have been underestimated as corticosteroid therapy was sometimes initiated on patients with NMOSD prior to MRI.

In conclusion, the results of this study suggest that a scoring system based on the findings of MRI of the anterior visual pathways may help to identify the etiology of acute optic neuritis. This has important clinical implications given the differences in evaluation and treatment of patients with NMOSD vs MS.

REFERENCES

Diagnosis of Traumatic Optic Neuropathy: Application of Diffusion Tensor Magnetic Resonance Imaging

Uttam K. Bodanapally, MBBS, Shanmuganathan Kathirkamanathan, MD, Elena Geraymovych, MD, Stuart E. Mirvis, MD, Andrew Y. Choi, MD, Alan B. McMillan, PhD, Jiachen Zhuo, PhD, Robert K. Shin, MD

Background: Using diffusion tensor imaging, we evaluated the directional diffusivities of the optic nerve in patients with traumatic optic neuropathy (TON).

Methods: Our study consisted of 12 patients with unilateral TON, 6 patients with severe traumatic brain injury (comparison group A), and 6 patients with normal conventional brain magnetic resonance imaging (comparison group B). The contralateral optic nerve in patients with TON also was evaluated (comparison group C). Two trauma radiologists, blinded to the clinical diagnosis, independently obtained the directional diffusivities. The intraorbital optic nerve was divided into anterior and posterior segments to evaluate intersegmental differences in directional diffusivities.

Results: The mean axial diffusivity (AD) in both optic nerve segments and the mean diffusivity (ADC) in the posterior segment on the affected side were significantly lower and differentiated subjects with TON from those in comparison groups A and B. Area under the receiver operating characteristic curve was 0.762, 0.746, and 0.737 for posterior AD, anterior AD, and posterior ADC, respectively. The mean AD, mean diffusivity, and radial diffusivity were lower in the affected nerves in comparison to the contralateral nerve (comparison group C), but the values did not reach statistical significance.

Conclusion: Decreased AD and mean diffusivity in the posterior segment of the optic nerve may serve as a biomarker of axonal damage in patients with TON and merits further investigation as a predictor of initial visual acuity and potential visual recovery.

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Traumatic optic neuropathy (TON) is a devastating acute injury of the optic nerve that causes disruption of visual function and leads to lifelong disability. TON is reported to have a high prevalence in young men in their early 30s (1). It is thought that the most common sites of nerve injury are at the foramina of the optic canal, the canalicular segment of the optic nerve, and under the falci-form dural fold (2).

The concept of primary and secondary injury in TON has been proposed by Walsh (3). It is presumed that the primary injury occurs because of irreversible contusion necrosis from shearing of retinal ganglion cell axons at the time of impact. Secondary injury occurs because of destructive postinjury metabolic and biochemical changes, resulting in optic nerve edema within the confines of the inflexible optic canal and exacerbates the ischemia and apoptosis (4).

The diagnosis of TON primarily is based upon clinical findings. Conventional magnetic resonance imaging (MRI) and multidetector computed tomography often have normal optic nerve imaging findings in patients with TON. In their current form, these neuroimaging techniques are unable to consistently demonstrate optic nerve injury. This limitation led us to evaluate functional imaging techniques such as diffusion tensor imaging (DTI) in patients with TON.

The human optic nerve is a white matter tract emanating from ganglion cells located in the retina. Diffusion tensor imaging offers a potential means to evaluate white matter injury. The cylindrical anatomy and symmetry of white matter tracts that run in the optic nerve makes it possible to
obtain directional diffusivities. Such measurements are helpful to predict axonal integrity and myelin disruption. Diffusion tensor imaging measurements are based upon changes in Brownian motion (diffusion) of water in white matter, influenced by barriers presented by axonal membranes and myelin sheaths. This technique measures the preferential directions of water diffusion across multiple spatial directions in the presence of a magnetic gradient. Diffusion of water in tissues is anisotropic (directionally dependent) or isotropic (directionally independent). Fractional anisotropy (FA) measures the fraction of diffusivity that can be ascribed to anisotropic diffusion. A value of 0 is equivalent to diffusion that is same in all directions of 3-dimensional space as occurs in cerebrospinal fluid (CSF), which has no barriers to diffusion. A value of 1 is seen in maximum anisotropy, and diffusion is unidirectional. The architecture of the parallel white matter tracts, and their myelin sheaths facilitate diffusion of water molecules preferentially along the direction of the nerve fibers, hence the FA is closer to a value of 1.

When there is damage to axonal membranes, diffusion at the injury site becomes unrestricted and isotropic, resulting in a decrease in FA value. Axial diffusivity (AD) represents water diffusion parallel to the axon fibers. Axonal injury results in decreased preferential diffusion along the fiber tracts, and AD decreases. Diffusion perpendicular to axonal fibers is denoted as radial diffusivity (RD). Myelin damage results in increased water diffusion in a perpendicular direction and increases RD. Mean diffusivity (ADC) is the average of diffusivities in all the directions. This measurement fails to account for the interfering effects of local barriers and calculates the value as if all the diffusion rates are solely because of Brownian motion. Mean diffusivity decreases in acute injury because of cellular swelling in cytotoxic edema. The intracellular compartment, bounded by cell membranes, organelles, and protein-rich environment, results in restriction of water movement. In addition, the water diffusion in extracellular spaces also becomes more restricted because of cell swelling. Both of these effects result in net decrease in mean diffusivity.

We hypothesize that the directional diffusivity measurements [AD, mean diffusivity (ADC), RD and FA] may detect structural changes within white matter tracts of the optic nerve in patients with TON and provide neuroimaging support for this clinical diagnosis.

METHODS

Our study was compliant with the Health Insurance Portability and Accountability Act, and permission was obtained from our institutional review board. The study was conducted at a level 1 trauma center. The inclusion criteria for this retrospective study were 1) presence of decreased visual acuity associated with relative afferent pupillary defect compatible with clinical diagnosis of TON, 2) history of blunt cranial trauma, 3) acquisition of diffusion tensor images as part of the MRI protocol of the brain (≤15 days after trauma), and 4) age ≥18 years and older, regardless of sex.

Comparison Groups

Comparison group A: 6 age- and sex-matched patients with severe traumatic brain injury (TBI) with postresuscitation Glasgow coma scale (GCS) ≤ 6T (T = tracheal intubation). Comparison group B: 6 age- and sex-matched patients with normal GCS, without relative afferent pupillary defect or abnormalities on conventional MRI sequences, who were scanned for reasons unrelated to head trauma. Comparison group C: contralateral optic nerves in study group patients with unilateral TON.

MRI PROTOCOL AND REGION-OF-INTEREST ANALYSIS

Magnetic Resonance Imaging

All imaging was performed on a 1.5T Avanto scanner (Siemens Medical Solutions, Erlangen, Germany) with parallel imaging capability. For MRI protocol, see Supplemental Digital Content 1, http://links.lww.com/WNO/A77. Diffusion gradients were sensitized in 6 or 12 collinear directions at an effective $b$ value of 1,000 s/mm$^2$.

REGION-OF-INTEREST ANALYSIS

All diffusion data were processed by using Trackvis software (A. A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Boston, MA). Maps of directional diffusivities were calculated using the AFNI tool “3dcalc” (5) automated by a MATLAB script (The Mathworks, Inc, Natick, MA). The region of interest (ROI) was manually placed over the optic nerve on the non–diffusion-weighted ($b_0$) image, which was defined in the axial map and adjusted in the coronal and sagittal images obtained by multiplanar reconstruction using the Trackvis software (Fig. 1). To avoid CSF partial volume artifacts, the ROI mostly included voxels at the center of the optic nerve. The orbital optic nerve was divided into anterior and posterior segments on axial $b_0$ images at approximately 10 mm behind the globe. The division was made to evaluate intersegmental differences in directional diffusivities as the posterior segment is thought to be more prone to injury. Regions of interest were selected independently by 2 radiologists blinded to the clinical status of the patients to include 10–15 voxels longitudinally in each segment. Data were extracted using the AFNI tool “3dROI-stats” to calculate the mean and standard deviation of directional diffusivities, for each respective ROI automated by a MATLAB script. The average of the directional diffusivities obtained from each set of ROIs selected by the 2 radiologists was used for analysis.
Statistical Analysis

Statistical analysis was performed using JMP software (versions 9 and 10; SAS Institute, Cary, NC). Analysis was conducted using Welch t test for unequal variances. For comparisons between each group, Welch t test was used to assess the difference in directional diffusivities for the anterior and posterior segments in the 4 comparison groups. Receiver operating characteristic (ROC) curve analysis was used to evaluate the usefulness of directional diffusivities in the diagnosis of TON. A P value of less than 0.05 was accepted as a statistically significant difference.

RESULTS

Demographics

The ophthalmology database from May 2008 to December 2009 at the University of Maryland Medical Center revealed 44 patients with a diagnosis of TON. Twelve of these 44 patients with unilateral TON were evaluated with DTI and formed the basis of this study. Imaging was performed in these patients for evaluation of associated TBI. Demographic, clinical, and imaging characteristics of the study group and comparison groups are given in Tables 1 and 2.

Group Differences in Directional Diffusivities

Table 3 summarizes the directional diffusivities of the optic nerve in both the anterior and posterior segments using the Welch t test. Each comparison group is correlated separately with the study group.

Low Axial Diffusivity as a Predictor of TON

The mean AD in both the posterior and the anterior segments of the optic nerve differentiated subjects with TON from those without TON in comparison group A (posterior segment, P = 0.012; anterior segment, P = 0.05) and comparison group B (posterior segment, P = 0.036; anterior segment, P = 0.027) (Fig. 2A, B). The mean AD in both the segments on the injury side were lower than in comparison group C, but the values were not statistically significant. Receiver operating characteristic curve analysis for posterior AD determined an area under curve (AUC) of 0.762 and for anterior AD an AUC of 0.746 (see Figures E2 and E3, Supplemental Digital Content 2 and 3, http://links.lww.com/WNO/A69 and http://links.lww.com/WNO/A70).

Low Mean Diffusivity in the Posterior Segment as a Predictor of TON

The mean of mean diffusivity in the posterior segment of the optic nerve differentiated subjects with TON from those without TON in comparison group A (P = 0.012) and comparison group B (P = 0.036) (Fig. 2A, B). The mean AD in both the segments on the injury side were lower than in comparison group C, but the values were not statistically significant. Receiver operating characteristic curve analysis for posterior AD determined an area under curve (AUC) of 0.762 and for anterior AD an AUC of 0.746 (see Figures E2 and E3, Supplemental Digital Content 2 and 3, http://links.lww.com/WNO/A69 and http://links.lww.com/WNO/A70).

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of 0.737 between TON and comparison group A and group B (see Figure E4, Supplemental Digital Content 4, http://links.lww.com/WNO/A71).

**Posterior RD and Anterior Mean Diffusivity**

The mean RD values in the posterior and anterior segments of the affected nerves were lower than the comparison group A and group B showing a trend toward statistical significance (0.05 < P < 0.1).

The mean anterior RD and FA values in both the segments of the nerve showed no significant differences. There were no statistically significant differences in directional diffusivities between the comparison groups A and B.

**DISCUSSION**

The DTI results in our study likely correspond to alteration in optic nerve microstructure and may act as a noninvasive biomarker of axonal damage caused by TON. We found that DTI may help in identifying TON patients with area under ROC curves ranging from 0.737 to 0.762 for the significantly different directional diffusivities (6). The pattern of damage observed in our sample showed anterior–posterior gradient of decrease in mean diffusivity and AD, that is, greater deterioration of diffusion values in the posterior segment of the optic nerve. This is consistent with greater propensity of damage to the posterior segment of the optic nerve near the optic canal.

**TABLE 3. Correlations between diffusion parameters in traumatic optic neuropathy patients and comparison groups**

<table>
<thead>
<tr>
<th>Groups Compared</th>
<th>TON (95% CI), μm²/ms</th>
<th>Group A (95% CI), μm²/ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior AD</td>
<td>2.09 (1.74–2.45)</td>
<td>2.58 (2.45–2.71), P = 0.012</td>
</tr>
<tr>
<td>Anterior AD</td>
<td>2.29 (1.92–2.66)</td>
<td>2.66 (2.55–2.77), P = 0.05</td>
</tr>
<tr>
<td>Posterior ADC</td>
<td>1.41 (1.16–1.66)</td>
<td>1.71 (1.6–1.83), P = 0.027</td>
</tr>
<tr>
<td>Anterior ADC</td>
<td>1.61 (1.34–1.89)</td>
<td>1.85 (1.78–1.92), P = 0.09</td>
</tr>
<tr>
<td>Posterior RD</td>
<td>1.07 (0.86–1.28)</td>
<td>1.28 (1.15–1.41), P = 0.08</td>
</tr>
<tr>
<td>Anterior RD</td>
<td>1.27 (1.03–1.53)</td>
<td>1.44 (1.38–1.51), P = 0.17</td>
</tr>
<tr>
<td>Posterior FA</td>
<td>0.44 (0.37–0.5)</td>
<td>0.45 (0.41–0.49), P = 0.73</td>
</tr>
<tr>
<td>Anterior FA</td>
<td>0.39 (0.33–0.45)</td>
<td>0.4 (0.38–0.42), P = 0.83</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups Compared</th>
<th>Group B (95% CI), μm²/ms</th>
<th>Group C (95% CI), μm²/ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior AD</td>
<td>2.5 (2.31–2.7), P = 0.036</td>
<td>2.25 (2–2.5), P = 0.42</td>
</tr>
<tr>
<td>Anterior AD</td>
<td>2.74 (2.57–2.91), P = 0.027</td>
<td>2.42 (2.12–2.72), P = 0.55</td>
</tr>
<tr>
<td>Posterior ADC</td>
<td>1.71 (1.55–1.86), P = 0.038</td>
<td>1.54 (1.34–1.74), P = 0.38</td>
</tr>
<tr>
<td>Anterior ADC</td>
<td>1.90 (1.76–2.02), P = 0.067</td>
<td>1.7 (1.48–1.91), P = 0.6</td>
</tr>
<tr>
<td>Posterior RD</td>
<td>1.31 (1.17–1.45), P = 0.05</td>
<td>1.18 (0.99–1.38), P = 0.39</td>
</tr>
<tr>
<td>Anterior RD</td>
<td>1.46 (1.35–1.58), P = 0.15</td>
<td>1.34 (1.14–1.53), P = 0.68</td>
</tr>
<tr>
<td>Posterior FA</td>
<td>0.42 (0.4–0.44), P = 0.6</td>
<td>0.43 (0.36–0.49), P = 0.8</td>
</tr>
<tr>
<td>Anterior FA</td>
<td>0.41 (0.39–0.43), P = 0.52</td>
<td>0.4 (0.34–0.47), P = 0.78</td>
</tr>
</tbody>
</table>

Statistically significant differences (P < 0.05) are highlighted in bold.

AD, axial diffusivity; ADC, near diffusivity; CI, confidence interval; FA, fractional anisotropy; RD, radial diffusivity; TON, traumatic optic neuropathy.
Pathological findings in TON include hemorrhage, demyelination, focal necrosis, and axonal damage (7). Closed-space edema, contusion necrosis, and infarction because of vascular thrombosis or spasm have all been implicated from autopsy studies (8). The decrease in axial and mean diffusivity found in our patients with TON could be because of axolemma damage, leading to axonal swelling (9). Axonal swelling also reduces space between neighboring axons, resulting in decreased RD (10). We found a similar reduction in posterior segment RD values although not to the level of statistical significance.

Cytotoxic edema from either contusion or acute ischemia within the optic nerve from vascular thrombosis or spasm also may explain the decrease in radial and mean diffusivity values (10,11). Ischemia alone fails to explain the changes in directional diffusivities in TON. In the affected optic nerve, AD, which is a surrogate for axonal injury, showed a disproportionate decrease in value compared with mean diffusivity and RD values. Hence, a combination of axonal damage because of contusion and nerve ischemia from vascular compression may be a plausible explanation for the diffusion changes in TON.

There were no significant differences in FA values between the comparison groups. This is in contrast to the findings of Yang et al (12) who found a significant decrease in FA value in patients with TON. The same study also reported a significant increase in mean diffusivity values, in contrast to our results. Yang et al explained the increase in mean diffusivity from ischemic demyelination or necrosis of nerve fiber bundles within the short period (mean time from injury to examination, 5.2 days), when in fact acute ischemia should decrease the mean diffusivity values (10,11).

Our observations showed a significant decrease in AD and posterior mean diffusivity values between injured nerve and optic nerves in comparison groups A and B. The reason for a nonstatistically significant reduction in AD and mean diffusivity between the affected optic nerve and the contralateral unaffected nerve in patients with TON remains unclear. Possible explanations include 1) presence of bilateral asymmetric optic nerve injury (13); 2) secondary damage of the contralateral optic nerve from associated TBI, mediated by various toxins released from dying cells resulting in oxidative stress, excitotoxic damage, and apoptosis (14); and 3) secondary transsynaptic degeneration of the contralateral optic nerve, caused by injury to the visual cortex or optic radiations from TBI (15).

A major limitation of our study was that it was retrospective, without a uniform orbital MRI protocol. Other limitations include the small number of patients, the inherent difficulty in imaging the optic nerve because of its size, mobility, and surrounding air in the paranasal sinuses. Interpretation of diffusion tensor anisotropy and selection of ROI were complicated by a variety of factors including artifacts and partial volume averaging, which may have influenced the measured directional diffusivities (10). There were time variations between the injury and acquisition of MRI as some of the patients were critically ill. Although time variations and differences in age and sex may have influenced the results, time to imaging after trauma, age and sex were matched between the groups.

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The authors thank Brigitte Pocta for reviewing the article.

REFERENCES

Pediatric Internuclear Ophthalmoplegia

Jennifer L. Rizzo, MD, Maureen Lloyd, BA, Mary A. O’Hara, MD

Background: Internuclear ophthalmoplegia (INO) is a rare eye movement disorder in the pediatric population.

Methods: We performed a retrospective review at a university-based tertiary referral ophthalmology practice from 2004 to 2012 to identify pediatric patients with INO.

Results: Three patients with INO were identified. Etiologies included high-grade astrocytoma, perinatal hypoxia and neonatal intracerebral hemorrhage. One of our patients, a 2 year-old girl, is the youngest reported case of INO.

Conclusion: While rare, INO in a pediatric patient requires a full neurologic evaluation and careful follow-up to assess eye position and potentially treat amblyopia.


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Internuclear ophthalmoplegia (INO) is a discrete localizing neuro-ophtalmic sign. Lesions in the medial longitudinal fasciculus cause an abduction deficit in the eye on the side of the lesion, with abducting nystagmus in the contralateral eye. INO occurs unilaterally, bilaterally, or in conjunction with other lesions affecting ocular motility (1).

The causes of INO are well delineated in the adult population, with brainstem ischemia and multiple sclerosis comprising approximately three-quarters of cases. Other less common etiologies in adults include trauma, tentorial herniation, infection, tumor, iatrogenic, hemorrhage, and vasculitis. The incidence in men nearly equals that of women (1). Bilateral INO suggests a demyelinating etiology, whereas unilateral INO is more commonly due to a brainstem vascular disease. Approximately half of adult cases of INO resolve within 1 year (2).

In contrast to INO occurring in adults, descriptions of INO in the pediatric population are sparse. We report 3 pediatric patients with INO illustrating the variety of causes of this eye movement disorder in children.

METHODS

A retrospective chart review was performed at the University of California Davis Eye Center to include pediatric patients from birth to 15 years of age. The patients included in the study were those diagnosed with INO, confirmed by clinical findings from 2004 through 2011. A single pediatric ophthalmologist (M.O.H.) examined each patient and made or confirmed the diagnosis of INO. Medical records were examined to collect data and prepare a descriptive case series.

REPORT OF CASES

Patient 1

An 18-month-old Hispanic girl presented to clinic with a history of normal birth. At age 3 days she suffered left-sided posterior intracerebral and subdural hemorrhages of unknown etiology. Her subsequent history included feeding problems requiring a gastric tube, microcephaly, neonatal seizures, and extensive encephalomalacia, particularly on the left side, as detected on magnetic resonance imaging (MRI). Her ophthalmic examination revealed an intermittent exotropia, and a conservative approach with close follow-up was recommended.

The patient returned 6 months later. Visual acuity appeared intact. On right and left gaze she had an exotropia of 20 prism diopters accompanied by limitation of adduction bilaterally with abducting nystagmus in the fellow eye. There was no ptosis, anisocoria, or skew deviation, and the eye movement disorder was consistent with bilateral INO.

The INO improved over the next year. Examination at age 3 years showed an exotropia of 10 prism diopters in primary position. The patient was orthophoric on right gaze and had an exotropia of 20 prism diopters on left gaze. On subsequent examinations over the following year, the INO completely resolved in the left eye, while the right eye continued to demonstrate an adduction deficit with abducting nystagmus in
the left eye. During the course of follow-up, the child was treated for amblyopia of the right eye.

**Patient 2**
A 5-year-old Caucasian boy with a history of prenatal cerebrovascular accident resulting in panhypopituitarism, respiratory distress, and seizures presented with bilateral INO and a compensatory head turn. MRI of the brain (Fig. 1) demonstrated an ectopic bright spot and a hypodeveloped pituitary, without other abnormalities. One year after the initial diagnosis of INO, the patient underwent left eye muscle surgery for exotropia. At age 8 years, he experienced the onset of new seizures and was noted to have a left gaze palsy and V-pattern exotropia. The motility pattern progressed to right gaze palsy, leaving the patient with very little horizontal eye movement. The remainder of the ophthalmic examination was normal. MRI was ordered, but not obtained as the child went into foster care for suspected abuse.

The etiology of the gaze palsy and V-pattern exotropia was never determined. Evaluation was hampered by the patient’s frequent changes in foster care and eventual reestablishment with the maternal family. The child was examined by a neurologist and serologic testing for myasthenia gravis was negative. The V-pattern exotropia did resolve, but the gaze palsies persisted. The child was last seen at age 11 years with no further changes in his ocular motility or evidence of new neurologic findings.

**Patient 3**
A 10-year-old Hispanic boy, with a history of multiple surgical resections and radiation therapy for high-grade astrocytoma of the cerebellum involving the pons and midbrain, presented with bilateral INO. There was limitation of adduction in both eyes with nystagmus of the contralateral eye on abduction. He had limitation of upgaze and gaze-evoked nystagmus in both vertical directions. There was no evidence of ptosis or skew deviation. Four years later, he required a ventriculoperitoneal shunt for obstructive hydrocephalus but his bilateral INO remained unchanged.

**DISCUSSION**
INO occurs rarely in childhood. Previously, the youngest reported patient with INO was a 3-year-old boy with a benign aqueductal cyst causing hydrocephalus and bilateral INO after placement of an external ventricular drain (3). Surgery was undertaken to open the cyst and restore cerebrospinal fluid drainage with resolution of the INO within 14 days.

Neoplasms of the brainstem causing INO were reported in 6 pediatric patients (ages: 4–17 years) by Cogan and Wray (4). Four occurred in the first decade of life, and 2 occurred in the second decade. Two of the patients had unilateral INO, 2 had bilateral INO, and 2 had one-and-a-half syndrome. The tumor types included medulloblastoma, glioma, and glioblastoma multiforme. The underlying disease was fatal in 4 patients, one improved, and another remained stable. Sharpe et al (5) described a 6-year-old boy who developed a one-and-a-half syndrome due to a left-sided pontine glioma.

A wide variety of other causes of INO in the pediatric population have been reported. Vascular infarcts in the brainstem associated with INO have been documented in patients with sickle cell trait (6), systemic lupus erythematosus (7), Fabry disease (8), and periarthritis nodosa (9). Additional etiologies of pediatric INO include head trauma (10,11), viral meningoencephalitis (12), iatrogenic embolism from cardiac catheterization (13), and brainstem hemorrhage (14). To the authors’ knowledge, no children with INO due to demyelinating disease have been reported.

All 3 patients in our series had bilateral INOs with different etiologies: hemorrhage, infarction, and tumor. All had multiple eye movement disorders that confounded the diagnosis of INO. One patient, a 2-year-old girl with neonatal intracerebral hemorrhage, experienced improvement with complete resolution of INO in the left eye and partial resolution in the right eye. She is the youngest reported child with INO.

The diagnosis of INO in a young child can be difficult due to the level of cooperation. Because of this, close follow-up and a conservative approach to surgery are appropriate. Treatment for amblyopia is often warranted during the follow-up care of these patients.

**REFERENCES**

Correlation of Inner Retinal Thickness Evaluated by Spectral-Domain Optical Coherence Tomography and Contrast Sensitivity in Parkinson disease

Christopher R. Adam, BA, Eric Shrier, DO, Yin Ding, MS, Sofya Glazman, MD, Ivan Bodis-Wollner, MD, DSc

Background: To compare inner retinal layer (IRL) thickness measured by spectral-domain optical coherence tomography (SD-OCT) and contrast sensitivity (CS) in patients with Parkinson disease (PD) and in healthy control (HC) subjects.

Methods: Consecutive patients with and without PD were prospectively analyzed using SD-OCT and Pelli-Robson CS testing. SD-OCT IRL (ganglion-cell complex) thickness, consisting of the nerve fiber layer, ganglion cell layer, and inner plexiform layer, was segmented using an RTVue Model-RT100 with an EMM5 scan parameter covering a 5.0 x 5.0 mm cube centered on the fovea. Thickness voxel measurements at 0.25-mm intervals at sequential radial distances from the foveola were acquired horizontally and vertically. SD-OCT thickness raw data files were imported and analyzed within MATLAB (version 7.10.0). A database of CS scores and IRL thickness values by foveal location was constructed and statistically evaluated using JMP 10 (SAS Institute, Inc, Cary, NC).

Results: The results were compared between 28 eyes of 14 patients with PD and 28 eyes of 14 HC subjects. Controlling for age, mean CS scores of monocular right and randomized eyes were statistically lower in PD eyes (P < 0.05). IRL was significantly thinner in PD eyes than in HC eyes at several distances from the foveola (P < 0.05). The most numerous and significant thickness differences by diagnosis were located in the superior quadrant at a distance of 1.00–1.75 mm from the foveal center (17 μm; P < 0.01, maximum significant thickness difference and P value). Correlation was demonstrated between monocular CS and IRL thickness by diagnosis at multiple foveal locations for HC eyes as follows: nasal quadrant, 0.75–1.00 mm (P < 0.02); temporal quadrant, 0.50–1.00 mm (P < 0.05); superior quadrant, 1.00 mm (P < 0.05); and inferior quadrant, 1.00 mm (P < 0.03). No significant correlation was found between monocular CS and IRL thickness within PD subjects (P > 0.05 for each foveal location measured).

Conclusion: CS and foveal IRL thickness are decreased in patients with PD. CS and IRL thickness correlated in HC subjects; however, no such correlation was demonstrated in PD. The functional deficit of dopaminergic interneurons, including amacrine cells, may outstrip the anatomic structural changes in the inner retina of PD patients. Inner retinal atrophic changes may underlie the pathogenesis of CS deficit and IRL thinning in PD.

First described as “shaking palsy” in 1817 (1), Parkinson disease (PD) affects more than 1 million people in the United States, has a peak incidence in the 5th to 6th decade of life, and occurs in approximately 1% of the elderly population (2,3). PD is a progressive neurodegenerative disease traditionally characterized by the presence of specific motor symptoms such as bradykinesia, resting tremor, cogwheel rigidity, postural instability, and altered gate. The histopathologic hallmark of PD is the presence of Lewy bodies composed of high concentrations of intranuclear alpha-synuclein and the progressive loss of dopaminergic cells and associated transmission pathways predominantly within the striatum and substantia nigra pars compacta. There are reports of nonmotor symptoms of PD, including sensory impairment, depression, anxiety, sleep disorders, and cognitive disabilities (4). Ophthalmic deficits include decreased visual acuity (5), contrast sensitivity (CS) (6), visual evoked potential latency (7), abnormal electroretinographic patterns (8), hallucinations, and altered color perception (9). Spectral-domain optical coherence tomography (SD-OCT) has demonstrated inner retinal thinning in PD (10) and...
other neurodegenerative disorders such as Alzheimer disease (11) and multiple sclerosis (12). For purposes of this study, the inner retinal layer (IRL) is defined as internal limiting membrane, nerve fiber layer, ganglion cell layer, and inner plexiform layer down to the inner nuclear layer interface (Fig. 1). Retinal dopaminergic amacrine cells are known to be localized in the IRL, while their rich interconnections are in the inner plexiform layer (13,14). Previous investigations indicate that overall retinal dopamine and associated metabolites are decreased in patients with PD (14–16). Additional lines of evidence demonstrate that retinal dopamine deficiency may play a central role in the pathogenesis of visual dysfunction in PD (17). In part, visual impairment is thought to occur through progressive loss of dopaminergic control over horizontal cell lateral coupling and photoreceptor coupling, influencing receptive field properties and dopaminergic modulation of various other retinal neurons (17,18). Numerous investigations have also documented reduced CS and retinal neuronal abnormalities in PD, which has been postulated to occur from decreased retinal dopaminergic activity (19,20).

Although IRL thinning has been reported with SD-OCT (10), it is unclear which specific retinal layers or topographic locations are most affected in PD, or the functional significance of this neural tissue loss on the visual system. We hypothesize that decreased IRL thickness may underlie decreased CS in patients with PD and may be clinically quantifiable with SD-OCT. The purpose of the present study was to prospectively evaluate the IRL thickness and CS in PD compared to healthy control (HC) subjects.

METHODS

Patients

This study was performed according to the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of the State University of New York at Downstate. All subjects underwent complete neurologic and ophthalmic examination including best-corrected Snellen visual acuity, visual field using Humphrey 750 Visual Field Analyzer (Carl Zeiss Meditec, Dublin, CA), intraocular pressure, and dilated ophthalmoscopy. All patients with PD met the UK Brain Bank Criteria for the diagnosis of PD and were clinically stable on current medical therapy. The patients with PD were a cohort that has previously been described (10), under the care of the Parkinson Disease and Related Disorders Center of the Department of Neurology, SUNY Downstate, and have been normalized with respect to disease severity and treatment. The HC consisted of family members/spouses of the patients with PD, community volunteers, and staff members with no prior ocular disease other than non–visually significant cataract or mild refractive error and with no prior ocular surgery. To prevent the confounding effect of age and improve the accuracy of data analysis, age-frequency matching (minimum, 50 years and maximum, 75 years) was implemented as a component of our inclusion criteria.

Contrast Sensitivity

CS was measured with the Pelli-Robson CS chart (PR). The PR chart has been utilized successfully in past studies to evaluate CS deficit in PD; it provides accurate, reproducible results and was found to be easily administered and tolerated by patients with PD. The PR chart provides optotypes of 20/120 Snellen-equivalent letters of consistent size, corresponding to a spatial frequency of 4 cycles per degree, estimated as the peak of human foveal CS (21) and shown to be most affected in PD (20). The PR chart contains equal 0.15 log contrast steps between consecutive 3-letter groups, with 2 triplets per line, and contrast decreasing from near 100% to <1%. Testing distance for CS is defined at 1 m. An illumination of 85 cd/m² is recommended for accurate results. Each subject’s right eye, left eye, and binocular CS was evaluated and recorded on the accompanying PR CS score sheet. The traditional scoring system adhered to throughout this study provides 0.15 credit per triplet if at least 2 of 3 letters within that triplet are confirmed. Scores can range from 0 to 2.25 corresponding to log CS.

Optical Coherence Tomography

SD-OCT was performed using an RTVue model RT100 (Optovue, Inc, Freemont, CA). This model uses a scan beam wavelength of 840 ± 10 nm, with a sampling frequency of 26,000 A-scans per second and scan depth of 2.0 to 2.3 mm. Depth and transverse resolution of 5.0 and 8.0 μm, respectively, has been reported. The EMM5 scan parameter was selected for the evaluation of IRL (ganglion-cell complex) thickness and covers a 5.0 × 5.0 mm cube centered on the foveal retina. Scans were performed on each eye for all eligible PD and HC subjects. Only scans of at least 80.0/100.0 were included. Any scan with inadequate fixation was manually re-centered and reevaluated in MATLAB 7.10.0 (MathWorks, Inc, Natick, MA) for

![FIG. 1. Spectral-domain optical coherence tomography protocol for inner retinal layer (IRL) thickness; IRL measured by automated computer segmentation as defined by white boundary; IRL consisting of the internal limiting membrane, retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and inner plexiform layer (IPL) down to the inner nuclear layer interface (arrow) are indicated.](image-url)
greater accuracy and optimal comparison of thickness differences among the groups. For purposes of this study, the foveola was designated as location 0.0 mm with IRL thickness voxel data analyzed at sequential equidistant locations in all 4 macular quadrants (nasal, temporal, superior, inferior) at 0.25-mm intervals out to a distance of 2.00 mm from the foveal center (22).

Data Analysis

Our study design allowed the direct comparison of patients with PD against age-frequency matched HC subjects, providing an initial method of controlling for age, a potential confounding variable. Analyzing and comparing the results of patients by segregating one eye (left eye, right eye, random) and not including both eyes of each subject within a statistical model prevented pseudoreplication of data.

RTVue OCT Browser was used to export unprocessed raw IRL thickness data into a MATLAB environment for analysis. MATLAB provided the ability to match PD and HC IRL thickness values to a digitally reconstructed and color-coded mathematically defined model of the fovea, which was developed by our research team to ensure accuracy and positioning of the scan data. A database of monocular and binocular CS scores and IRL voxel thickness values by foveal location was constructed in Microsoft Excel 2007 (Microsoft, Corp, Redmond, WA). All data were statistically evaluated using JMP 10 (SAS Institute, Inc, Cary, NC).

Initial data analysis consisted of comparing the mean age among groups through a 2-tailed t test (Table 1). The relationship of CS scores by diagnosis (PD vs HC) was first analyzed through an analysis of variance (ANOVA). ANOVA testing was performed on the monocular (left, right, random) and binocular CS scores of all subjects. After analyzing the ANOVA results, an additional model was constructed to further control for age by performing an analysis of covariance (ANCOVA) designating age as a linear covariate. The relationship between mean randomized IRL thickness difference by diagnosis as measured by SD-OCT was performed through an ANCOVA analysis designating age as a linear covariate. The final data analysis consisted of performing a bivariate analysis by diagnosis of randomized monocular CS by randomized IRL thickness.

To perform the random eye analyses, randomization of each subject’s CS and IRL thickness data was obtained through commercially available "true" random number generator software. Each subject including their right eye and left eye with corresponding CS scores and IRL thicknesses were randomly assigned a value of 0 or 1. After running the randomization program with equal allocation only one eye of each subject, either left or right, was randomized to and used in the analysis of both CS and IRL thickness.

RESULTS

Overall, 28 eyes of 14 patients with PD and 28 eyes of 14 HC subjects were included. Patient demographics are summarized in Table 1. Mean CS scores segregated by left eye, right eye, random eyes, and binocular vision compared by diagnosis (PD vs HC) demonstrated statistically significant decreased CS in PD eyes for all segregated parameters (P < 0.05). Assuming a linear relationship of age as a covariate in the final ANCOVA model, mean CS scores by diagnosis are demonstrated in Table 2. Controlling for age within the ANCOVA analysis, CS differences between left eye and binocular scores among the groups approached statistical significance (Table 2). IRL thickness differences between PD and HC were statistically different in each of the 4 macular quadrants at various perifoveal locations. A summary of IRL thickness differences between the groups is presented in Figures 2 and 3.

Bivariate analysis of randomized monocular CS by randomized IRL thickness evaluated by diagnosis revealed a significant correlation for only HC subjects at multiple foveal locations in all 4 macular quadrants from the foveal center. Location ranges and significance values were as follows: nasal quadrant, 0.75–1.00 mm (P < 0.02); temporal quadrant, 0.50–1.00 mm (P < 0.05); superior quadrant, 1.00 mm (P < 0.05); inferior quadrant, 1.00 mm (P < 0.03). No significant correlation was found between CS and IRL thickness within patients with PD (P > 0.05 for each foveal location measured).

### Table 1. Patient demographics for Parkinson disease patients and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>PD (n = 14)</th>
<th>HC (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)*</td>
<td>68.6 ± 6.4</td>
<td>64.4 ± 6.4</td>
</tr>
<tr>
<td>Men</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Women</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Caucasian</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>African American</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*No significant difference between the groups via 2-tailed t test (P > 0.05).

### Table 2. Pelli-Robson contrast sensitivity evaluation by diagnosis

<table>
<thead>
<tr>
<th>Contrast Sensitivity</th>
<th>PD</th>
<th>HC</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left eye</td>
<td>1.73 ± 0.25</td>
<td>1.90 ± 0.11</td>
<td>0.072</td>
</tr>
<tr>
<td>Right eye</td>
<td>1.67 ± 0.27</td>
<td>1.92 ± 0.09</td>
<td>0.015</td>
</tr>
<tr>
<td>Binocular</td>
<td>1.86 ± 0.18</td>
<td>1.98 ± 0.07</td>
<td>0.078</td>
</tr>
<tr>
<td>Random</td>
<td>1.67 ± 0.29</td>
<td>1.92 ± 0.09</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Values are represented as mean ± standard deviation.

*Analysis of covariance (age as linear covariate).

HC, healthy controls; PD, Parkinson disease patients; random, randomly selected eyes.
DISCUSSION

The results of our study are in agreement with previous reports indicating that age is a significant variable related to both IRL thickness (23,24) and CS (25–28). The progressive loss of ganglion cell axons throughout life is a well-described phenomenon and is a component of normal retinal aging (29–33). Compared with HC, however, it appears that eyes of patients with PD have a particularly thin parafoveal IRL, in agreement with recent reports (10). Retinal nerve fiber layer (RNFL) thinning in PD has been previously described (34). Subsequent investigations have confirmed retinal nerve fiber layer (RNFL) thinning in PD with various results and diagnostic yields (10,35–38). A majority of these studies concentrated on the RNFL or total macular volumes and not on the inner cellular retina, which was the basis of our current investigation and the presumable location of dopaminergic amacrine cells implicit in CS function. We hypothesize that IRL thinning in PD may represent the combined result of accelerated normal age-related ganglion cell loss secondary to an underlying neurodegenerative process, transsynaptic degeneration from cortical and subcortical neuronal loss, or may represent the primary loss of dopaminergic neurons including amacrine cells and decreased retinal dopamine. Decreased levels of retinal dopamine have been reported in patients with PD (14–16,39), and dopaminergic neurons have been localized experimentally to the inner retina (13–16,40). In addition, dopamine’s role in multiple dopamine-dependent physiologic and neuronal trophic processes within the retina has been described, including cellular functional modulation, cell growth, and survival (17).

Our findings of markedly decreased CS in patients with PD are consistent with multiple previous reports (5,6,19,39,41). Interestingly, while IRL thickness correlated with CS among HC subjects, we did not observe this correlation in PD eyes. We hypothesize that the lack of correlation between the observed CS deficit and foveal inner retinal thinning may be the result of simultaneous retinal and cortical dysfunction of the visual pathway occurring in PD. Our investigation was limited to monocular CS because of evidence documenting significant interocular asymmetry of foveal thickness in PD (42). These results indicate that while IRL and CS may simultaneously be decreased, the functional deficit of dopaminergic interneurons, including amacrine cells, appears to outstrip the anatomic structural changes in the inner retina of PD. While the normal age-related loss of ganglion cell axons may underlie decreased CS in HC, we hypothesize that additional neuronal dysfunction contributes to the pathogenesis of decreased CS in patients with PD. This further supports the notion that there may be a primary degenerative retinal cellular abnormality in PD (17,20,43,44).

The present study may have important implications regarding the clinical diagnosis and functional deficit in patients with PD. SD-OCT may be used to quantify IRL thickness, screen as a biomarker for high-risk patients,
monitor disease progression, and evaluate effectiveness of neuroprotective therapies. However, it appears that the degree of CS decline present in PD may outweigh the SD-OCT findings. Further investigation should focus on the localization of specific dopaminergic cells and associated pathologic changes leading to distinct anatomic and biochemical markers within the inner retina of PD.

Our prospective study is limited by relatively small sample size, assumption of a linear relationship between age and the studied variables, automated image segmentation of retinal tissue, quantification of only foveal IRL, and potentially unrecognized confounding variables. Nevertheless, we conclude that both IRL thickness and CS appear to be markedly reduced in PD compared with that of HC.

REFERENCES


Suppression of Experimental Autoimmune Optic Neuritis by the Novel Agent Fingolimod

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Purpose: Fingolimod is an immunomodulating agent that has been approved for the treatment of multiple sclerosis. Fingolimod-phosphate is an antagonist of sphingosine-1-phosphate receptor and known to act by preventing infiltration of autoreactive lymphocytes into the central nervous system. In this study, we investigated whether fingolimod prevents experimental autoimmune optic neuritis (EAON).

Methods: EAON was induced by immunizing C57BL/6 mice with myelin oligodendrocyte glycoprotein–derived peptide 35–55 (MOG-p). After MOG-p immunization, fingolimod was administered intragastrically from day 1 (entire phase study) or from day 9 (effector phase study) until day 35. Visual acuity of the mice was measured using OptoMotry on days 7, 14, 21, 28, and 35 after immunization. On day 35 after immunization, the mice were killed and eyes and entire length of the optic nerves were submitted for histopathologic evaluation.

Results: In the positive control group, visual acuity decreased markedly from approximately day 14 after immunization, reaching a nadir on day 21. In the fingolimod-treated groups in both entire phase and effector phase studies, there was only minimal decline in visual acuity on day 14 after immunization, and mild deterioration on day 21, followed by recovery. Histopathologic study showed that fingolimod given throughout the entire phase or only from the effector phase suppressed murine EAON. Immunohistochemical study for neurofilament demonstrated no irregularity of the linear structure of the optic nerve in the fingolimod-treated mice compared with the positive control group.

Conclusion: Fingolimod ameliorated EAON even when started after optic neuritis had developed. Further study is warranted to examine whether these findings are applicable to human disease.

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The pathogenesis of multiple sclerosis (MS)-associated optic neuritis remains incompletely understood but is known to have a strong association with organ-specific autoimmune disease (1). Some central nervous system–specific antigens such as the myelin oligodendrocyte glycoprotein (MOG) and myelin-specific proteolipid protein (PLP) have been shown to induce autoimmune encephalomyelitis and optic neuritis, mimicking the disease spectrum of MS (2,3). MOG antigen, which causes optic neuritis at a high rate, has been shown to be present abundantly within the optic nerve, and inflammatory cells presumably react with the antigen to cause tissue damage. In the mouse model that develops both encephalomyelitis (experimental autoimmune encephalomyelitis [EAE]) and optic neuritis (experimental autoimmune optic neuritis [EAON]), the onset of disease is usually observed on average 13 days after adjuvant immunization with the MOG35–55 peptide (4). When T cells obtained from these mice are injected intraperitoneally (adoptive immunization) into normal mice, optic neuritis also develops in these mice (4).

Fingolimod (FTY720; Gilenya, Imusera) is an immunomodulating agent that has been approved as a new therapeutic drug for MS (5,6). As an antagonist of sphingosine-1-phosphate (S1P) receptor, fingolimod-phosphate is known to act by preventing infiltration of autoreactive lymphocytes into the central nervous system. Fingolimod ameliorates EAE probably by reducing infiltration of myelin antigen-specific Th17 and Th1 cells into the central nervous system (7). Foster et al (8) reported that fingolimod rapidly blocked ongoing disease processes by inhibiting...
autoimmune T-cell infiltration and directly modulating microvascular and/or glial cells. Moreover, as late-stage rescue therapy, fingolimod reversed blood–brain barrier leakiness and reduced demyelination (7). In this study, we investigated whether fingolimod could prevent EAON and evaluated its clinical potential for the treatment of optic neuritis in humans.

**METHODS**

**Animals and Anesthesia**

Six- to 8-week-old female C57BL/6 mice were obtained from Japan Charles River (Ibaraki, Japan). All animal experiments were performed according to the approved guidelines of the Institutional Review Board of Tokyo Medical University, Tokyo, Japan. All animals were treated according to the Association for Research in Vision and Ophthalmology resolution on the use of animals in research. Intraperitoneal injection of a mixture of Nembutal (30 mg/kg) and xylazine hydrochloride (125 mg/kg) was used for anesthesia.

**Reagents**

MOG<sub>35-55</sub> peptide was synthesized by conventional solid-phase techniques, as described elsewhere (4). Purified Bordetella pertussis toxin (PTX) was from Sigma Chemical (St. Louis, MO). Complete Freund’s adjuvant (CFA) and Mycobacterium tuberculosis strain H37Ra were from Difco (Detroit, MI). Lipopolysaccharide was purchased from Sigma–Aldrich (St. Louis, MO). Fingolimod agent was provided by Novartis Pharma (Basel, Switzerland) and Tanabe Mitsubishi Pharma (Osaka, Japan).

**EAON Induction and Histopathological Evaluation**

EAON was induced by the method described by Shao et al (4) with some modifications. The MOG<sub>35-55</sub> peptide was diluted to a concentration of 10 mg/mL in phosphate buffer solution (PBS, pH 7.35) containing 50 μL dimethyl sulfoxide/1 mg MOG<sub>35-55</sub> peptide and further diluted in PBS and used at a concentration of 200 μg/200 μL per mouse. The MOG<sub>35-55</sub> peptide was emulsified at a ratio of 1:1 in CFA containing 5 mg/mL of M. tuberculosis H37Ra and used to immunize C57BL/6 mice subcutaneously at the neck region. The mice were also injected intraperitoneally with PTX (1 μg/100 μL per mouse) at the same time. The C57BL/6 mice were immunized with MOG<sub>35-55</sub> on day 0, followed by peroral administration of fingolimod from day 1 for entire phase study or from day 9 for effector phase study until day 35.

Mice were subjected to euthanasia at 35 days after immunization. The eyes and entire optic nerves were removed and fixed in 10% buffered neutral formalin solution. Fixed and dehydrated tissue was embedded in methacrylate, and 5-μm sections were cut through the pupillary–optic nerve plane and stained with hematoxylin and eosin. The pathological scores of the eyes lesion were evaluated according to the previous report (4): 0, no lesion; 0.5, slight cell infiltration in optic nerve; 1, moderate cell infiltration in optic nerve; 2, strong cell infiltration in optic nerve; and 3, massive cell infiltration in optic nerve.

**Immunohistochemistry**

Immunohistochemical studies for neurofilament (axons) were performed in the entire phase study, on day 0 and day 14 after immunization (n = 5; 5 nonimmunized mice were also measured as normal controls). Mice were subjected to euthanasia, and the eyes and optic nerves were fixed in 10% buffered neutral formalin solution. After deparaffinization in xylene and washing in graded ethanol, endogenous peroxidases were quenched with 0.3% H<sub>2</sub>O<sub>2</sub> methanol for 15 minutes. Antigen retrieval was performed using 10M sodium citrate solution (pH 6.0) at 100°C (microwave) for 20 minutes. Rabbit anti-neurofilament monoclonal antibody (1:400; Dako, Tokyo, Japan) was used as primary antibody and applied to the sections for 3 hours at room temperature. Swine polyclonal anti-rabbit IgG (Dako) was used as secondary antibody. Horseradish peroxidase (HRP)–streptavidin conjugate (Dako) and 3’-3’-diaminobenzidine tetrahydrochloride and HRP reaction were used for visualization. Nuclei were stained by hematoxylin. After immunostaining, images were acquired by a light microscope equipped with a digital camera (Olympus BX50, DP70; Olympus, Tokyo, Japan).

**Fingolimod Administration**

For the entire phase study, after myelin oligodendrocyte glycoprotein–derived peptide 35–55 (MOG-p) immunization on day 0, fingolimod at a dose of 0.3 mg/kg was administered by an intragastric route using a probe from day 1, once daily until the end of study on day 35. For the effector phase study, fingolimod was administered intragastrically to MOG-p–immunized mice at a dose of 0.3 mg/kg from day 9, once daily until the end of study on day 35. Positive controls were prepared by intragastric administration of distilled water to MOG-p–immunized mice. Nonimmunized and nontreated mice were used as negative controls.

**Evaluation of Visual Acuity**

Visual acuity of the mice was assessed using a recently developed virtual reality optomotor system (OptoMotry; Cerebral Mechanics, Inc., Lethbridge, Canada) on days 7, 14, 21, 28, and 35 after immunization (9,10). This system measures optokinetic responses to sine wave gratings of varying spatial frequencies. A contrast sensitivity function is created by identifying the minimum contrast that generates tracking behavior.

**Statistical Analysis**

The significance of differences between means was determined using the t test, Mann–Whitney U test, or analysis of
variance followed by Sheffé test. *P* values less than 0.05 were considered significant.

**RESULTS**

**Effect on EAON Development**

Mice were subjected to euthanasia at 35 days after immunization and EAON was evaluated by histopathological examination of the optic nerves. Frequency of EAON was calculated by number of mice with EAON/total number immunized mice.

The entire phase study was conducted by immunizing C57BL/6 mice subcutaneously with MOG peptide and then treated with fingolimod from day 1. Eight of 8 positive control mice (100%) (administered distilled water) developed EAON, whereas only 9 of 20 mice (45%) treated with fingolimod developed EAON. The severity of EAON in mice that developed EAON was reduced from a mean score of 2.1 (8 mice in control group) to 0.9 (9 mice in fingolimod-treated group). The difference in EAON scores between fingolimod-treated mice and positive controls was statistically significant (*P* < 0.001: Mann–Whitney *U* test) (Fig. 1A). Examples of the inflammatory response within the optic nerve are shown in Figure 1B.

Neurofilament immunostaining of the optic nerve on day 14 showed partial irregularity of the linear neurofilament structure in positive control group, which may represent the onset of axon damage. In the fingolimod-treated group, no irregularly stained axons were seen in the optic nerve (Fig. 2).

The effector phase study was conducted by immunizing C57BL/6 mice subcutaneously with MOG peptide and then treated with fingolimod from day 9 (effector phase). The severity of EAON was suppressed by administration of fingolimod compared with positive controls. EAON developed in 9 of 10 positive control mice (90%), with mean histopathological score of 2.0 in the 9 mice that developed EAON. In the fingolimod-treated group, EAON developed in 12 of 20 mice (60%), with mean histopathological score of 0.5 in the 12 mice that developed EAON (Fig. 3). The EAON scores between fingolimod-treated mice and positive controls were significantly different (*P* < 0.001: Mann–Whitney *U* test). Histologically, infiltration of inflammatory cells in the optic nerve was observed in the positive control group (Fig. 3A), whereas there was less cellular infiltration in the fingolimod-treated group (Fig. 3B).

**Effect on Visual Acuity**

In the entire phase study, visual acuity on day 14 in positive controls (*n* = 20) decreased markedly to 0.21 ± 0.11 cycles per degree, whereas visual acuity in the fingolimod-treated group (*n* = 20) was maintained at 0.36 ± 0.03 cyc/deg. There was a significant difference between two groups (*P* < 0.001) (Fig. 4). On day 21, visual acuity in the positive controls deteriorated further to 0.08 ± 0.10 cyc/deg, whereas visual acuity in the fingolimod-treated group was reduced only mildly to 0.28 ± 0.11 cyc/deg, also with a significant difference between two groups (*P* < 0.0001). Thereafter, visual acuity in the fingolimod-treated group began to recover and was restored to a normal level on day 35. In positive controls, visual acuity did improve from day 28 but remained significantly (*P* < 0.05) lower than that in the fingolimod-treated group on day 35. In the positive control group, visual acuity decreased gradually from day 14 after immunization and

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**FIG. 1.** A. Histopathological scores of optic nerve infiltration in the entire phase study of mice treated with fingolimod vs positive controls. B. Histopathology of optic nerve in EAON mice administered distilled water (left) and fingolimod (right). The positive control shows an inflammatory cellular infiltration (arrowheads), whereas the response is markedly reduced in the mouse administered fingolimod (hematoxylin and eosin, ×100).
reached its lowest level on day 21. In the fingolimod-treated group, there was only minimal decline in visual acuity on day 14 and mild deterioration on day 21, followed by recovery to normal. Fingolimod administration before optic neuritis developed was effective in preserving visual acuity in EAON mice.

In the effector phase study, visual acuity in the fingolimod-treated group (n = 20) was preserved, with significant differences compared with positive control group on days 14, 21, 28, and 35 (P < 0.05) (Fig. 5). Results of the effector phase experiment suggest that fingolimod
administered even after optic neuritis develops is potentially useful in preserving vision.

**DISCUSSION**

In this study, MOG immunization produced EAON in all immunized mice, indicating a high efficiency of MOG antigen in inducing optic neuritis. Oral administration of fingolimod, either from day 1 or from day 9 of MOG immunization, suppressed the development of EAON. Clinically, MOG antigen appears only partially related to MS-associated optic neuritis. In a previous study, we reported data that only 8 of 23 patients (34%) with optic neuritis were MOG antibody seropositive (11). Although MOG-immunized mouse model is an excellent tool for the study of MS, other antigens require further study.

Fingolimod is an orally bioavailable compound that has shown efficacy in phase III clinical trials and subsequently was approved for the treatment of MS (12). Fingolimod is phosphorylated to fingolimod-phosphate in vivo, which resembles naturally occurring S1P. Fingolimod-phosphate, not fingolimod itself, is a functional antagonist of S1P1. There are five S1P receptor subtypes, and these receptors are expressed on a wide range of cells involved in many biological processes relevant to MS. S1P1 plays a key role in the immune system, regulating lymphocyte egress from lymphoid tissues into the general circulation. Fingolimod crosses the blood–brain barrier and may have direct central nervous system effects, in contrast to other MS therapies that are immunologically targeted (12). Köhne et al (13) reported that fingolimod not only exhibits anti-inflammatory properties but also promotes myelination in the central nervous system by direct interaction with oligodendrocytes. Using a rat model of EAE, Foster et al (14) found that fingolimod rapidly reduced peripheral lymphocyte counts with sustained activity at a low subtherapeutic dose. Although blood lymphocyte counts serve as an indicator of fingolimod efficacy, we did not perform these counts, creating limitation of our study.

Using a rat optic neuritis model, Rau et al (15) reported that oral administration of fingolimod reduced inflammatory cellular infiltration in the optic nerve but had no effect on pattern visual evoked potential (VEP) or the reduced number of retinal ganglion cells. Furthermore, fingolimod treatment did not prevent apoptosis of retinal ganglion cells, and these cells showed persistent activation of apoptotic signaling pathways during fingolimod treatment. In this study, we did not evaluate pattern VEP but used OptoMotry to measure murine visual acuity. This virtual reality optomotor system developed by Prusky et al (9) quantifies murine visual function in awake animals avoiding adverse effects on electrophysiological recordings caused by narcotics (16,17). We found in EAON mice treated with fingolimod only mild visual disturbance even at day 21 in the entire phase study and almost no vision loss in the effector phase study with subsequent recovery to normal acuity. Potential factors explaining the difference in the effect of fingolimod on visual function in optic neuritis observed in Rau’s study and our effector phase study include differences in the model (mouse vs rat) and the dose (our dose was one third the dose) used in the two studies. The basis for vision preservation in the mice treated with fingolimod in our study is unknown. Interestingly, fingolimod treatment subsequent to lysolecithin-induced demyelination in organotypic cerebellar slice cultures enhanced remyelination and process extension by mature oligodendrocytes, while increasing microglia numbers and immunoreactivity for the astrocytic marker glial fibrillary acidic protein (18). It may be that fingolimod treatment for optic neuritis induces remyelination in EAON mouse model.

Our experiment demonstrates that oral administration of fingolimod both from the induction phase and effector phase ameliorated EAON. However, since the entire phase study and effector phase study were conducted at different times, there were some differences in results. The disturbance of visual acuity in positive controls in the effector phase study (Fig. 5) was milder than that in the entire phase study (Fig. 4). Also, optic neuritis appeared to be slightly milder in the effector phase study (Fig. 3) than in the entire phase study (Fig. 1). These differences could be due to the season of the year, condition of the immunized mice, or other factors. In the effector phase study (Fig. 5), the disturbance of visual acuity on the day of starting fingolimod administration (day 9) was similar in the positive control group and fingolimod-treated group. Despite the milder
disturbance of visual acuity in positive controls, visual acuity was significantly preserved in fingolimod-treated mice compared with positive controls.

Adverse effects of fingolimod have been documented in human studies. Thirteen of 2564 patients (0.5%) treated with fingolimod in the phase III FREEDOMS and TRANSFORMS studies developed macular edema (19). Fingolimod-associated macular edema in the eye seems to be dose dependent and typically resolves upon cessation of therapy. We did not examine the mice treated with fingolimod for macular edema either clinically or histologically.

This study demonstrated both preventive and therapeutic effects of fingolimod on EAON and provides proof of concept for the treatment of optic neuritis. It seems that evaluating this medication in human trials is warranted.

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REFERENCES

Central Retinal Artery Occlusion Caused by Fat Embolism Following Endoscopic Sinus Surgery

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Abstract: Endoscopic sinus surgery (ESS) can lead to a variety of ophthalmic complications. Central retinal arterial occlusion (CRAO) is one such complication, usually due to orbital compartment syndrome. We report a case of CRAO following endoscopic sinus surgery as a result of fat embolism.

A 43-year-old man reported visual loss in his right eye after awakening from general anesthesia for endoscopic sinus surgery (ESS). Routine intranasal injection of epinephrine mixed with lidocaine was used to reduce bleeding and no associated cardiovascular side effects were reported during the procedure.
procedure. During ESS, lamina papyracea was breached with direct injury to the right medial rectus and the procedure was stopped immediately. Five hours later, visual acuity was light perception, right eye, and 20/20, left eye. Intraocular pressure was 12 mmHg in the right eye. There was mild periorbital swelling and ecchymoses of the right upper and lower eyelids, and a large right exotropia with complete loss of adduction of the right eye (Fig. 1A). Subconjunctival hemorrhage was noted in the right eye on slit-lamp examination and the right pupil was dilated and nonreactive to light. The right fundus revealed a cherry red spot in the macula, pale and with extensive retinal edema, and diffuse retinal arterial narrowing (Fig. 1B). Yellow-colored fat emboli were seen within the retinal artery (Fig. 1C). Examination of the left eye was unremarkable. Neurological, physical, and laboratory findings were all within normal limits.

Fluorescein angiography (FA) of the right eye revealed a filling defect, due to emboli noted in the proximal retinal artery (Fig. 1D). In addition, there were marked filling delays in the retinal arteries combined with flow interruption of several arterial branches. Optical coherence tomography revealed diffuse thickening of the inner retinal layers and a central foveal thickness of 388 μm in the right eye, compared with 294 μm in the left eye. Kinetic visual field examination showed a diffuse visual field loss in the right eye, with vision preserved only in an inferonasal island.

Computed tomography demonstrated a right medial orbital wall fracture with a small amount of retrobulbar hemorrhage (Fig. 1E), while magnetic resonance imaging revealed disruption of the right medial rectus muscle (Fig. 1F). The right optic nerve was normal in appearance and no intracranial abnormalities were detected.

After 6 months, vision in the right eye remained light perception and the right exotropia was unchanged with complete loss of adduction. The fat emboli were no longer visible on fundus examination and FA showed normal retinal arterial perfusion.

While the frequency of ophthalmic complications following ESS is low (1,2), when they occur, they may have devastating consequences. Rene et al (3) reported a case of unilateral blindness following ESS in which direct optic nerve damage occurred in combination with central retinal arterial occlusion (CRAO). This was presumed to have occurred because of ophthalmic arterial spasm. A recognized cause of CRAO following ESS is the orbital compartment syndrome resulting from orbital hemorrhage (2–6). Patients generally present with pain, proptosis, tense eyelids, periorbital edema, subconjunctival hemorrhage, and external ophthalmoplegia.

We assume that the fat emboli from adjacent damaged bones or retrobulbar fat were released into the circulation leading to occlusion of the central retinal artery. Although pharmacomechanical thrombolysis was not performed in this case, it may be considered as a therapeutic option (7).

ACKNOWLEDGMENT

We thank Dr. Jae Hyoung Kim for his effort in selecting the best magnetic resonance imaging and computed tomography images.

REFERENCES

Toxocariasis of the Optic Disc

Yong Joon Kim, MD, Chan Hee Moon, MD, Jee Ho Chang, MD, PhD

Abstract: A healthy 46-year-old man presented with decreased vision in the right eye after ingestion of raw meat. On funduscopic examination, a cystic lesion was found on an edematous right optic disc with adjacent serous retinal detachment. Optical coherence tomography confirmed a peripapillary serous retinal detachment and a well-demarcated cystic lesion (200 × 200 × 500 μm) in the right eye. The patient had moderate eosinophilia and was seropositive for anti-Toxocara IgG antibody. Diagnosed with ocular toxocariasis, he was treated with systemic corticosteroids and albendazole with improvement in vision and fundus appearance.

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A 46-year-old man complained of decreased vision in his right eye for 3 days associated with headache. He had a history of eating raw beef liver over the past month. Visual acuity was 20/40 in the right eye and 20/20 in the left eye. A relative afferent papillary defect was present in his right eye, and anterior segment examination was normal. Automated perimetry revealed an enlarged blind spot in the right eye, and the left visual field was normal. The left fundus was normal; the right eye...
fundus showed optic disc edema with a cystic lesion at its center and adjacent serous retinal detachment (Fig. 1A). Spectral-domain (Cirrus HD-OCT; Carl Zeiss Meditec Inc., Dublin, CA) optical coherence tomography (OCT) revealed a peripapillary serous retinal detachment and a well-demarcated cystic lesion (200 × 200 × 500 μm) overlying the right optic disc (Figs 1B and 1C; see Videos 1 and 2, Supplemental Digital Contents 1 and 2, http://links.lww.com/WNO/A62 and http://links.lww.com/WNO/A63).

Complete blood count showed moderate eosinophilia of 1,561 cells/μL (normal <350 cells/μL). Liver function tests, C-reactive protein, and reactive plasma reagin were within normal limits. Rheumatoid factor was positive, but antinuclear antibody was negative as were antibody tests for herpes simplex, varicella zoster, cytomegalovirus, and human immunodeficiency virus. Stool examinations were negative for helminthic and protozoan ova and larvae. Antibody tests for Toxoplasma, Taenia solium, Sparganum, Clonorchis sinensis, and Paragonimus westermani were negative, but positive for anti-Toxocara IgG using an enzyme-linked immunosorbent assay (ELISA). The patient was diagnosed with ocular toxocariasis and treated with systemic corticosteroids and albendazole.

One week later, visual acuity was 20/25 in the right eye. OCT showed the cystic lesion to be resolving, and there was less optic disc edema and peripapillary serous retinal fluid (Fig. 2).

Toxocariasis results from a parasitic infection by the ascarid larvae of Toxocara canis or Toxocara cati, which are usually found in the intestinal tract of dogs and cats (1). The adult nematode produces eggs, which are released into the environment via the host’s stool. The main source of eggs is young dogs, which become infected mainly through transplacental or transmammary transmission (2). Human infection is caused by accidental ingestion of embryonated eggs, via consumption of contaminated soil, raw vegetables, or meat (3). After ingestion, the embryonated eggs hatch in the duodenum and release larvae that penetrate the intestinal mucosal epithelium. They are carried to a wide variety of tissues, including the liver, lungs, muscles, brain, heart, and eyes. In human tissue, through the circulation, the larvae remain developmentally arrested, showing no growth or morphological differentiation and cannot complete their life cycle (4).

Clinical manifestations of toxocariasis are dependent on the parasite load, the immune response, and the migration pattern of the Toxocara larva (5). Ocular larva migrans is caused by the migration of Toxocara larvae through retinal and choroidal blood vessels into the posterior segment of the eye (6). Ocular toxocariasis usually presents as peripheral granuloma, posterior granuloma, or nematode endophthalmitis (7). Disease-related complications of ocular toxocariasis include amphotycia, retinitis, retinal folds and detachment, macular scarring, and phthisis bulbi (1).

Serological testing, using an ELISA, is currently the standard technique for diagnosing ocular toxocariasis (8). Unlike viscera larva migrans, which shows marked peripheral blood eosinophilia, in some ocular larva migrans patients, the number of eosinophils may be normal or mildly elevated even in patients with severe ocular manifestations. This is likely due to the blood-ocular barrier (9).

There are few reports of OCT findings in ocular toxocariasis (10), but to the best of our knowledge, Toxocara overlying the optic nerve previously has not been reported.

REFERENCES
Macular Hole: A Rare Complication of Ocular Bartonellosis

Michael Adam Alterman, DO, Blair Katherine Young, DO, Eric Robert Eggenberger, DO, David Irwin Kaufman, DO

Abstract: A 37-year-old woman presented with an anterior optic neuropathy related to Bartonella henselae. Twenty-nine days after symptom onset, a partial thickness macular hole developed in the involved eye. Fundus photography and optical coherence tomography confirmed the conversion to a full-thickness macular hole in 2 months. Macular hole as a complication of cat scratch disease is a rare entity, with 2 prior reported cases in children. The development of a macular hole following cat scratch disease can appear without the clinical picture of multiple white chorioretinal lesions, macular star, or vitritis.

CASE REPORT

A 37-year-old woman with a history of migraine headaches and hypothyroidism developed fever and noticed a scotoma in the right upper quadrant of the right eye, which progressed over 3–4 days. Visual acuity was 20/40 in the right eye and 20/25 in the left eye. The patient developed pain with eye movement, headache, dizziness, and fever of 103.5°F prompting hospital admission. Magnetic resonance imaging of the brain and orbits was normal. Cerebrospinal fluid opening pressure was 17.5 cm of water with 35 mg/dL of protein (normal, 15–45 mg/dL), 59 mg/dL of glucose (normal, 48–95 mg/dL), 4 red blood cells (RBCs), 1 white blood cell (WBC), and no malignant cells or oligoclonal bands. Bacterial and fungal culture yielded no growth, while acid-fast stain and cryptococcal antigen were negative. Antinuclear antibody, Lyme antibodies, angiotensin-converting enzyme, anti-neutrophil cytoplasmic...
antibody, complement factors, blood cultures, and Toxoplasmosis gondii polymerase chain reaction were negative. Initial Bartonella henselae IgM titer was <1:20 with IgG titer <1:128. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated at 99 mm/hour and 10 mg/dL (normal, 0.0–1.0 mg/dL), respectively. A urine specimen showed positive nitrites, moderate leukocyte esterase, 15–20 WBCs, 5–10 RBCs, and many bacteria. She was discharged on oral fluoroquinolone.

The patient was reevaluated 13 days later because of persistent fever, headache, chills, dizziness, eye pain, nausea, vomiting, abdominal pain, and difficulty with memory. On further questioning, she reported living with 1 cat and 1 dog, but she did not recall a scratch or bite. Visual acuity was 20/80 in the right eye and 20/20 in the left eye, with decreased color vision in the right eye and a right relative afferent pupillary defect. Fundus examination revealed severe disc edema in the right eye with surrounding peripapillary hemorrhages and a solitary white chorioretinal lesion without macular star (Fig. 1A). The left optic disc had a splinter hemorrhage at 12-o’clock without edema. Repeat ESR and CRP were 99 mm/hour and 5.5 mg/dL, respectively. Cortisol was 28.3 μg/dL (normal, 6–23 μg/dL), and fibrinogen was 976 mg/dL (normal, 200–400 mg/dL). Repeat B. henselae IgG and IgM titers were both elevated at ≥1:1,024 and ≥1:20, respectively. The patient was started on 500 mg of ciprofloxacin twice a day for 3 weeks for suspected B. henselae infection.

One month later, she reported that her headache and vision were improving and had been afebrile for 1 week. Visual acuity was 20/50 in the right eye with normal color vision and diminished optic disc edema. A macular hole had developed in the right eye (Fig. 1B), and this was confirmed on optical coherence tomography (Fig. 1C). Fluorescein angiography showed optic disc edema in the right eye without macular edema, and B-scan ultrasound revealed normal scleral thickness.

Laboratory testing showed CRP <1.0 mg/dL, fibrinogen 391 mg/dL, ESR 41 mm/hour, negative rapid plasma reagin and Lyme antibodies, and elevated B. henselae IgG (>1:1,024) and IgM (>1:20) titers.

DISCUSSION

Macular hole formation following infection with B. henselae has been reported in 2 previous cases, both of which were children. Albini et al (1) noted vitritis, anterior uveitis, keratic precipitates, serous retinal detachment, and deep white patchy chorioretinal lesions in a 10-year-old girl with Bartonella neuroretinitis who later developed a full-thickness macular hole. Donnio et al (2) reported a case of treated B. henselae neuroretinitis in an 11-year-old boy with the formation of a macular hole 7 months after the infection. Other reported inflammatory causes of macular holes include idiopathic posterior uveitis, presumed ocular histoplasmosis, fungal endophthalmitis, intraocular nasal T/NK lymphoma, immune recovery uveitis, and juvenile rheumatoid arthritis after cataract extraction (1). It has been proposed that inflammation could result in vitreous traction on the macula by inflammatory contraction of the pre-macular cortical vitreous, but the pathogenesis of inflammatory causes of macular holes remains poorly understood (1,3).

Before serologic testing, the diagnosis of B. henselae was made via clinical criteria, a lymph node biopsy, and a positive skin test (4). Initial antibody titers to Bartonella often are negative and become positive weeks later. Therefore, high clinical suspicion warrants repeat blood work (5, 6), as demonstrated in our report.

REFERENCES

Intravitreal Bevacizumab in the Treatment of Peripapillary Choroidal Neovascular Membrane Secondary to Idiopathic Intracranial Hypertension

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Abstract: A 14-year-old Caucasian boy with idiopathic intracranial hypertension (IIH) presented with blurred vision in his left eye. Visual acuity was 20/20, right eye, and 20/80, left eye, and funduscopy revealed bilateral papilledema. In addition, there was peripapillary choroidal neovascular membrane (PPCNVM) in the left eye. Oral acetazolamide improved the symptoms and signs of IIH, but seven weeks later, acuity remained 20/80, left eye, with an increase in subretinal hemorrhage. Two weeks following an intravitreal injection of bevacizumab, visual acuity on the left had improved to 20/30 with resolution of subretinal hemorrhage and fibrosis of PPCNVM. After an additional 2 weeks, visual acuity improved to 20/20, and there has been no sign of recurrence over 3.5 years of follow-up.

CASE REPORT

A 14-year-old healthy Caucasian boy presented with a history of blurred vision for 4 months and intermittent diplopia and headaches for several weeks. He had no significant medical or ophthalmological history. Visual acuity was 20/20, right eye, and 20/80, left eye. There was a left relative afferent pupillary defect, and impaired color vision on the left eye. Extraocular movements were full. Automated perimetry revealed only an enlarged blind spot in the left eye. On ophthalmoscopy, there was bilateral optic disc edema and subretinal hemorrhage extending from the temporal aspect of the left disc toward the fovea (Fig. 1). Intravenous fluorescein angiography showed leakage from a PPCNVM (Fig. 2).

The patient’s blood pressure was 110/60 mm Hg, and hematologic screening for causes of optic disc edema was normal. Magnetic resonance imaging of the orbits and brain and magnetic resonance venography were unremarkable. Lumbar puncture revealed an opening pressure greater than 35 cm H2O with normal cerebrospinal fluid analysis. The patient was placed on oral acetazolamide (250 mg 4 times a day, which was decreased 7 days later to 250 mg twice a day).

Seven weeks later, despite an improvement in symptoms of intracranial hypertension and papilledema, visual acuity in the left eye remained 20/80 with an increase in the area of subretinal hemorrhage. The option of intravitreal anti-VEGF treatment was discussed with the patient’s family, and with parental consent, a single-dose intravitreal injection of 1.5 mg of bevacizumab (Avastin; Roche, Copenhagen, Denmark) was given under general anesthesia.

Two weeks later, left visual acuity was 20/30, and 4 weeks after treatment, it was 20/20. At 9 weeks, ophthalmoscopy revealed a flat and fibrosed PPCNVM with
decreased subretinal hemorrhage (Fig. 3). The patient’s visual acuity has remained 20/20 over 3.5 years with no sign of recurrence of idiopathic intracranial hypertension (IIH) or PPCNVM.

**DISCUSSION**

Although a recognized complication of chronic papilledema, PPCNVM is rare (1,2). Juxtapapillary subretinal

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**FIG. 1.** A. At presentation, there is bilateral papilledema with pigmentary change and subretinal hemorrhage temporal to the left optic disc extending toward the macula. B. Optical coherence tomography of the temporal peripapillary retina of the left eye shows subretinal and subretinal pigment epithelial fluid.

**FIG. 2.** Fluorescein angiogram of left eye from early arterial phase (A) to late venous phase (D). There is blockage of fluorescence by subretinal blood and hyperfluorescence of the neovascular membrane in the late stages of the angiogram.
neovascularization has been reported to complicate IIH in only 0.53% of cases (2).

In a retrospective review of 6 patients with IIH having PPCNVM, Wendel et al (2) noted that once the papilledema is treated adequately, these neovascular membranes are unlikely to cause severe visual loss provided that they do not enroach upon or cause hemorrhage into the fovea. They concluded that argon laser therapy may not improve visual outcome in more advanced cases and that photodynamic therapy may be a less destructive treatment option. Kaeser and Borrut (5) described a 14-year-old boy with IIH. At presentation, visual acuity was 20/20, right eye, and 20/200, left eye, with bilateral papilledema and PPCNVM in the left eye. Following treatment with acetazolamide, the patient’s vision returned to 20/30 in the left eye after 1 year, and the neovascular membrane resolved without treatment. However, Sathornsumetee et al (4) reported a case of IIH in which PPCNVM and reduced visual acuity persisted 9 months after a dramatic improvement in papilledema from optic nerve sheath fenestration.

The natural history of PPCNVM is unpredictable, as it may spontaneously involute, remain stable, or expand and lead to devastating visual loss. Management options for PPCNVMs include observation alone, surgery, laser photocoagulation, photodynamic therapy, or intravitreal anti-VEGF agents. Intravitreal bevacizumab has been reported as a successful management option for PPCNVM secondary to age-related macular degeneration (ARMD) (6) and peripapillary atrophy (7), but its use in cases of papilledema including IIH has not been described. The issue of using this agent in a pediatric patient was specifically discussed in the process of informed consent. Bevacizumab has been used in the treatment of retinopathy of prematurity, and there are no reports of local or systemic adverse events with follow-up of up to 10 months in this pediatric population (8).

The pathophysiology of PPCNVM associated with longstanding papilledema in IIH is uncertain, but it is thought to be different from ARMD (9–11). In ARMD, it has been proposed that the accumulation of drusen between retinal pigment epithelium (RPE) and Bruch membrane initiates a cascade of inflammatory and immune reactive processes, causing RPE dysfunction and breaks in Bruch membrane. Persistent RPE dysfunction results in chronic hypoxia, thus tipping the complex balance of pro- and antiangiogenic mechanism toward angiogenesis, leading to choroidal neovascularization (11,12). With papilledema, it has been postulated that discontinuity is formed in the peripapillary border of Bruch membrane from pressure exerted by the swollen disc. This discontinuity, in conjunction with focal hypoxia induced by axonal swelling, promotes angiogenesis and subsequent neovascular membrane formation (3).

REFERENCES

Conjugal Giant Cell Arteritis

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Abstract: While the pathogenesis of giant cell arteritis (GCA) remains unclear, a number of factors may be contributory, including genetic, environmental, and immune. There have been few reports of GCA occurring in a conjugal pair, all originating from Northern Europe or the Northern United States. We document GCA occurring in a husband and wife from the southern Gulf Coast of the United States and discuss the implications of this, as well as the current understanding of the pathogenesis of GCA.

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While the pathogenesis of giant cell arteritis (GCA) is unknown, immune, genetic, and environmental causes have been proposed. While rare, reports of GCA occurring in conjugal pairs (1–3) might provide information regarding immune and environmental factors. However, the subjects of these reports were either from Northern Europe or the northern United States of America (USA). In contrast, our patients (husband and wife) are from the southern USA, specifically the Gulf Coast region.

REPORT OF CASES

A 76-year-old man was admitted to the hospital with the chief complaint of acute onset of temporary “vision loss in both eyes.” For 6 days, he had been experiencing crescento episodes of bilateral transient visual loss, associated with new temporal and frontal headaches. He had been given a 6-day course of methylprednisolone 2 weeks previously for neck and back pain. Additional medical and social history is presented in Table 1. Visual acuity was 20/20 bilaterally. Examination of pupils, eye movements, visual fields, and the anterior and posterior segments was unremarkable.

The erythrocyte sedimentation rate (ESR) was 29 mm/hr, and a C-reactive protein (CRP) was 8.74 mg/dL (normal <1.52 mg/dL). Evaluation for thromboembolic disease, including cardiac and carotid catheter angiograms, was negative. Temporal artery biopsy showed chronic inflammation composed of lymphocytes and histiocytes at the internal elastic lamina, with areas of necrosis, consistent with treated GCA. The patient was started on prednisone 60 mg/d, and headaches and the episodes of transient visual loss resolved. A rheumatology consultant added methotrexa as a steroid-sparing agent.

The patient reported that his wife also had biopsy-proven GCA, which had been diagnosed 10 years before his diagnosis. Her ophthalmologic examination was normal, but she had an elevated ESR of 94 mm/hr and a CRP of 17.7 mg/dL (normal 2.0 mg/dL). A temporal artery biopsy, showing foci of epithelioid cells and histiocytes, was consistent with GCA. She was treated with 60 mg of prednisone daily, which was tapered over 7 months.

The spouses were not consanguineous, but both were of Scottish–English ancestry and had lived in the Gulf Coast for most of their lives. They met at college in Texas and resided primarily in Houston, Texas, but they also had lived in New York and New Jersey (6 years), England (5 years), and Australia (2 years). Both were fair skinned and reported spending approximately 2 months each year at a lake house, with increased sun exposure during the summer. Neither patient had any radiation or environmental toxin exposure.

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The authors report no conflicts of interest.

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They did not own any pets during the wife’s initial GCA presentation, although they have owned a dog for the past 8 years. There was no pertinent travel history, and neither patient had any history of tick bite, viral infection, or flulike illness at the time of presentation with GCA.

Regarding systemic disease, neither had ever tested positive for hepatitis B antigens. Although anticentromere and anti-Scl-70 antibodies were negative, the wife was diagnosed with scleroderma 22 years ago via skin biopsy. With progression of her symptoms, she was ultimately diagnosed with limited scleroderma and treated with plasmapheresis, leading to gradual improvement in her symptoms. Both the wife and her daughter have been diagnosed with fibromyalgia.

**DISCUSSION**

While the cause of GCA is unknown, a number of reports suggest that genetic factors may be important. Review of the literature revealed 3 previously reported cases of GCA occurring in married couples (1–3). There have been 4 published cases of married couples with mixed presentations of polymyalgia rheumatica and GCA (4–7). These publications are summarized in Table 2.

There are 2 large studies of GCA occurrence in the southern USA, where our patients primarily live. In an 11-year retrospective review of GCA patients seen at the University of Texas Medical Branch, Gonzalez et al (8) found only 27 cases of GCA out of 101,239 patients (0.027%). Smith et al (9) found that from 1971 to 1980, in Shelby County, Tennessee, the average annual incidence of biopsy-confirmed GCA was 1.78 per 100,000 (0.00178%).

Both of our patients are of Scottish–English ancestry. Numerous studies have documented a higher occurrence of GCA in individuals of Northern European descent (10–12). In a 14-year retrospective study from Scotland, Jonasson et al (10) found the average annual incidence of
biopsy-proven GCA to be 4.23 per 100,000 (0.00423%), which is approximately twice that found in Tennessee. There are other epidemiologic traits of GCA, including a higher frequency in women and occurring almost exclusively in persons older than 50 years (13).

Environmental factors may also play an etiologic role in GCA. Solar radiation may accelerate the fragmentation and degeneration of elastic fibers, a histologic feature of temporal artery biopsies. Both of our patients had an increased risk for sunlight exposure during frequent visits to their lake house. Additionally, the wife admitted to having a much greater exposure to sunlight than her husband did, and she developed GCA symptoms 10 years earlier. Both patients had long histories of smoking. In a multicenter, prospective study of 400 patients, Duhut et al. (14) found that in women, smoking was associated with a 6-fold increase in developing GCA, and heavy smoking (defined as >10-pack-years) was associated with a 13-fold increased risk. Interestingly, in men, while both smoking and heavy smoking cause slight elevations in GCA risk, this was not statistically significant. While the reason why smoking leads to greater susceptibility to GCA in women is unknown, Duhut et al postulated that smoking, which causes arterial wall damage, might lead to the generation of antigens that incite inflammatory/immunologic activity.

The immune system is heavily involved in GCA. The histologic hallmark of a positive temporal artery biopsy is infiltration of the tunica media by lymphocytes, histiocytes, and multinucleated giant cells, with disruption of the internal elastic lamina. Immunohistochemical studies have found that infiltrating lymphocytes are mostly CD4+ T-cells that secrete interferon-γ and interleukin-2, suggesting a Th1 response (15). Studies have also shown that in the adventitia, dendritic cells differentiate to present antigen and activate CD4+ T-cells to secrete cytokines. This increased immune activity and inflammation result in intimal proliferation and arterial occlusion.

In searching for the antigen trigger for GCA, a variety of infectious etiologies have been proposed, including hepatitis B, rubella, herpes simplex, varicella zoster, measles, cytomegalovirus, Epstein–Barr virus, and other herpes viruses (3, 17). All remain unproven (18, 19). Katz et al (20) have found evidence of Burkholderia in blood and temporal artery biopsy specimens in patients with GCA using polymerase chain reaction, immunostaining, and bacterial culture. Other studies have focused on an infectious agent, based on cyclical GCA patterns or peak incidences of GCA after infectious epidemics. One large study of 10,818 patients in Denmark found 5 distinct peaks of GCA occurring in close association with 2 epidemics of Mycoplasma pneumoniae, 2 of parvovirus B19, and 1 of Chlamydia pneumoniae (21).

REFERENCES

Transient Optic Perineuritis as the Initial Presentation of Central Nervous System Involvement by Pre-B Cell Lymphocytic Leukemia

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Abstract: A 20-year-old man with a history of pre-B cell acute lymphocytic leukemia (ALL) presented with optic perineuritis of the right eye while undergoing chemotherapy. Evaluation failed to reveal an infectious or neoplastic cause, and the patient improved with oral corticosteroid treatment. He returned 10 weeks later with complete loss of vision in the right eye. Optic nerve biopsy revealed leukemic infiltration of the optic nerve, and the patient was treated for central nervous system (CNS) relapse of ALL. Transient optic perineuritis may be the initial manifestation of CNS involvement of pre-B cell ALL.

CASE REPORT
A 20-year-old man with a 9-month history of pre-B cell ALL complained of right eye pain. He had received 5 cycles of chemotherapy using a Hyper-CVAD protocol, consisting of cyclophosphamide, vincristine, doxorubicin, dexamethasone courses alternated with methotrexate and cytarabine. There was no prior history or evidence of ALL central nervous system (CNS) involvement throughout his clinical course and per protocol had received 2 cycles of prophylactic intrathecal chemotherapy. A recent bone marrow biopsy done 2 months previously had shown no evidence of active leukemia.

The visual acuity was 20/20 in each eye, with no relative afferent pupillary defect, full ocular motility but mild right eye pain on right gaze, and right optic disc edema. The patient reported light brightness of 90% in the right eye compared to the left. Automated visual field testing revealed only an enlarged blind spot of the right eye. Magnetic resonance imaging (MRI) demonstrated enhancement of the right orbital optic nerve sheath and possible thickening of the optic nerve (Fig. 1A). He was diagnosed with optic perineuritis.

Cerebrospinal fluid (CSF) analysis was normal and negative for neoplastic cells and infectious agents. Rapid plasma regain, blood cultures, and purified protein derivative skin test and chest radiography were all unremarkable. The patient’s upcoming cycle of chemotherapy was temporarily held, and he was treated with 60 mg of oral prednisone daily. His symptoms rapidly improved, with the ocular pain resolving in 2 days, followed by resolution of optic disc edema and asymmetric brightness perception in 4 days. The visual acuity remained stable at 20/20 in each eye. He then underwent his sixth cycle of Hyper-CVAD and received an additional dose of intrathecal methotrexate, cytarabine, and hydrocortisone.

The patient did not keep his follow-up appointment. Without our knowledge, he presented to an outside emergency room with chest pain 3 weeks later. He was found to be pancytopenic. Chest computed tomography
(CT) revealed pulmonary nodules, and serum analysis for antibodies to aspergillus was negative.

Ten weeks later, the patient reported a 2-day history of acute visual loss in the right eye. He had no light perception and funduscopy showed findings of a CRAO and venous stasis (Fig. 2A). Fluorescein angiography confirmed absent retinal arterial perfusion in the right eye. Repeat MRI showed persistent right optic nerve sheath enhancement and thickening of the optic nerve (Fig. 1B). Four days later, flocculent material was found protruding from the right optic nerve head (Fig. 2B), and the patient was diagnosed with an infiltrative optic neuropathy. Malignant cells were not found in CSF and bone marrow. Vitreous biopsy including material from the surface of the right optic disc was inconclusive, and cultures were negative. Right optic nerve biopsy revealed a monomorphic infiltrate and B cell monoclonal population on flow cytometry (Fig. 3). The patient received radiation therapy to the brain and both orbits, high-dose intrathecal chemotherapy, and systemic chemotherapy.

Repeat CSF analysis 2 months later revealed malignant cells. The patient’s subsequent course was complicated by bacterial meningitis, Rhodotorula mucilaginosa sepsis and right-sided sinus mucormycosis with orbital involvement. He eventually achieved complete CNS and systemic remission and received a matched, unrelated donor bone marrow transplant. At the last follow-up, 19 months after initial presentation, his vision remained no light perception, right eye, with optic disc pallor and attenuated retinal vessels. The left eye retains visual acuity of 20/20 with a normal ocular examination.

**DISCUSSION**

Optic perineuritis is an inflammatory optic neuropathy with symptoms similar to those of optic neuritis including pain with eye movement, variably decreased visual acuity and optic disc edema (4). Optic perineuritis has distinct neuroimaging features compared to optic neuritis, specifically predominant enhancement of the optic nerve sheath and perineural fat stranding rather than enhancement of the optic nerve itself (1). Following intravenous contrast, there is a “tram track” appearance on axial views, or a “doughnut” on coronal views, at times resembling optic nerve sheath meningioma. Compared to optic neuritis, visual loss is less profound in optic perineuritis with >50% of patients retaining acuity of at least 20/20 (4). Perineuritis is usually slowly progressive, and patients typically have a good response to oral corticosteroids although recurrence upon tapering of steroids has been reported. There is no increased risk of multiple sclerosis in patients with optic perineuritis (1).
A wide spectrum of disorders are associated with optic perineuritis, including inflammatory (idiopathic orbital inflammation, Wegener granulomatosis, sarcoidosis), infectious (herpesviridae, mycobacterium, syphilis, Toxocara, HIV [1,2]), and toxic (imatinib, methotrexate, cytarabine, linezolid [2,3]).

Our patient presented with optic perineuritis as the initial manifestation of leukemic invasion of the CNS. After initial recovery, he lost vision due to leukemic infiltration of the optic nerve with venous stasis.

Infiltrative optic neuropathy causes visual loss through progressive, compressive necrosis, or ischemia of the optic nerve (5). Multiple neoplastic processes have been reported to manifest as an infiltrative optic neuropathy, including leukemia, lymphoma, optic nerve glioma, meningioma, and metastatic malignancy (6,7). The optic nerve and perineural structures are an infrequent yet important site of CNS leukemic involvement. Active bone marrow and systemic disease is typically present with leukemic infiltration of the optic nerve (8,9). However, there are reports of optic nerve involvement during systemic remission, as in our case (10,11).

An infectious optic neuropathy also must be considered in patients undergoing chemotherapy, who are at an increased risk for opportunistic infections. Sino-orbital aspergillosis and rhino-orbital–cerebral mucormycosis are 2 disorders of particular concern in the immunocompromised patient (12).

In our patient, the rapidity of the infiltrative process and high concern for opportunistic infection led to aggressive diagnostic evaluation and treatment. After vitreous biopsy was nondiagnostic, we proceeded to biopsy the optic nerve in order to differentiate leukemic disease from opportunistic infection (13).

Optic nerve biopsy was definitive for neoplastic involvement. Other diagnostic modalities including CSF and bone marrow analysis remained noncontributory for an additional 2 months. By that time, the patient had received intrathecal and systemic chemotherapy and radiation therapy (7,10,14,15). His fellow optic nerve remained free of leukemic involvement at the conclusion of his treatment course, achieving CNS and systemic remission.

REFERENCES

Radiation Optic Neuropathy After Proton Beam Therapy for Optic Nerve Sheath Meningioma

Jamal D. Siddiqui, MD, Jay S. Loeffler, MD, Marjorie A. Murphy, MD

Abstract: A 63-year-old woman with a 1-month history of blurred vision in the right eye was found to have a right optic nerve sheath meningioma. She was treated with fractionated proton beam therapy using a total dose of 50.4 cobalt gray equivalent (CGE) in 1.8 CGE fractions, with subsequent improvement in vision. Twenty-seven months later, the patient reported a 6-week history of progressive blurred vision in her right eye. Magnetic resonance imaging revealed enhancement of the right optic nerve consistent with radiation optic neuropathy (RON). We are unaware of any previous reports of RON when radiotherapy doses fall within the current recommended guidelines of <55 CGE fractionated into daily doses <2 CGE.

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Optic nerve sheath meningioma (ONSM) is a benign neoplasm arising from meningoeipithelial cap cells of arachnoid villi encapsulating the optic nerve or, less commonly, from intracranial extension of tumor through the optic canal. ONSM frequently leads to painless progressive visual loss due to optic nerve, tract, or chiasmal compression. Fractionated radiation therapy has been established as the preferred treatment modality for this neoplasm (1).

Radiation optic neuropathy (RON) is an uncommon but devastating adverse complication of radiation therapy directed at or adjacent to the visual pathways. Kline et al (2) proposed diagnostic criteria for RON, including acute visual loss, visual field defects consistent with optic nerve or chiasmal injury, lack of optic disc edema, absence of visual pathway compression on neuroimaging, and onset usually within 3 years of radiation.

While a variety of factors may contribute to RON, it is clear that, with external beam radiotherapy, total dose and fraction size are important. Our patient with ONSM developed RON after receiving proton beam therapy. We are unaware of previous reports of RON for ONSM when current recommended treatment guidelines are followed.

CASE REPORT

A 63-year-old woman presented with a 1-month history of blurred vision in the right eye. Visual acuity was 20/40, right eye, and 20/25, left eye. There was a right relative afferent pupillary defect, diminished color vision in the right eye, and right optic disc pallor. The right visual field showed generalized depression (Fig. 1A).

Her medical history included treatment for hypertension and hyperlipidemia. Medical evaluation, including testing for sarcoidosis, was unremarkable. Magnetic resonance imaging (MRI) showed tram-track enhancement of the right optic nerve consistent with ONSM (Fig. 2).

Three months after diagnosis, the patient was treated with fractionated proton beam therapy with a total dose of 50.4 cobalt gray equivalent (CGE) in 1.8 CGE fractions. Three months later, the visual acuity was 20/20, right eye, and pupillary reactions were normal. By 17 months, visual fields were markedly improved (Fig. 1B).

Twenty-seven months after proton beam therapy, the patient reported a 6-week history of progressive blurred vision in the right eye, particularly temporally. Visual acuity was 20/40, right eye, and 20/20, left eye, with a right relative afferent pupillary defect and no change in the optic disc pallor. The right visual field showed primarily temporal loss (Fig. 1C). MRI demonstrated enhancement of the right optic nerve approaching the chiasm (Fig. 3). The patient was diagnosed with RON in the right eye and treated with 1 g of methylprednisolone intravenously daily for 5 days.
Over 11 months of follow-up, the patient’s visual acuity and field in the right eye has remained stable (Fig. 1D).

**DISCUSSION**

Current treatment guidelines to avoid RON include total dose of 50–55 Gy fractionated into individual doses of less than 2 Gy. Andrews et al (3) reported no cases of RON from 33 optic nerves irradiated with 50.4 Gy. Metellus et al (4) also reported no cases of RON in 9 patients with ONSM treated with total doses of 50.4 Gy. Abouaf et al (5) did not report RON occurring in 10 patients treated for ONSM, with total doses ranging from 50 to 64 Gy.

When these recommendations are exceeded, RON has been reported in treating head and neck tumors in close proximity to the visual pathways. Parsons et al (6) found no cases of RON in 106 optic nerves that received doses less than 59 Gy, but reported 17 cases of RON in optic nerves that received higher doses. Bhandare et al (7) described RON in 32 optic nerves receiving mean total doses of 67 Gy.
Our patient was treated with proton beam therapy rather than conventional external beam radiation therapy using photons. Proton therapy has the advantage of a finite energy path, limiting radiation exposure to adjacent structures (8). For ONSM, it eliminates potential damage to the contralateral optic nerve and chiasm. Protons are highly adaptable to irregular targets of irregular shape and are believed to have a high relative biological effectiveness compared with photons. For proton beam therapy, radiation doses are measured in CGE (proton Gy × 1.1). There have been no reports of RON following proton beam treatment for ONSM or head and neck tumors when doses fall within current recommendations (9–12).

Lessel (13) reported that RON may occur at radiation dosages lower than those believed safe in patients with Cushing syndrome, pituitary tumor, diabetes mellitus, or those receiving chemotherapy. None of these factors was present in our patient.

A variety of treatment options have been described for RON, including corticosteroids (14–16), anticoagulation (17,18), hyperbaric oxygen (14–17,19), and anti-vascular endothelial growth factor agents (20,21). None is of proven efficacy. We were gratified but have no good explanation as to why a 5-day course of high-dose intravenous steroids led to stabilization of our patient’s visual function.

In summary, although fractionated radiotherapy remains the treatment of choice for ONSM, our report illustrates that RON may occur even at recommended radiation doses believed to be safe.

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FIG. 2. A. Contrasted T1 axial magnetic resonance imaging shows tram-track enhancement of right optic nerve (arrow) consistent with optic nerve sheath meningioma. B. More rostral image shows no intracranial involvement.

FIG. 3. A. Contrast-enhanced T1 axial magnetic resonance imaging reveals no change in size of right optic nerve sheath meningioma (arrow). B. There is enhancement of the prechiasmal portion of the right optic nerve (arrowhead) consistent with radiation optic neuropathy.


Variable Ptosis after Botulinum Toxin Type A Injection with Positive Ice Test Mimicking Ocular Myasthenia Gravis

Ahmad M. Alaraj, MD, Darren T. Oystreck, MMedSci, Thomas M. Bosley, MD

Abstract: We describe a patient who received cosmetic botulinum toxin type A injections to the brow and subsequently developed unilateral ptosis that was variable during examination and was transiently improved after the ice pack test. Ptosis gradually resolved spontaneously over approximately 3 months. This is the third patient to have variable ptosis documented after botulinum toxin type A injection to the brow and the second to have a positive ice test. The ice test is not completely specific for myasthenia gravis but may, at times, improve ptosis resulting from other defects at the neuromuscular junction. Wound botulism now is much more common because of illicit drug use, and the ice test also might be positive in this setting.

CASE REPORT

A 52-year-old woman presented with a 1-week history of a drooping right upper eyelid. She denied diplopia, pain, dysphagia, dysarthria, dyspnea, generalized weakness, or any other focal neurologic symptoms, and initially, she did not mention receiving cosmetic botulinum toxin injections. Medical history was significant for diabetes mellitus and hypertension, and her medications were glibenclamide and amlor. Family history was unremarkable.

Visual acuity was 20/20 in the right eye and 20/40 in the left eye. She had 3 mm of right upper eyelid ptosis (Fig. 1A) with fatigability of the right levator on sustained upgaze and a positive Cogan lid twitch sign. The left upper eyelid was normal, as was examination of the pupils. Ocular motility was full, and funduscopic was normal. The remainder of her neurologic examination was unremarkable without dysarthria or midline or appendicular weakness. A 5-minute ice test was performed resulting in transient improvement in ptosis of 2 mm (Fig. 1B).

General physical examination and chest x-ray were normal. Acetylcholine receptor antibody titer was within the normal limits. On a follow-up visit, the patient admitted receiving cosmetic botulinum toxin type A injection to the right eyebrow 3 days before the onset of right ptosis. There was complete resolution of ptosis over 12 weeks (Fig. 1C).

DISCUSSION

Our patient developed unilateral upper lid ptosis shortly after cosmetic botulinum toxin type A injections to the ipsilateral brow and forehead. Initial clinical examination mimicked MG with variable lid position, Cogan lid twitch sign, and transient resolution of ptosis after cooling of the involved lid with an ice pack (3,4). The patient did not have diplopia, limited ocular motility, or any other systemic signs or symptoms of generalized MG, and acetylcholine receptor
antibody levels were normal. Ptosis resolved spontaneously over 3 months. It seems most likely that ptosis was the result of botulinum toxin type A injections in the area above the right upper lid (5).

Two similar patients have been reported with variable ptosis mimicking MG after cosmetic botulinum toxin type A injections. Sunness and Kelman (6) described a 70-year-old woman with variable right upper lid ptosis and diplopia associated with esotropia and hypertropia. A tentative diagnosis of ocular MG was made, and an ice test improved ptosis but not ocular motility. At the second visit, the patient admitted that she had received cosmetic botulinum toxin type A injections around the lids 6 days before the onset of symptoms. Ptosis resolved within 2 weeks and diplopia some time later. Parikh and Lavin (7) encountered a 58-year-old woman with unilateral ptosis after a botulinum toxin type A “party” during which she received a relatively high dose. She also had fatigability of the lid, but an ice test was negative. Ptosis completely resolved in 12 weeks. All 3 patients with ptosis following botulinum toxin type A injections had clinical evidence of neuromuscular junction impairment with fatigability and Cogan lid twitch sign, and 2 had a positive ice test. Ptosis in all 3 resolved within 2–12 weeks.

Reports describing ptosis as a side effect of therapeutic botulinum toxin type A injection generally have not mentioned variability, but the patients described in previous reports (6,7) and in the present study indicate that variability may occur. This may create potential confusion regarding the diagnosis of MG, particularly if the patient is not questioned about or initially denies botulinum toxin type A injections (6).

The etiology of improvement in ptosis following lid cooling is unknown (8–10). Cooling may decrease cholinesterase activity (11) and/or increase acetylcholine efficiency at the postsynaptic junction (12,13). In patients with myasthenic ptosis, ice applied to a ptotic lid improves ptosis more than 2 mm in most (3,14) or all (4,15) individuals. Decreasing temperature seems superior to rest alone (4,15), while heat may have the reverse clinical effect (16). Cooling also improves myasthenic facial weakness (17), decremental response to repetitive nerve stimulation (9,17), and in most (15,17), but not all (6,8), instances of restricted ocular motility.

Improvement of ptosis after cooling of an eyelid for 2 minutes has been reported to be both sensitive and specific for MG (3,14). A positive response is considered to be specific for MG because a number of studies have described no improvement in ptosis (3,4,18,19) or ocular motility restriction (19) of nonmyasthenic origin. However, the ice test has been found to be positive in patients with the congenital myasthenic syndrome caused by CHRNE mutations (20), as well as in patients with ptosis resulting from the cosmetic use of botulinum toxin type A. No study has specifically investigated the effect of cooling on ptosis resulting from neuromuscular junction defects that are not autoimmune in origin (15).

While botulism in general is uncommon, wound botulism has become much more common because of an increase in the subcutaneous injection of illicit drugs (18,21,22). At times, the responsible wound is not mentioned nor is it apparent on physical examination (19). Patients commonly present with bilateral ptosis and facial weakness, dysarthria, and difficulty swallowing (21,22). A positive ice test in this setting might be interpreted incorrectly as diagnostic of MG.

REFERENCES


Erratum

A Mystery Case of Proptosis, Optic Neuropathy, and Peripheral Neuropathy: Erratum

In the article that appeared on page 77 of the March 2013 issue of the *Journal of Neuro-Ophthalmology*, two hyperlinks were omitted which grant access to Supplemental Digital Content figures. To view Supplemental Digital Content 1, visit http://links.lww.com/WNO/A48; to view Supplemental Digital Content 2, visit http://links.lww.com/WNO/A49.

Additionally, a typo appeared in the footnote regarding Supplemental Digital Content on the first page of the article. The correct journal web site is http://www.jneuro-ophthalmology.com, and the Supplemental Digital Content figures can be found accompanying the article online.

REFERENCE

Drug-Related Mitochondrial Optic Neuropathies

Michelle Y. Wang, MD, Alfredo A. Sadun, MD, PhD

**Background:** There is a group of optic neuropathies of either genetic or acquired origin characterized by similar clinical manifestations with preferential involvement of the papillomacular bundle (PMB). PMB fibers are most susceptible to injury as they are small, unmyelinated, and have high-energy demands. These optic neuropathies share a presumed common pathophysiology of mitochondrial dysfunction.

**Evidence Acquisition:** A variety of medications cause optic neuropathy by interfering with mitochondrial function. The evidence linking these therapeutic agents as a cause of mitochondrial optic neuropathy (MON) is well established in some and less certain in others. The differential diagnosis includes other optic nerve disorders producing bilateral, symmetric visual loss, including certain nutritional deficiencies, toxins, and genetic diseases.

**Results:** Ethambutol, chloramphenicol, linezolid, erythromycin, streptomycin, and antiretroviral drugs can cause drug-related MON. In many cases, drug toxicity is dose and duration dependent, and discontinuation of the drug in a timely manner can lead to significant visual recovery.

**Conclusions:** Mitochondrial optic neuropathies are increasingly recognized as a spectrum of conditions that reach a similar end point by compromising a common pathway of mitochondrial dysfunction. Clinicians should be aware of drugs that can cause a MON. Prompt recognition of this association is critical in preventing irreversible, profound visual loss.

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**MITOCHONDRIAL OPTIC NEUROPATHY**

Mitochondrial optic neuropathy (MON) is increasingly recognized as a major spectrum of optic neuropathies resulting from different genetic and acquired etiologies (1).

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The authors report no conflicts of interest.

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**Clinical Features**

The clinical presentation of MON is characterized by slowly progressive bilateral loss of central vision, dyschromatopsia, central or cecocentral scotomas, and loss of high spatial frequency contrast sensitivity (2) (Table 1). Patients often describe the visual loss as a central haze or dark cloud. Pain is not a feature of MON. Ophthalmoscopic features during the acute/subacute stage often reveal a hyperemic optic disc and peripapillary retinal nerve fiber layer (PRNFL) swelling (3). With time, temporal pallor of the optic disc develops. There is no relative afferent pupillary defect due in part to symmetric optic nerve involvement.

Clinical findings such as poor visual acuity, dyschromatopsia, and central visual field loss can be explained by selective damage to the papillomacular bundle (PMB). The fibers of the PMB are most susceptible due to their long unmyelinated segment in the retina and their small caliber. Preferential involvement of the PMB is a feature common to a wide range of acquired and genetic mitochondrial optic neuropathies (4,5).

Figure 1 summarizes the spectrum of MON. Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA) are 2 well-documented examples due to mitochondrial or somatic DNA mutations. Other examples include nutritional deficiencies, such as lack of folic acid and vitamin B12, and combinations of nutritional deficiency and toxicity causing tobacco-alcohol and Cuban epidemic optic neuropathies. In all instances, MON begins with dysfunction of mitochondrial oxidative phosphorylation (6) and results in impaired function of the PMB.

**Common Pathway**

Mitochondria provide the majority of cellular energy by oxidative phosphorylation. During the process, electrons are transferred down a chain of complexes. When electrons do not complete the process, reactive oxygen species are generated as a byproduct. The combination of energy depletion and oxidative stress results in the opening of the mitochondrial permeability transition pore, allowing for leakage of cytochrome c, a key activator for apoptosis (Fig. 2).
The axons of retinal ganglion cells (RGCs) converge toward the optic nerve head and pass through the lamina cribrosa. Myelination of axons begins only posterior to the lamina cribrosa.

The fibers of the PMB are anatomically distinct in 2 regards. First, like all axons emanating from RGCs, they run an unmyelinated course through the retinal nerve fiber layer (RNFL). Second, they are narrow in caliber. Membrane potential must be recharged at each node of Ranvier and along any other unmyelinated segment. A number of factors probably lead to selective vulnerability of the PMB axons. These include high energy needs coupled with low energy production, a high surface area to volume ratio, and absence of saltatory conduction due their unmyelinated structure (7).

As a part of a compensatory mechanism, mitochondria accumulate within RGC axons. These axonal changes can be detected by optical coherence tomography (OCT) (8,9). Appearance of optic disc pallor usually occurs in later stages, indicating irreversible axonal loss. With cessation of triggering factors, improvement in visual fields and corresponding reduction in the nerve fiber layer thickness can be observed in some acquired cases with resolution of axonal engorgement.

**Workup and Ancillary Testing**

The best screening tests for MON are those that measure the functions subserved by the PMB, including visual acuity, color vision, contrast sensitivity at high spatial frequencies, central visual field testing and, possibly, pattern visual-evoked potentials. The extent of visual loss varies widely; however, visual acuity of hand motions, light perception, or no light perception is very rare as non-PMB retinal nerve fibers usually are spared. Color vision loss sometimes may be more profound than visual acuity loss. Contrast sensitivity may be effective in detecting subclinical toxic optic neuropathy (10). Central or cecocentral scotomas are the hallmark visual field defects. The red Amsler grid is a particularly useful screening test. OCT is a useful ancillary test in the subacute and chronic stages by measuring the RNFL thickness and confirming thinning involving the PMB beginning in the inferotemporal sector (11–14). In the later stages, OCT demonstrates thinning of RNFL thickness in all quadrants (9).

**DRUG-INDUCED MITOCHONDRIAL OPTIC NEUROPATHY**

A number of drugs injure the optic nerve by interfering with mitochondrial oxidative phosphorylation, thereby producing a classic clinical picture of MON.

Drugs proven to cause MON by blocking oxidative phosphorylation include ethambutol, chloramphenicol, linezolid, erythromycin, streptomycin, and antiretroviral drugs (15–17). A number of other drugs that can cause optic neuropathy but less strongly associated with mitochondrial dysfunction are amiodarone, infliximab, cloquinol, dapson, quinine, pheniprazine, suramin, and isoniazid (16,18).

**Ethambutol**

Worldwide, there are approximately 9.2 million new cases of tuberculosis (TB) each year, and about 55% of these patients take ethambutol to prevent or delay the emergence of drug resistance (19). As a consequence, ethambutol is the

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**TABLE 1. Clinical features of mitochondrial optic neuropathy**

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<th>Feature</th>
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<td>Fairly symmetric visual impairment</td>
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<td>Loss of high spatial frequency contrast sensitivity</td>
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<tr>
<td>Early and profound loss of color vision</td>
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<td>Central or centrocecal visual field defects</td>
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<td>Temporal pallor of the optic discs (delayed)</td>
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**FIG. 1.** Mitochondrial dysfunction plays a central role in the pathogenesis of many optic nerve diseases, either inherited or acquired. Instead of classifying them as separate entities, mitochondrial optic neuropathies have now been recognized as a spectrum of conditions leading to optic atrophy by a similar pathway. CEON, Cuban epidemic of mitochondrial optic neuropathy; TAA, tobacco-alcohol amblyopia.
most common cause of toxic optic neuropathy accounting for 100,000 new cases each year (20).

Ethambutol is a metal chelator, destroying bacteria by inhibiting arabinosyltransferase, an important enzyme in mycobacterial cell wall synthesis. Due to the similarity between mammalian mitochondrial DNA (mtDNA) and bacterial ribosomes, ethambutol also disrupts oxidative phosphorylation and mitochondrial function by interfering with iron-containing complex I and copper-containing complex IV (17). Copper is a required cofactor for cytochrome c oxidase, an essential component in the electron transport chain. Ethambutol may reduce the level of copper, thereby interfering with oxidative phosphorylation. Replacing copper leads to improved RGC survivability in in vivo models of ethambutol optic neuropathy (21). It is interesting that copper deficiency due to malabsorption from bariatric surgery also has been associated with visual loss from optic neuropathy (22,23). Other studies suggest that zinc also might play a role in ethambutol toxicity (21,24), and individuals with reduced serum zinc level may be more susceptible to ethambutol ocular toxicity (25,26). A study using cell cultures demonstrated that the chelating effect of ethambutol may inhibit lysosomal activation, resulting in accumulation of zinc in lysosomes with increased lysosomal membrane permeability and cell death (27).

Ethambutol ocular toxicity has been well documented in the literature shortly after its introduction in 1960s (28–44). The frequency of vision impairment has been reported in 50% of patients at a dose of 60–100 mg/kg/d, 5%–6% at 25 mg/kg/d, and 1% at ≤15 mg/kg/d (45). Visual loss is typically insidious and symmetrical, occurring typically 2–8

FIG. 2. Accumulation of reactive oxygen species (ROS) leads to a decrease in the electrical potential across the mitochondrial membrane, which allows for an opening of the mitochondrial permeability transition pore (MPTP), allowing for leakage of cytochrome c (Cyt c) into the cytosol. Cyt c then binds to apoptosis activating factor-1 (APAF-1), which activates procaspase-9, triggering the caspase cascade and apoptosis.

FIG. 3. Ethambutol optic neuropathy. A. A 65-year-old woman developed vision of 20/400, right eye, and 20/800, left eye, after beginning ethambutol at a dose of 26.5 mg/kg/d for Mycobacterium avium. Automated visual fields show bilateral cecocentral scotomas with temporal field depression. B. Three months after cessation of ethambutol, visual acuity was 20/60, right eye, and 20/80, left eye, with improvement in visual fields. One year later, vision was 20/30 bilaterally.
months after the initiation of therapy. Central field loss usually is detected (38,39) (Fig. 3) but other patterns such as bitemporal defects have been described (46–48), and neuroimaging may be required because these findings suggest chiasmal involvement. Age, hypertension, and renal disease have been reported as risk factors (49). The standard treatment regimen for newly diagnosed cases of TB consists of an initial phase lasting 2 months, followed by a continuation phase of 4–6 months. The initial phase usually includes isoniazid, rifampicin, pyrazinamide, and ethambutol. Ethambutol toxicity is duration dependent and dose dependent. The recommended single daily dose for the initial phase in adults is 15–20 mg/kg body weight for 2 months or 20–35 mg/kg body weight 3 times a week (50). The dose is as efficacious when given 3 times weekly as when given daily with the potential advantage of better compliance, reduced cost, and less ocular toxicity (51). Typically, toxic levels of ethambutol occur when dosage is not adjusted according to the patients’ weight or renal function. However, vision loss has been reported in 1% of patients taking even the recommended dose (52,53).

The Centers for Disease Control has a dosing table for adults based on estimated body weight (54). The World Health Organization has recommended a daily dose of 20 mg/kg (range, 15–25 mg/kg) for children of all ages with drug-susceptible TB (55). A higher range of daily dose (20–30 mg/kg) should be considered only for drug-resistant TB (56).

Optic neuropathy is rare with treatment of less than 2 months and often reversible with early withdrawal. However, irreversible damage may occur especially if treatment exceeds 6 months (57,58). After cessation of ethambutol, visual impairment often worsens over a period of months, followed by stabilization and gradual improvement over the next 6 months. Although vision may improve after cessation of the drug, it is not unusual to have permanent visual deficits (59,60). As ethambutol is renally excreted, patients with impaired renal function are at greater risk for toxicity (61). Most cases of vision loss in patients on recommended doses occur in those with poor renal function (58).

It is important to individualize the treatment regimen and monitor patients closely for early signs of optic neuropathy. Patients should be educated to withdraw the drug at the onset of any visual symptoms. There is no consensus on the standard of treatment for ethambutol ocular toxicity or specific screening and monitoring recommendations for asymptomatic patients. A baseline ophthalmologic examination, including visual acuity, color vision, and visual fields, should be performed before initiation of ethambutol and repeated at the onset of visual symptoms. During the treatment phase, asymptomatic patients taking the recommended doses may be monitored every 1 to 3 months (62). Monthly monitoring may be necessary for patients with increased risks for toxicity, such as diabetes, chronic renal failure, renal TB, alcoholism, old or young age, or coexisting ocular deficits (63). Contrast sensitivity and multifocal ERG also may be helpful tests to detect subclinical changes (64). Pattern visual-evoked responses may demonstrate an increased mean latency of the P100 wave (65), and OCT assists in monitoring RNFL thickness (66).

Chloramphenicol

In the 1970s, chloramphenicol was frequently used as chronic treatment for children with cystic fibrosis (67). Chloramphenicol inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit, thereby inhibiting mitochondrial protein synthesis as well (68). The incidence and severity of optic neuropathy is dose dependent. Prompt cessation of the drug and treatment with vitamin B complex usually leads to substantial recovery of visual function. Transmission electron microscopy of bone marrow cells of patients taking chloramphenicol has shown swollen mitochondria with disrupted cristae and an abnormally high level of intramitochondrial iron deposits, confirming the toxic effect of the drug (69). The clinical findings of chloramphenicol optic neuropathy are characterized by hyperemic optic discs with blurred margins, swelling of the PMB, and central scotomas (70).

Linezolid

Linezolid was first introduced in 2000 to treat methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus. Linezolid inhibits protein synthesis by binding to 23S ribosomal RNA (rRNA) of the bacterial 50S ribosomal subunit and inhibiting formation of the 70S initiation complex. As mitochondrial ribosomes are similar to those of bacteria, protein synthesis in mitochondria also is disrupted. Linezolid is generally well tolerated when used up to 28 days. Both optic and peripheral neuropathies have been reported in patients taking linezolid for longer periods (71). Linezolid reaches inhibitory concentrations for most gram-positive pathogens within 4 hours after a single oral dose of 600 mg (72). Toxicity has been associated with off label extended therapy of 5–50 months (73–75). Full visual recovery has been reported in some cases after discontinuing the drug (76); however, the peripheral neuropathy is often irreversible. The initial optic disc edema and PRNFL resolves after cessation of the drug (76). In a rat model, linezolid has been shown to induce a dose-dependent and time-dependent decrease in the activity of mitochondrial complex I and complex IV (77).

Other Antibiotics

Erythromycin binds to the 23S rRNA of the 50S ribosomal subunit, impairing protein synthesis. Erythromycin-induced mitochondrial dysfunction has also been noted to be dose dependent (78). Similarly, streptomycin, an aminoglycoside, better known for toxicities involving the eighth cranial nerve and peripheral nerves, also may cause optic neuropathy (79).
Genetic Mitochondrial Dysfunction Predisposes Patients to Greater Toxicity

Pre-existing dysfunction in mitochondrial metabolism from genetic causes such as LHON and ADOA likely makes patients more vulnerable to drug-induced MON.

The nucleoside analog azidothymidine (AZT), also known as zidovudine, is an important component of highly active anti-retroviral therapy (HAART), in the treatment of HIV. It belongs to a class of drugs known as nucleoside reverse transcriptase inhibitors that function by interfering with viral DNA replication. This class of drugs is used not only by retroviral reverse transcriptase but also by the mtDNA polymerase gamma (80). Therefore, all nucleoside analogue reverse transcriptase inhibitors may induce mitochondrial toxicity by inhibiting mitochondrial polymerase gamma and mtDNA replication (81,82).

Case reports of profound visual loss and color deficiencies in LHON patients harboring either the 11778 or 14484 mutations after initiation of HAART have been reported, suggesting that antiretroviral therapy may be associated with increased risk in genetically predisposed patients (83,84). Ethambutol and erythromycin have also been suggested to trigger LHON (85–87). Similarly, ethambutol has been linked to visual loss in a patient with dominant optic atrophy (DOA) with an OPA1 mutation (88). If possible, these drugs should be avoided in patients harboring genetic mitochondrial defects.

Differential Diagnosis of Drug-Induced Optic Neuropathy

A careful history usually provides key information allowing identification of MON. A complete list of medications may identify the causal agent. Serum vitamin levels of B1, B2, B12, and folic acid as well as red blood cell pyruvate may be helpful in detecting nutritional causes. A 24-hour urine collection for heavy metal screening may help identify particular toxins. A positive family history of optic nerve disease, presence of telangiectatic vessels around the optic disc, and the sequential involvement of both eyes are very suggestive of LHON. This diagnosis may be confirmed by genetic testing. An autosomal dominant family history and slowly progressive optic neuropathy starting in late childhood favors DOA.

Optic neuritis may occasionally occur bilaterally and produce central or cecocentral scotomas. However, a history of multiple sclerosis, presence of white matter defects on magnetic resonance imaging, and recovery of visual acuity over several weeks support the diagnosis of optic neuritis.

Similarly, pituitary tumor or other chiasmal syndromes produce bitemporal visual field loss, which, on occasion, may simulate a cecocentral defect. In such cases, neuroimaging is warranted.

Systemic associations such as combinations of paresthesias, ataxia, or hearing loss suggest multifactorial, mixed nutritional optic neuropathies. These cases do not usually result from toxic exposure or single vitamin deficiency (89).

The 5 Postulates for Toxic Optic Neuropathy

It is not unusual to find published case reports claiming to describe a new toxic optic neuropathy. Such a collection of anecdotal cases or case series may suggest an association. But establishing an agent to be causal requires a higher standard. We propose the following postulates for establishing toxic optic neuropathy:

1. There should be a strong scientific rationale to explain why there is an optic neuropathy. Why would RGCs or their axons be vulnerable?
2. There should be something resembling a clinical dose–response curve. Higher doses should make the optic neuropathy worse and more likely.
3. Longer duration of exposure is a risk factor. Longer periods of exposure or a higher total dosage should increase the risk.
4. At least some recovery after discontinuation. Stopping the toxin should help, at least a little.
5. Asymmetry should be the exception and explicable. Toxins will not preferentially choose one optic nerve over the other.

Generally, the more postulates satisfied, the greater the likelihood of causation.

Preventive Measures and Public Health Concerns

With MON, there is often a window of reversibility because mitochondrial dysfunction may lead to functional impairment without immediate axonal loss. Axons may undergo compensatory stages of mitochondrial congregation, slowed axonal transport, and axonal swelling before apoptosis. However, if the injury is long standing and the axons have already suffered irreversible damage as reflected by severe optic atrophy, there will be little or no recovery. Therefore, prompt recognition of drug-induced toxicity and cessation of the medication is critical in preventing irreversible vision loss.

References


A Case of Extraocular Muscle Enlargement Causing Diplopia: Thinking Beyond Thyroid Eye Disease

Kian Eftekhari, MD, Collin M. McClelland, MD, Roberta E. Gausas, MD, Bo Jian, MD, PhD, John Woo, MD, Nicholas J. Volpe, MD, Madhura A. Tamhankar, MD

Dr. Eftekhari and Dr. McClelland:

A 64-year-old woman complained of insidious onset of binocular vertical diplopia for 4 weeks. The diplopia was present in upgaze and downgaze and was worse in the morning and improved as the day progressed. She denied pain with eye movements, eyelid droop, generalized weakness, or difficulty swallowing. Her medical history was significant for colon cancer that was treated with surgery and chemotherapy 4 years previously and cardiac arrhythmia. She had a history of narrow anterior chamber angles treated with laser peripheral iridotomies. She worked as a dog groomer.

The patient’s visual acuity was 20/20 in the right eye, and 20/15 in the left eye, with normal color vision bilaterally. External examination showed bilateral eyelid retraction and lid lag in downgaze (Fig. 1). Evaluation of extraocular movements revealed mild decrease in elevation and depression of the right eye and normal motility of the left eye. Despite the lack of diplopia in primary gaze, her sensorimotor examination showed a 12-prism diopter (PD) right hypertropia that increased in downgaze to 16 PD. The hypertropia measured 10 PD in right gaze and 6 PD in left gaze. In addition, the patient had 18 PD of comitant exotropia. The pupils and funduscopy examination were normal in both eyes.

Orbital echography (A and B scans) showed mild, diffuse thickening of all extraocular muscles in both orbits and marked enlargement of the right inferior rectus muscle (Fig. 2). The right inferior rectus muscle showed low internal reflectivity on A scan, whereas the other extraocular muscles had high internal reflectivity. We considered the possibilities of thyroid eye disease, orbital pseudotumor, a mass lesion of the inferior rectus muscle, or a combination of these processes. Thyroid studies revealed an elevated thyroid stimulating hormone level of 6.12 mIU/L (normal, 0.40–5.50 mIU/L), a normal thyroid-stimulating immunoglobulin level, and negative acetylcholine receptor–binding antibodies. Magnetic resonance imaging (MRI) of the brain and orbits was obtained.

Dr. Eftekhari and Dr. McClelland:

In view of the patient’s clinical presentation and the results of ultrasonography and MRI, a biopsy of the right inferior rectus muscle was performed.

Dr. Gausas:

The patient underwent biopsy of the right inferior rectus muscle via an inferior transconjunctival approach combined with a lateral canthotomy and cantholysis to obtain additional exposure. The periosteum of the orbital floor was elevated and incised to obtain access to the inferior rectus muscle from which multiple specimens were obtained.
Dr. Jian:
The biopsy specimen from the right inferior rectus muscle showed fibrotic skeletal muscle with a dense mononuclear infiltrate. The cells were intermediate to large in size with scant cytoplasm, round to slightly irregular nuclei, and finely granular chromatin without cytological atypia. No cytological atypia, mitotic figures, or necrosis were noted (Fig. 4). Immunohistochemical stains showed that these cells were positive for chromogranin, synaptophysin, and pancytokeratin (Fig. 5). Additionally, the cells were positive for CD10, and a substantial portion were Ki-67 positive, indicating active proliferation. Because of the patient’s history of colonic adenocarcinoma, the slides from her hemicolectomy specimen were obtained from an outside institution and reviewed. The colectomy specimen was consistent with adenocarcinoma, and it did not have the same features of the mass in the right inferior rectus muscle. The final diagnosis was a neuroendocrine tumor most consistent with a carcinoid.

Dr. Eftekhari and Dr. McClelland:
The patient underwent a systemic screening for a primary lesion. Computed tomography (CT) of the chest and abdomen revealed a 2.5-cm mass in the lower lobe of the left lung and 2 suspicious lesions in the liver. Laboratory studies including urinary 5-hydroxyindoleacetic acid levels were normal, suggesting that she did not have a functional carcinoid syndrome. Biopsies of the lung and liver lesions revealed a low-to-intermediate grade neuroendocrine tumor, consistent in appearance with the specimen from the right inferior rectus muscle.

Final Diagnosis
Metastatic bronchial carcinoid.

Dr. Eftekhari and Dr. McClelland:
The patient received palliative stereotactic radiation therapy to the right orbit. She developed a large right hypotropia from radiation-induced fibrosis of the right inferior rectus muscle and underwent strabismus surgery.

Dr. Volpe and Dr. Tamhankar:
Intraoperatively, the patient had positive forced ductions in depression as well as elevation, indicating restriction of both superior and inferior rectus muscles of the right eye. Accordingly, she underwent recession of the right inferior rectus and superior rectus muscles. Postoperatively, the patient had significant improvement in her symptoms, with a larger field of single vision in primary gaze.

Dr. Eftekhari and Dr. McClelland:
A positron emission tomography/CT 9 months after the diagnosis revealed enlargement of the lung and liver lesions. The patient was placed on octreotide and underwent palliative hypofractionated stereotactic radiosurgery for her lung and liver lesions. However, the patient’s disease progressed, and she ultimately succumbed to her illness less than 2 years after the diagnosis.

Dr. Tamhankar:
Carcinoid tumors comprise 0.49% of all malignancies and are derived from enterochromaffin cells that are found mainly in the gastrointestinal tract (67%) but also are present in the...
bronchopulmonary tract (25%), ovaries, biliary tract, and testes (1). The term karzinoide was first used by Oberndorfer in 1907 to classify these tumors as benign compared with the more malignant intestinal adenocarcinoma (1). Carcinoid tumors commonly are slow growing, although they can be aggressive and lethal. The most common site for carcinoid metastases is the liver, while ocular metastases are rare (2,3).

In patients with metastatic carcinoid, the 5-year survival is approximately 38% (1). About 10% of patients with carcinoid tumors secrete vasoactive substances that can lead to the carcinoid syndrome characterized by paroxysmal facial flushing, diarrhea, asthma, cardiac arrhythmias, and cardiac valvular abnormalities (1).

Carcinoid tumors comprise 4%–5% of orbital metastases (2) and 1% of uveal metastases (3). There are at least 33 reported cases of carcinoid metastatic to the orbit, involving one or more extraocular muscles, the retrobulbar soft tissues, or a combination of both (4,5). Previous studies have reported that bronchial carcinoid tumors are more likely to metastasize to the uveal tract and gastrointestinal carcinoid tumors tend to metastasize to the orbit (6–8). However, there are reports of bronchial carcinoids metastasizing to the orbit (5,9–12). The apparent association between the site of origin of the carcinoid tumor and the site of metastasis may reflect the frequency of gastrointestinal and bronchial carcinoid tumors rather than a true relationship.

An interesting aspect of our case was that the orbital metastasis was the presenting feature of an undiagnosed primary neoplasm. In a large series of orbital carcinoid metastases, 69% of patients had a known carcinoid prior to presentation (4). On average, these patients were diagnosed with the primary carcinoid tumor 10 years before presenting with orbital metastases. An analysis of published data revealed that about one-fifth of patients (22%) with orbital carcinoid metastases present with orbital disease before discovery of the primary tumor (4).

The most common presenting symptom of carcinoid tumor metastatic to the orbit is diplopia, followed by decreased vision, ptosis, and pain. In our patient, the differential diagnosis for diplopia and an enlarged extraocular muscle included a neoplasm, thyroid eye disease, and idiopathic orbital inflammatory syndrome (IOIS). The absence of pain and the insidious onset of her symptoms made IOIS unlikely. Thyroid eye disease was a diagnostic consideration in our patient because of the insidious onset of diplopia, the presence of eyelid retraction, diffuse enlargement of all hyperreflective extraocular muscles on ultrasonography, and an elevated thyroid stimulating hormone level. It is possible that our patient had thyroid eye disease. However, we were suspicious of another disease process for a variety of reasons: the pattern of her ocular misalignment indicated that her diplopia was due, in part, to paresis of the right inferior rectus muscle rather than restriction, the muscle had low internal reflectivity, and MRI demonstrated focal, heterogeneous enlargement of the right inferior rectus muscle, which is unusual for thyroid eye disease. In addition, the patient had a history of a colonic neoplasm, and a biopsy was necessary to exclude a malignancy of the inferior rectus muscle.

It is important for the clinician to be aware of the nonthyroid causes of extraocular muscle enlargement and to

**FIG. 4.** Biopsy specimen from the right inferior rectus muscle showing fibrotic skeletal muscle with a dense infiltration of mononuclear cells with scant cytoplasm without atypia, mitoses, or necrosis (hematoxylin and eosin: ×10 (A), ×40 (B)).

**FIG. 5.** The right inferior rectus biopsy specimen showing positivity for chromogranin (A), synaptophysin (B), and pan-cytokeratin (C), indicating a neuroendocrine tumor (A, B, C, ×40).
have a high index of suspicion in patients presenting with diplopia with atypical clinical and imaging features. This was highlighted in a series of 103 patients by Lacey et al (13) who reported that inflammatory, vascular, and neoplastic disorders (including melanoma, breast cancer, and lymphoma) were the most common nonthyroid causes of extraocular muscle enlargement, with rare disorders such as cysticercosis also in the differential diagnosis (13).

REFERENCES
Optic Nerve Sheath Fenestration vs Cerebrospinal Diversion Procedures: What Is the Preferred Surgical Procedure for the Treatment of Idiopathic Intracranial Hypertension Failing Maximum Medical Therapy?

Arielle Spitze, MD, Amina Malik, MD, Nagham Al-Zubidi, MD, Karl Golnik, MD, MEd, Andrew G. Lee, MD

Although most patients with idiopathic intracranial hypertension (IIH) can be effectively treated with conservative measures, such as lumbar puncture, weight loss, acetazolamide, medical treatment of headaches, surgery is sometimes necessary, particularly in patients with visual loss secondary to chronic papilledema (1–4). Recently, endovascular venous stenting of a stenosed dominant intracranial transverse venous sinus has been proposed as a possible treatment (5); however, cerebrospinal fluid (CSF) shunting and optic nerve sheath fenestration (ONSF) remain among the most commonly used surgical procedures to treat IIH in the United States (6). In the absence of any prospective, randomized clinical trials comparing these procedures for the treatment of IIH, opinions vary greatly between ONSF and CSF shunting procedures as the most appropriate recommended surgical treatment (7,8). The decision to use one or the other is often based on local preferences and the availability of specific surgeons; some centers always perform ONSF as a first-line treatment, some use both procedures based on patient’s symptoms and signs (ONSF for visual loss and shunts for headaches), while others exclusively recommend lumboperitoneal shunt (LPS) or ventriculoperitoneal shunt (VPS) when surgery is necessary (9).

**PRO—ONSF is the preferred treatment for IIH patients who require a surgical treatment.**

Arielle Spitze, MD, Nagham Al-Zubidi, MD, Andrew G. Lee, MD

**Opening Statement:**

In our experience, ONSF is superior to CSF shunting based on the following: 1) ONSF directly treats the major morbidity of IIH, namely, visual loss from chronic papilledema; 2) ONSF may also treat the headache of IIH; 3) ONSF has less morbidity (and mortality) than CSF shunting; and 4) CSF shunting has poor long-term efficacy and may require multiple revisions.

Interestingly, unilateral ONSF may not only result in ipsilateral improvement of papilledema and visual function but also lead to improvement in the nonoperated fellow eye.
This was emphasized in a recent retrospective study of 62 IIH patients who underwent unilateral ONSF (13). Although the reduction in papilledema was greatest on the operated eye, a reduction in papilledema grade was also seen in the contralateral eye at 3, 6, and 12 months postoperatively. The reduction in papilledema correlated with a corresponding increase in visual function in both operated and contralateral eyes. In a retrospective literature review by Felдон (14), the majority of ONSF were bilateral (59%), although he emphasized that in patients with significantly asymmetric loss of vision, unilateral ONSF can be employed in the more severe eye first. Although bilateral ONSF might require 2 surgical sittings with separate anesthesia compared with a single anesthesia session in a CSF shunting procedure, bilateral ONSF may not always be necessary even in patients with bilateral visual loss and papilledema.

ONSF may improve headaches in IIH patients

In one review, a significant improvement in or resolution of headaches was reported in more than half of the patients with IIH after ONSF (15). Some studies support the finding of up to 50% improvement in headaches following ONSF (16,17), while Banta and Farris (10) reported improvement in 31% of their ONSF cases. The mechanism for this is unclear. One hypothesis is that the reduction in headache is related to reduced intracranial pressure (ICP) secondary to CSF drainage through the fenestration, although this mechanism is questionable given the small size of the sheath fenestration slits or windows. Alternatively, this may result from placebo effect with increased patient compliance with medical therapy. A prospective standardized evaluation of the sustainability of any treatment effect of ONSF on headache does not exist, and this makes it difficult to draw any meaningful conclusions on the pathogenesis or long-term efficacy.

ONSF has low morbidity and mortality

The ONSF procedure initially was described using a lateral approach with or without disinsertion of the lateral rectus muscle (17). However, many important vascular structures and nerves as well as the lacrimal gland are located laterally. A medial subconjunctival approach was devised and is commonly used today, although it also requires medial rectus disinsertion and/or significant medial rectus retraction, which can still lead to muscle or third nerve–related surgical complications. Another technique gaining popularity is using an anterior medial upper eyelid crease approach to gain access to the medial intraconal space (18). This approach offers a relatively avascular plane between the superior oblique and medial rectus muscles and fairly offers direct access to the retrobulbar optic nerve. Although the risk for nerve or muscle injury is still present, it is minimized because there is no need to disinsert any of the extraocular muscle or use significant heavy traction on the muscles.

It is difficult to compare ONSF complication rates among institutions and studies because of the many different surgical techniques. Most studies of ONSF have reported that surgical complications are usually transient and resolve without sequelae (9–11,14). Chandrasekaran et al (11) found a 15.6% overall complication rate (5 of 32 patients) after ONSF. All complications were self-limited (3 patients had diplopia, 2 had anisocoria, and 1 patient had a disc hemorrhage). In this study, all surgeries were performed by the same surgeon using a medial subconjunctival approach. Plotnik and Kosmorsky (19) reported a higher (40% overall) complication rate, including temporary motility disorders (29%), and pupillary dysfunction (11%), in addition to more severe vascular complications (11%) (1 episode of transient outer retinal ischemia, 1 superotemporal branch retinal artery occlusion, and 2 central retinal artery occlusions). Mauriello et al (20) identified 5 patients with poor outcome after ONSF including 1 postoperative retrobulbar hemorrhage, 1 infectious postoperative optic neuropathy, and 3 patients with a gradual decline in vision without a particular surgical complication identified (the mechanism was suspected to be persistently elevated ICP).

Although a wide range of complication rates were reported to be associated with ONSF, most studies are in agreement with a range between 5% and 45% (9). The large range is likely secondary to variable surgeons and ONSF techniques, as surgical procedures between institutions are often not standardized, or can differ between surgeons within the same institution. Even with such wide variability, severe complications remained rare, and no fatalities were reported.

CSF shunting procedures have high morbidity and mortality compared with ONSF

Shunt-related complications in a study by the Karabatsou et al (21) included 17 shunt migrations, 1 case of temporary radiculopathy, 7 shunt-related infections (1% infection rate per procedure or 33% per patient), and 7 patients with tonsillar herniation (although only 2 patients were symptomatic). El-Saadany et al (22), although reporting an improvement in headaches in the majority of their 22 patients, also reported a 9% (2 of 22) shunt infection rate, a 27% (6 of 22) rate of shunt obstruction, and a 13% (3 of 22) rate of shunt overdrainage. El-Saadany et al (22) found that the migration of the peritoneal catheter was the most common cause for shunt obstruction and result in the need for shunt revision. Tarnaris et al (23) reported on 29 patients who underwent a shunt procedure. Of these patients, 20.5% (6 of 29) had complications, and 35% (10 of 29) ultimately required a shunt revision. Complications in this series included shunt infection, shunt obstruction, intra-abdominal pain, and CSF leak. LPS procedures (n = 24) were advantageous in avoiding intracranial complications but involved more problems with infection, subdural hematoma, cerebellar tonsillar descent, and distal catheter migration and obstruction.
VPS (n = 5) had lower revision rates, but this may be because of the fact that far fewer VPS were performed than LPS. VPS have a greater risk of intracranial complications and difficulty with shunt placement within the small ventricles of IIH patients (23). Newer techniques such as stereotactic VPS placement have been introduced, which could lower shunt placement complications in the future. More long-term, prospective studies are needed to compare shunt placement techniques (24).

Between 1988 and 2002, the incidence of CSF shunting for IIH reported by Curry et al (25) increased up to 350% nationwide. While this study had limitation, out of 2,779 admissions for CSF shunting in IIH patients, overall inpatient mortality was 0.5% (0.9% mortality rate for VPS and 0.3% for LPS). Thus, our strongest argument against CSF shunting as the primary surgical option in IIH is the unacceptable mortality rate of up to 0.9% for what is a non-life-threatening condition and for which there is a reasonable surgical alternative, namely, ONSF. In addition, shunts often require an inpatient hospital stay, unlike ONSF, which are performed on an outpatient basis.

**CSF shunts (VPS, LPS, and ventriculoatrial) have weaker long-term efficacy in IIH**

A large literature review summarized the findings of 7 different retrospective series including a total of 423 eyes of 252 IIH patients post-ONSF. In a mean follow-up period of 21.1 months, the revision or reoperation rate was 12%, with only 4% ultimately requiring CSF shunting (20).

In contrast, Sinclair et al (26) found that shunt revisions were commonplace, with 51% of the patients requiring a revision and 30% requiring multiple revisions. This high rate may be secondary to the large number of primary LPS (49 of 53 patients). This type of shunt is reported to have a higher revision rate than VPS. It may also be surgeon and institution dependent. Although CSF shunting was found helpful in halting visual deterioration, Sinclair et al (26) suggested that because of the high rate of shunt complications, shunt revisions, and persistent postshunt headaches, headaches alone should not be an indication for shunting. Karabatsou et al (21) retrospectively reviewed the outcomes of 21 patients post-LPS placement and also reported high shunt revision rates. There was an average of 3 revisions per patient, with a total of 63 revisions in 21 patients over an average follow-up period of 24 months. Only 3 patients did not undergo shunt revision.

Despite decreasing ICP, CSF shunts do not always improve symptoms. This finding could in part be the result of the non-ICP-related nature of many IIH-associated headaches. In their 10-year review, Sinclair et al (26) reported an overall improvement in visual symptoms after shunting, but headaches remained in a majority of patients (79%). The lack of improvement in headache after shunting may be because of the fact that not all headaches in IIH patients are related to increased ICP.

In summary, we argue that ONSF is a superior surgical option to CSF shunting in IIH because 1) ONSF effectively treats the major morbidity of IIH, namely, the papilledema and related vision loss; 2) ONSF may also treat the headache of IIH; 3) CSF shunting has poor long-term efficacy in IIH and may require multiple shunt revisions; and 4) ONSF has less morbidity and less surgical procedure–related mortality (compared with up to 0.9% mortality for VPS) for a non-life-threatening condition.

**CON—Cerebrospinal diversion procedures are the treatment of choice in patients with IIH failing maximal medical therapy: Amina Malik, MD, Karl Golnik, MD, MEDE**

Opening Statement:

We would argue that in patients with both headache and visual loss, CSF shunting is the preferred treatment for IIH. We make this argument based on the fact that 1) CSF shunting works to directly lower the ICP, which is the underlying problem in IIH patients; 2) CSF shunting, unlike ONSF, does not pose any direct risk to vision, which is what our treatment is aimed toward improving; and 3) patients who undergo ONSF may eventually require CSF shunting procedures.

**CSF diversion procedures lower ICP and improve signs and symptoms of IIH**

Shunting procedures (LPS or VPS) often result in the improvement of neurologic symptoms related to increased ICP, including headache, nausea, vomiting, memory loss, pulsatile tinnitus, or diplopia from sixth nerve palsy (27). In a retrospective review of 30 cases of IIH treated with LPS, Burgett et al (28) reported that 82% of their patients experienced improvement in the symptoms of increased ICP, including headache. There was an improvement of at least 2 lines of visual acuity in 71% of patients with preoperative decreased vision, including one patient who improved from no light perception to 20/25. Only 1 eye had worsened visual acuity, for which the patient previously had undergone ONSF. Twenty-eight patients had preoperative abnormalities on kinetic visual field testing, of which 18 patients showed improvement and none worsened. Papilledema resolved in 96% of patients. The most common complication was shunt revision, with a total of 126 revisions in 30 patients, with a mean revision rate of 4.2. However, 87 of these revisions occurred in only 4 patients. Excluding these patients, the revision rate was 2.5 per patient. As noted in previous series,
the need for shunt revision was not distributed evenly among all patients but was concentrated in a subgroup of patients who seemed particularly prone to shunt failure. Shunt infection, the only life-threatening complication, occurred in only 1 of the 30 patients (28).

Eggenberger et al (29) reported a series of 27 patients with IIH treated with LPS. The indications for LPS were intracerebral headache in 18 patients (67%) and progressive optic neuropathy in 14 patients (52%). Visual function improved to normal in both eyes of 6 patients, had no change in either eye in 4 patients, and improved in at least 1 eye in the remaining 4 patients. Additionally, 5 patients had sixth nerve palsies, all of which fully resolved postoperatively. All patients in this study had improvement in neurologic symptoms, and no shunt-related symptoms, such as low-pressure headache or abdominal pain, were noted within 2 months of the surgery. Although 56% (15 of 27) of patients required shunt revision, there were no major complications from LPS other than shunt failure. Angiari et al (30) reported 3 cases of IIH with significant visual defects who underwent LPS. All 3 patients experienced visual recovery and alleviation of neurologic symptoms without any life-threatening complications. Similarly, McGirt et al (31) reported 42 patients with IIH who underwent 115 shunt placement procedures. Forty patients (95%) experienced a significant improvement in their headaches immediately after the shunt was performed. Abubaker et al (32) reported 25 patients who underwent shunting procedures. Eighteen patients underwent LPS, of which all experienced immediate postoperative improvement in visual acuity and visual fields. The majority (11 of 19) experienced improvement in headache and papilledema. Ten patients required shunt revisions. Other complications seen were radicular pain in 1 patient, abdominal pain in 2, low pressure headaches in 2, and shunt infection in 1 patient.

The study by Curry et al (25) (cited above) reported that the mortality in CSF diversion procedures is 0.9%, which is an initially alarming number. However, this is a review from a national hospital discharge database where no individual cases can be identified. It is unclear exactly why these patients died, and why the CSF diversions were performed. We know of no documented cases of death directly related to CSF diversion for IIH.

These studies suggest that LPS is an effective treatment for both visual and neurologic symptoms in IIH patients with a low rate of overall morbidity and mortality, with the main complication being shunt revisions. Nevertheless, shunt revisions have low morbidity and mortality, and thus, CSF diversion procedures benefit outweigh the downside of this complication.

**ONSF can pose a direct threat to vision**

While improvement in visual function and papilledema after ONSF has been well documented (10–13,19,33), this surgical procedure can pose a direct threat to vision. In the study by Plotnik and Kosmorsky (19), 2 of 38 patients (5%) had permanent visual loss from central retinal artery occlusion. Mauriello et al (25) reported 5 patients with IIH who underwent ONSF and had postoperative visual loss. One had an abrupt decrease in vision 6 days after the surgery, caused by bleeding from a vessel on the nerve sheath. This patient had a 20/20 vision 1 day postoperatively but decreased to 20/200 after five days. High-dose intravenous corticosteroids failed to improve vision, but emergency LPS resulted in full visual recovery. An infectious optic neuropathy developed in another patient 3 days after the surgery, although visual acuity did improve from 20/600 to 20/15 after 72 hours of intravenous antibiotics. The other 3 patients had gradual visual loss after ONSD, all of which stabilized after LPS. In an animal study by Gellrich et al (34), ONSF was performed on 22 rats and with a significant reduction in the number and size of retinal ganglion cells and amacrine cells 30 days after the surgery, compared to rats that did not undergo ONSF. Although ONSF is thought to have “low” risk, in patients with relatively good vision, even a 1% risk of permanent visual loss is too high. We argue that because vision preservation (and improvement) is the primary treatment goal in IIH patients, performance of a surgery with a direct threat to vision is less desirable than CSF diversion, which poses no direct risk to vision.

**Patients who undergo ONSF may go on to require CSF diversion procedures**

Headache is the most common symptom in IIH and present in 92%–94% of patients (8). While CSF diversion procedures have been documented to improve headaches (28–32), only 50% of patients who undergo ONSF will experience significant, persistent relief from headache (29). Banta and Farris (10) documented that only 31% of patients who underwent ONSF experienced improvement in headache. Even a 50% reduction in headaches is not adequate for patients debilitated by this symptom.

Additionally, patients who undergo ONSF may require future CSF diversion procedures to treat intractable visual loss (35). In a study by Acheson et al (35), 20 eyes of 14 patients underwent ONSF. Of these, 11 patients had IIH. Eleven eyes had reduced vision preoperatively, of which 5 improved, 3 stabilized, and 3 deteriorated. Four patients (20%) required additional CSF diversion surgery for persistent headache and/or visual loss. Herzau and Baykal (36) reported a long-term follow-up of ONSF in 23 eyes of 14 patients. Improvement or stabilization in visual acuity and visual field testing was documented in 17 eyes. Six eyes, however, showed a recurrence of papilledema after an interval of 7–121 months. Three eyes of 2 patients progressed to develop optic atrophy and extensive visual loss. In performing ONSF in 75 cases, Spoor and McHenry (12) found only 36% sustained improvement in visual function, 32% had stabilization, and 32% experienced deterioration. In their series, 24 eyes required repeat ONSF for decreasing visual function. Of these, 6 eyes had persistently decreased visual function and required either repeat
ONSF or shunting procedure. In the cases that required yet another ONSF, extensive scarring and arachnoidal adhesions were found at the site of previous surgery, and these patients rarely enjoyed long-term improvement in visual function. Since many patients may end up requiring CSF diversion procedures after undergoing ONSF, we maintain that it is not worth subjecting patients with IIH to 2 surgeries, when CSF diversion procedures can alleviate both visual and neurologic symptoms.

In summary, we believe that in patients with IIH who present with neurologic symptoms and visual loss, CSF diversion procedures are preferred to ONSF because 1) CSF diversion procedures address the underlying problem and lower ICP, 2) ONSF can pose direct threat to vision, and 3) patients who undergo ONSF may go on to require CSF diversion procedures. We reserve ONSF for patients with rapid visual loss or progressing visual loss without headaches or other neurologic symptoms.

Rebuttal: Arielle Spitze, MD, Nagham Al-Zubidi, MD, Andrew G. Lee, MD

We offer the following point-by-point rebuttal to the advantages of shunting proposed by Malik and Golnik. First, they propose that CSF diversion procedures address the underlying problem of IIH by lowering ICP. This is true, but only if the shunt is functional. Our main contention with CSF shunting is that the effect may not be sustained and the long-term efficacy of CSF diversion procedures remains problematic. Second, although we acknowledge that ONSF can pose a direct threat to vision, so can shunting—both from failure of the shunt (shunt related visual loss) or from direct or indirect injury by the shunt catheter—shunt infection (e.g., meningitis related visual loss), or problems related to overdrainage. We also acknowledge that patients who undergo ONSF may still require a CSF diversion procedure. In fact, we believe that it is appropriate in some settings to have both procedures (fulminant IIH with severe and progressive visual losses). Malik and Golnik state that they have no direct knowledge of shunt-related mortality and question the nature of underlying etiologies for death from shunting in the study by Curry et al (25). In our referral practice, we see many patients with shunt-related complications that are potentially life threatening including shunt infection (bacterial and fungal), proximal or distal shunt obstruction, migration, disconnection, slit ventricle syndrome, overdrainage (with worsening of headaches), acquired Chiari 1 malformations, and both intraventricular and subdural hemorrhages. In addition, we speculate that some of the causes of mortality may be related to the more prolonged recovery time for CSF shunting vs ONSF and may increase the risk of deep venous thrombosis and pulmonary embolus. Other cases with morbidity or mortality after shunting may have included occult dural arteriovenous fistulas with venous sinus thrombosis mimicking IIH for which an LPS might create a dramatic ICP gradient change, tonsilar herniation, or autoregulatory failure at the disc head and worsening visual loss. Cognard et al (37) stated that an LPS in this setting would be contraindicated.

Rebuttal: Amina Malik, MD, Karl Golnik, MD, MEd.

First, we do acknowledge that while CSF shunting often requires revisions over time, the surgery still works by lowering the overall ICP, in contrast to ONSF. Even if revisions are performed, the surgery addresses the underlying problem of increased ICP in IIH. Second, we would still argue that CSF diversion does not pose a direct threat to optic nerve function. We know of no cases of direct vision loss because of the performance of a CSF diversion procedure, while cases of blindness after ONSF have been reported, as discussed above. Third, we acknowledge and have observed complications related to CSF shunting procedures, but unlike our colleagues, we have not experienced mortality as a complication of shunting.

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

This debate confirms the need for a study directly comparing ONSF with CSF-shunting procedures in the treatment of IIH. In most cases, the decision to perform an ONSF or a CSF shunting procedure in a patient with severe IIH is based on local preference: some centers mostly have access to ONSF, whereas others do not have skilled surgeons able to perform a safe ONSF, and therefore choose a CSF shunting procedure (or even an endovascular stenting procedure [5]). The risk of shunt-related complications should decline with newer surgical techniques such as VPS placed under stereotactic guidance and with programmable valves in order to maximize their efficacy and tolerance. However, because
the expertise of the surgeon strongly correlates with the surgical outcomes, decisions based on local preferences and expertise need to be followed until a clinical trial demonstrates the superiority of one surgical procedure over the other or allows better characterization of which patients will benefit most from a specific procedure.

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It is a great honor and pleasure and very humbling to deliver this lecture. I stand in awe of William Hoyt and the august list of past awardees. Most of my training in neuro-ophthalmology was with Simons Lessell and my debt to him can’t be overstated. One of the many kindnesses he did for me was to send me to San Francisco to spend the last 6 weeks of my fellowship with Dr. Hoyt (see Supplemental Digital Content, Figure E1, http://links.lww.com/WNO/A78).

I am also humbled by the prospect of discussing the topic I may have foolishly chosen for myself. Are we there yet? Is neuro-ophthalmology at the cusp of a paradigm shift? This comment is in reference to the classical work of Thomas Kuhn. In 1962, Kuhn, a physicist, a philosopher, and a professor at Massachusetts Institute of Technology published “The Structure of Scientific Revolutions” (1). In this book, he described what became popularly known as the “paradigm shift.” Kuhn pointed out that scientists accumulate evidence that supports their model of the real world. However, such evidence eventually becomes messy and even self-contradictory until at such time as the revolution, or paradigm shift, re-establishes a fundamentally different model. Kuhn described 3 stages for each science as: the central paradigm, the anomalous elements, and the reconfiguration of the new paradigm.

What has all this got to do with neuro-ophthalmology? Well, the central paradigm for neuro-ophthalmology was that a single physical lesion produced a classical set of signs and symptoms. However, with the arrival of neuroimaging, it appeared that computed tomography and magnetic resonance imaging might do the job better than a neuro-ophthalmologist. In fact, when I was with Dr. Hoyt, I recall him bemoaning the possible end of neuro-ophthalmology with the success of neuroimaging. However, there are diseases that do not conform to the localizing lesion paradigm and are not detectable with neuroimaging techniques.
MITOCHONDRIAL OPTIC NEUROPATHIES

The metabolic injury that characterizes mitochondrial optic neuropathies (MON) might be characterized as a biochemical paradigm. MON can be genetic, as in Leber hereditary optic neuropathy (LHON) or dominant optic atrophy, secondary to nutritional deficiencies, such as with vitamin B12 or folic acid, or due to a variety of toxic agents, many of which are antibiotics that interfere with both bacterial and mitochondrial ribosomes (2,3).

The prototypic MON, LHON, was first described in 1858 by Von Graefe. In 1871, Leber reported 4 families and proposed that this was a hereditary and probably X-linked disease (4–7). However, it wasn’t until 1988 when Wallace et al (8) described the 11778 mitochondrial DNA (mtDNA) mutation that we began to get a handle on both the genetics and the pathophysiology of this MON.

Neuro-ophthalmologists are well aware of the typical presentation of LHON. But you might find it interesting to know that what we often see in the United States is a little different in Brazil. In the United States, I might see a young man in good health without a family history of blindness. He goes off to college and adopts a lifestyle, which includes smoking and heavy drinking. A few months later he suffers subacute loss of vision in one eye and is seen at the student health center and diagnosed with optic neuritis. The work-up for multiple sclerosis is entirely negative and within a month or two he loses vision in the fellow eye. It’s about then that he gets referred to neuro-ophthalmology and the diagnosis becomes clear. I’ll tell you later how this plays out a little bit differently in Brazil.

FOUR FUNDAMENTAL QUESTIONS

There are many mysteries in LHON. Let me point out 4:

1. Why are some individuals with the mutation affected and others not? (The problem of penetrance.)
2. Why are men much more likely to lose vision than women? (The problem of gender bias.)
3. Why is it almost always just the optic nerve that succumbs? (The problem of tissue specificity.)
4. Why does the catastrophic loss of vision occur during young adulthood? (The problem of mass tipping point.)

Mitochondria are remarkable organelles. We tend to describe them as individual little beans that float freely in the cytoplasm but of course that isn’t really accurate. Mitochondria usually fuse into a syncytium, which follows the cytoskeleton and then sometimes they undergo fission, perhaps for special functions such as transport. The mitochondria coordinate with the nucleus in a variety of functions, including their own reproduction, which occurs in the soma of the retinal ganglion cell (RGC) in proximity to the nucleus. They may then hitch a ride on kinesin and dynein motors, to travel down the axons and provide adenosine triphosphate (ATP) to distal elements. In producing ATP, mitochondria utilize oxy-

FIG. 1. Leber hereditary optic neuropathy pedigree composed of 8 generations. The affected individual in generation 2 was born in 1861 and emigrated from Verona to the state of Spirito Santo, Brazil, at the age of 16 years, where she became the founder of the seventh-generation 332-member pedigree. Another 30 members still living in Italy have also been identified (adapted from Sadun et al (14)).

dative phosphorylation and, as a consequence, produce great amounts of reactive oxygen species (ROS) (9,10).

LHON PEDIGREE IN BRAZIL

I was extremely fortunate to lead a team of international investigators, numbering up to 40 at a time, in yearly field investigations to rural Brazil. We utilized an ophthalmology clinic in Colatina, Brazil, and received support from many volunteers organized through the Federal University of Sao Paulo (11). The first such visit in 2001 allowed us to define a large pedigree of 11778 LHON. In subsequent years, we worked out the psychophysics, came to understand that there was subclinical disease in carriers of LHON, monitored the natural history of conversions, and established a number of psychophysical, clinical, subclinical, and serum biomarkers (12–18). We characterized a pedigree with 362 members from 8 generations that all began in 1861 in Verona, Italy (Fig. 1). From there, a 16-year-old girl immigrated to Brazil to become the founder of this family. Almost all her progeny have remained in the same area in rural Brazil (11).

All of this came to our attention through a series of e-mails that originated from the mother of a 14-year-old boy who had just lost vision in one eye. This mother recalled that 30 years before, her 2 older brothers had experienced similar profound visual loss. By way of the Internet, she resolved to better understand her family’s disease and then to contact experts in the field whom she hoped could provide a means of keeping her child from going blind in the second eye. Through the International Foundation for Optic Nerve Diseases, she found me and, despite the complications of language and culture, we
concluded that the diagnosis that she proposed, LHON, was correct. She told of a 100 family members who might be carriers of LHON with several having already lost vision, and she was anxious that we evaluate her son. We resolved to assemble a large team to conduct a field investigation in Brazil. We arranged for her, with her son and 2 brothers, to be evaluated at the Federal University in Sao Paulo. Measurements of visual acuity, visual fields, and fundus photographs were sent to us along with blood for genetic testing. Unfortunately, by the time that they arrived in Sao Paulo, her 14-year-old son had already lost vision in the second eye. He had visual acuity of 20/200, right eye, and 20/800, left eye, and his fundus appearance is shown in Figure 2.

The logistics were challenging to bring expertise and sophisticated equipment from around the world into a remote area of Brazil. We managed these for 11 consecutive years and made a number of interesting findings. For example, although we found that the average age of onset for the entire family was 29 years, subgroup analysis showed this age to be 23 years for men and 33 years for women. Women had a bimodal distribution, with some losing vision at about the same age as the men but others losing vision as they approached menopause. The visual acuity of those who became affected and lost vision averaged 5/400. Remarkably, the penetrance rate was much higher if the mother herself had lost vision. In other words, if a mother lost vision, it was almost certain that her sons would be affected and her daughters were at high risk. But if a mother was an unaffected carrier, her daughters were very unlikely to lose vision and even her sons had good odds of preserving their sight. Similar to reports from other pedigrees (19–24), we found a male to female ratio of about 4:1 in this 11778 family. It was intriguing that the most common month for vision loss in Brazil was April. We will later revisit this

![Figure 2](image1.png)

**FIG. 2.** Leber hereditary optic neuropathy index case of a 14-year-old boy. There is pseudooptic disc edema and retinal nerve fiber swelling (arrows) in the both eyes (left and right), mild left optic disc pallor, and decreased nerve fiber layer in the papillomacular bundle of each eye (adapted from Sadun et al (12)).

![Figure 3](image2.png)

**FIG. 3.** Light (A) and electron microscopic (B) photographs of fibers in the retrobulbar optic nerve from a 76-year-old woman with Leber hereditary optic neuropathy who had lost vision about 50 years ago. A. The remaining fibers (arrows) are swollen and beaded. B. Some fibers are actively undergoing degeneration (arrow) (A, paraphenylene diamine stain; scale bar = 10 μm; B, scale bar = 1 μm).
seasonal phenomenon in the light of the likely 6-week lag period between the triggering insult and the loss of vision in LHON. We found that the likelihood of conversion from carrier status to affected was much higher in those exposed to pesticides, cigarette smoking, and alcohol (11,12). Sixty-five percent of our affected LHON patients smoked compared with 26.1% of the off-pedigree controls and 13.5% of our LHON carriers. With regards to the consumption of at least 2 drinks of alcohol per day, LHON affected (60%) were much more likely to consume compared with controls (38.2%) or carriers (33.8%). Thus, there was a statistically significant increased rate of smoking and alcohol use in LHON affected compared with either carriers or controls.

After examining close to 300 members of the LHON pedigree every year for 11 years, what did we learn? Our conclusions can be summarized as follows: Although there is an apoplectic loss of vision that occurs over a period of weeks to months, there is also clinical evidence of further progression that continues long term, year after year. This progression is hard to monitor because visual acuity does not continue to change but there is progressive visual field loss well beyond the central 30° angle. One lesson here is that you should keep seeing these patients, keep getting visual fields, and try to use visual field strategies that extend beyond 30° angle. This late progression is probably life-long. We obtained histopathological tissue from a 76-year-old patient who had lost her vision about 5 decades earlier. Her vision had been estimated as counting fingers for decades before she died of cardiovascular complications. In examination of her optic nerves, there was still active degeneration of some remaining fibers found in the superonasal quadrant, shown by light and electron microscopy (EM) (Fig. 3). The appearance on EM reflects degeneration that occurred in the last 4–6 days of her life or 50 years after she first noted visual loss!

What about the asymptomatic carriers? These patients may be asymptomatic but they often harbor subclinical disease. We found zones of mild sectoral disc edema, sometimes with telangiectatic vessels, in more than one-third of the carrier cases (Fig. 4) (15). Using more sophisticated psychophysical techniques (Cambridge color system), we were able to demonstrate some dyschromatopsia in about half of the carriers (16). This dyschromatopsia may be too subtle to show up on standard Ishihara color test plates. Finally, optical coherence tomography (OCT) turned out to be an excellent means of discerning structural changes in asymptomatic carriers. Several female carriers and almost 90% of male carriers demonstrated retinal nerve fiber layer (RNFL) thickening in the inferotemporal quadrant (25–27).

In this extensive longitudinal study, OCT was the most reliable method to demonstrate structural changes, which preceded and then reached a crescendo at the time of visual loss. This began with swelling of the peripapillary RNFL in the inferotemporal quadrant and was followed by swelling superiorly and temporally. Eventually, each quadrant took turns in first swelling and then undergoing atrophy. Barboni et al (26,27) demonstrated this RNFL thickening in carriers and the orderly wave of thickening followed by atrophy that occurs during conversion to affected status. However, not all LHON carriers with OCT changes or pseudo-disc edema lost vision. Some waxed and waned for many years and some even improved without any significant visual loss.

**REACTIVE OXYGEN SPECIES**

Many LHON patients in Brazil experienced vision loss each year in April. In our discussions, it became evident that the visual loss was preceded, in February, by attendance at Carnival, a week-long festivity in Brazil characterized by

![FIG. 4. Twelve-year-old male carrier with 11778 Leber hereditary optic neuropathy. The patient had no visual complaints with visual acuity of 20/20 bilaterally. Yet there is retinal nerve fiber layer swelling associated with telangiectatic vessels (arrows). This patient underwent subacute loss of vision about 2 years after this photograph was taken.](image1)

![FIG. 5. Sagittal sections (lamina cribrosa at the top) of plastic embedded normal human optic nerve (A) and from a patient with Leber hereditary optic neuropathy (LHON) (B). Optic nerve staining with nitrotyrosine immunolabeling is light in normal optic nerve and heavy (arrowheads) in LHON patient (scale bars = 200 μm).](image2)
a great deal of binge drinking. In most cases, the carrier was a teenager who, for the first time, was allowed to accompany a family member to Carnival where they both participated in heavy consumption of alcohol.

The Brazil longitudinal studies take into consideration a number of epidemiological findings that suggest both genetic and environmental risk factors for conversion. Gene linkage analysis points to a “hot spot” on the X chromosome, which may harbor a nuclear modifying factor. There are many genes in this area. One candidate gene is for manganese superoxide dismutase (MnSOD) or SOD2, a specific form of superoxide dismutase used by mitochondria to help neutralize ROS. Of course, ROS may also come from the environment introduced by activities such as heavy drinking and exposure to smoke. We reported several members of the same LHON family who lost vision while being exposed to smoke from a tire fire (28).

This vulnerability to ROS has also been modeled in cybrid experiments. Cybrids are cell cultures that take advantage of an immortalized cell line, such as osteosarcoma, in which the original mitochondria have been destroyed and replaced with mitochondria obtained from the white blood cells taken from LHON patients. These cultures can be grown indefinitely and harbor only the mitochondria of interest. With these experiments, it has been shown that the 3 primary LHON mutations only produce a modest (approximately 20%) decrease in oxygen consumption and ATP production but proportionately a much greater increase in ROS production (29–32).

To look further at the role of ROS, we looked for the presence of nitrotyrosine in optic nerves from LHON patients. Nitrotyrosine is a product of accumulated ROS damage. As demonstrated in our optic nerve sections, nitrotyrosine immunostaining is minimal in control optic nerves and extreme in nerves from patients with LHON (Fig. 5). This suggests a life-long exposure to high levels of ROS in LHON.

ROS overproduction makes sense regarding the pathophysiology that leads to RGC death in LHON, for we know that the mtDNA mutation leads to insufficiency at complex I. This produces a small decrease in ATP but a very large increase in ROS (29,32). Smoke or drinking of alcohol can add significant amounts of ROS, which may then exceed a certain threshold, causing apoptotic cell death (33,34). Furthermore, RGCs may be at particular risk because of their long unmyelinated intraretinal segment.

Mitochondria are likely the lynchpin of this pathological process that ends with RGC apoptosis. To gain greater insight into the nature of mitochondria, let us consider their origin. The well-known theory of Margulis brings us back billions of years ago to when the world was populated by aerobic bacteria, anaerobic eukaryotes, and blue green algae. The blue green algae slowly brought the oxygen levels in the atmosphere from as low as 2% to about 22% (35). This was catastrophic for the anaerobic eukaryotes, which could not easily survive these high oxygen levels. Fortuitously, as Margulis et al (36) suggested, a small miracle of life occurred, which she termed “endosymbiosis.” That is to say, a eukaryote consumed but did not destroy a bacterium that it had ingested, and this surviving bacterium went on to become a proto mitochondrion. This unified cell prospered with the mitochondria providing relief from the oxygen and an

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**FIG. 6.** Three potential triggers of mitochondrial optic neuropathy lead to both a reduction of adenosine triphosphate (ATP) and accumulation of reactive oxygen species (ROS) that can, by changing the mitochondrial membrane’s electrical potential, open the mitochondrial permeability transition pore (MPTP) and trigger apoptosis (modified from Sadun and Wang (2)).
efficient source of ATP for the new amalgam eukaryote. Mitochondria represent vestige bacteria within the modern eukaryote. The eukaryote, with many sophisticated subsystems and organelles, brought a lot to the table as well. Specifically, the modern eukaryote provided a safe haven in the form of a nucleus that was sheltered away from the high ROS levels naturally generated by mitochondria. With this cooperative system, some eukaryotes eventually became the multicellular organisms, including humans, that now populate the earth.

This leads us to ask a few more questions about LHON. Why does blocking oxidative phosphorylation in mitochondria lead to apoptosis? Why the tissue specificity (optic nerve) and why the predilection for the fibers of the papillomacular bundle (PMB)? Once again we have to think of the Margulis paradigm and understand that for a billion years preceding this symbiosis, bacteria were constantly destroying and being destroyed by eukaryotes (35). Consequently, each type of cell developed an arsenal of biochemical weapons as part of an arms race with the other. After the symbiosis, the DNA library for this arsenal sat as an unused time bomb. But this time bomb could be set off by unleashing the machinery of the protomitochondria. Generally, there is not much selection advantage for a single cell to commit suicide. However, once multicellularity occurred, this system became an extremely useful tool as part of what we now term apoptosis; it permitted a variety of key processes such as ontogeny, which allowed for the development of organs and appendages, and immunosurveillance for the consequent destruction of cancer cells. Developmental neuronal specificity can occur by the selective pruning of neurons based on their connections, which, if appropriate, provide chemical signals that modulate apoptosis. RGCs use this method as they go from 5 million to about 1 million during fetal development (37).

How does the mitochondrion control one aspect of apoptosis? The inner membrane of the mitochondrion has an electrical potential. This electrical potential is altered by a variety of signals. ROS lower the electrical potential of the membrane, which, at a key voltage gate, can lead to opening of the mitochondrial permeability transition pore (MPTP) (33,34). Once the MPTP opens, it releases cytochrome c, which in turn permits pro-caspase 9 to become caspase 9, and the entire cascade of apoptosis can be triggered (Fig. 6).

**WHAT MAKES THE RGCs VULNERABLE?**

The brain weighs approximately 2% of the body weight and yet consumes 20% of its oxygen (38). This reflects the extremely high energy needs required to maintain neurons and, specifically, axons, which bear the high-energy costs

![Pattern and Spectrum: LHON Optic Nerves](image)

**FIG. 7.** Six optic nerves from 1 normal and 5 Leber hereditary optic neuropathy (LHON) patients have been oriented such that the temporal side is to the left. They have been graded from normal (0—upper left) to mild (1) to grades of moderate to very severe (5—lower right) optic atrophy. The brown staining shows the fascicles of myelinated axons in epon embedded sections. There is a specific pattern of increasing atrophy extending from the papillomacular bundle to involve the entire optic nerve with only sparing of axons in the supranasal quadrant (paraphenylenediamine stain; scale bars = 500 μm). The number in the equation of mitochondrial stress index shows the number of nodes of Ranvier (N#) times the length of the node (NL) times the circumference of the axon (NC) at the node. The denominator is the number of mitochondria (mt#) that exist to sustain this surface area. The equation can be reduced assuming that the retinal nerve fiber layer acts as a giant node of Ranvier. Substituting for circumference and area the equation reduces further to 2/r (r = radius of the axon). The smallest fibers are predicted to be involved first in a mitochondrial optic neuropathy and this holds true in LHON.
of membrane repolarization following every action potential. This is minimized by saltatory conduction made possible by myelination, which not only allows for faster conduction velocity but also a greater economy of energy expenditure and hence less strain on the greatest source of ATP—the mitochondria. However, this is problematic for RGCs whose axons, that must be transparent, run an unmyelinated course in the retina. We know from the usual clinical presentation of MON (poor visual acuity, dyschromatopsia, and central scotomas) that the PMB is selectively and initially affected (7). In LHON, not only is there the tissue specificity of the optic nerve but more selective still, early involvement of the PMB. We hypothesized that this is due to the small size of the fibers that constitute the PMB. We calculated that the energy required for repolarization of an axon potential should be the number of nodes (of Ranvier) times the average length of each node times the axonal circumference at the node (Fig. 7). This represents the numerator of an equation reflecting the mitochondrial axonal stress, where the denominator would be the number of mitochondria that can provide these quantities of ATP. This latter number is limited by the volume of the axon cylinder, which is calculated as the length times \( \pi r^2 \), where \( r \) is the radius of the axon (small in the PMB). Further reduction of this equation leads to an index that goes as \( 2/r \). The question then is, can we predict the areas of optic nerve involvement based solely on the distribution of axon fiber size?

To test this hypothesis, approximately 100,000 axons from normal human optic nerves were measured in 32 regions. The fibers in each region and then the regions were ranked according to size (producing a series of spectra). This was painstaking work by Pan et al (39) and included extensive computations. The histograms of the nerve fiber spectra showed a narrow range of small fibers coming from the PMB that were found in the inferotemporal regions (Fig. 8A) and a broader range of larger fibers coming from the superonasal regions (Fig. 8B). Seen another way, a gray scale representation of a normal human optic nerve shows that the smallest fibers are inferotemporal and central, and larger fibers are peripheral, and especially superonasal; this matches exactly the distribution as seen in the patterns of degeneration in LHON optic nerves (Fig. 7). In Figure 9, we have displayed a schematic superimposing on an optic nerve from a LHON patient with only mild pathology, the rank order distribution of fibers by size. The smallest fibers are found in the areas numbered 1 and the largest in the areas numbered 5. These numbers 1–5 also represent the order of progression of LHON degeneration and as predicted by the mitochondrial stress index equation.
And so yesterday’s discovery becomes today’s tool. Although neuro-ophthalmology is not physics, and our paradigm shift might not be as dramatic, we do well in avoiding polemics. We will watch with delight as the next generation of investigators take what we’ve done to a whole new level.

ACKNOWLEDGMENTS

Much of this work has been in close collaborations with the author’s colleagues. The author thanks Fred Ross-Cisneros, lab supervisor, who has patiently pushed himself to the limit in generating critical data and the perfect photomicrographs. The author thanks Michelle Wang for meeting every deadline and Billy Pan who spent countless hours measuring hundreds of thousands of axons. The author particularly thanks scientific siblings, Valerio Carelli and Chiara La Morga, and the core group of field investigators of the Brazil-LHON team, Solange Salomao, Adriana Berezovsky, Rubens Belfort, Milton Moraes (father and son), Dona Ventura, Peter Quiros, Piero Barbini, Filipe Chicani, Federico Sadun, and Anna Maria DeNegri. The author also thanks the others who participated in the field investigation team. Finally, the author thanks the hundreds of members of the Brazilian family who are descendants of that intrepid immigrant, Maria Franchi.

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CONCLUDING THOUGHTS

So, are we there yet? Well, research in LHON and other MONs has moved in several important fronts leading to the consideration of new treatment options such as quinones that might potentially redirect the electron that spills off complex I back into complex III and reduce some ROS production. Recent publications have described the use of a second-generation quinone, idebenone, with some success. A third-generation quinone, EPI-743, has shown that, at least in some cases, there may be significant amelioration of vision and visual field loss in cases of LHON.

But are we there yet? I would have to say not quite, insofar as we lack testing on an appropriate animal model. But we have good reason to think that we are close. We and other groups are conducting such research on recently developed faithful animal models of LHON.

To paraphrase Enrico Fermi, who was describing the great advances in physics in the 20th century, “theory stimulates experimentation which in turn stimulates new theory.”

FIG. 9. Cross section of optic nerve from a mild case of Leber hereditary optic neuropathy. Superimposed are numbers (1–5) that represent the fiber calibers ranked by size. These numbers (1–5) also represent the stages of involvement/severity as a wavefront that begins on the temporal side (papillomacular bundle), then, in stages, progresses to the nasal side until only the superonasal region is relatively spared. Compare with cross-sectional photographs in Figure 7 (paraphenylendiamine stain; scale bar = 500 μm).


To compare the incidence of cardiac and cerebrovascular events following non-arteritic anterior ischemic optic neuropathy (NAION) compared to published control data using the Framingham, United Kingdom Prospective Diabetes Study (UKPDS) and the National Vascular Disease Prevention Alliance (NVDPA) data.

Methods: A retrospective study of all consecutive cases of NAION between 1990 and 2005. Patients were stratified into those with or without prior ischemic events and into diabetics and non-diabetics. Outcome measures included cardiovascular morbidity, cerebrovascular events and the Framingham, UKPDS and NVDPA scores for each patient.

Results: According to the NVDPA, the average absolute 5-year risk for cardiovascular disease (CVD) was 8.98, compared to 9 CVD events in our study. In the diabetic patients, 5 (17%) had a cardiac event and 2 (8%) had a cerebral vascular accident (CVA). Based on the UKPDS risk calculator, the average 10-year risk for cardiac events is 21.6%, CVA –6.8%. In the non-diabetics, there were 3 cases (7.5%) of myocardial infarction, compared to the average 10-year Framingham risk for myocardial infarction or coronary death of 11% (±8 SD).

Conclusions: Following NAION, the incidence of cardiovascular or cerebrovascular events in patients taking aspirin is not in major excess from that expected in risk-factor age-matched controls.

Published risk calculators exist for cerebrovascular and cardiovascular events. To compare accurately nonarteritic anterior ischemic optic neuropathy (NAION) patients with these risk calculators, the authors divided NAION patients into 2 groups—those with (Group 1) and without (Group 2) atheroembolic disease. They further subdivided Group 2 into those with (Group 2A) and without (Group 2B) diabetes. They captured cardiovascular and cerebrovascular events using medical records and telephone interviews of all patients. Published, validated control data were used to compare risk of events following NAION by group. The number of events did not exceed published risk calculations for any group, suggesting that NAION does not lead to an increased risk of cardiovascular or cerebrovascular event over that expected for patient age or medical history.

The authors likely captured all events because they made telephone contact with each patient. I do not like the fact that they compared NAION patients with published controls instead of finding their own. However, based on the assumption that the pathophysiology of NAION is more likely a compartment syndrome, I do not see a strong reason why NAION patients should be at increased risk for vascular events. Personally, I counsel patients that NAION does not, in and of itself, increase their risk of cerebrovascular or cardiovascular event over their baseline risk, and this study supports that notion.

—Michael S. Lee, MD

This study has some encouraging news in that NAION by itself may not be a vascular risk factor rather it may be a consequence of other risk factors. It is consistent with the understanding that NAION is a problem of hypoperfusion and not a thrombotic or embolic phenomenon. Perhaps, in the previous studies showing NAION as a risk factor, it was the other pre-existing factors (e.g., diabetes, hypertension) that increased the risks for stroke and cardiac events.

—Mark L. Moster, MD


Objective: It is well-known that migraine attacks can be precipitated by various stimuli. More than 50% of patients with migraine with aura (MA) know of at least one stimulus that always or often triggers their MA attacks. The objective of this study was to expose patients with MA to their self-reported trigger factors in order to assess the causal relation between trigger factors and attacks.

Methods: We recruited 27 patients with MA who reported that bright or flickering light or strenuous exercise would trigger their migraine attacks. The patients were experimentally provoked by different types of photostimulation, strenuous exercise, or a combination of these 2 factors. During and following provocation, the patients would report any aura symptoms or other migraine-related symptoms.

Results: Of 27 provoked patients with MA, 3 (11%) reported attacks of MA following provocation. An additional 3 patients reported migraine without aura attacks. Following exercise, 4 out of 12 patients reported migraine, while no patients developed attacks following photostimulation.
Experimental provocation using self-reported natural trigger factors causes MA only in a small subgroup of patients with MA. Prospective confirmation is important for future studies of migraine trigger factors and in the clinical management of patients with migraine.

Previous studies report that most migraineurs can identify environmental triggers that induce their migraine with aura. These include certain foods, sleep deprivation, caffeine withdrawal, emotional stress, physical exertion, or bright light. This study was unable to provoke migraine with aura in most patients who reported an exercise or bright light trigger. Only 17% of those who reported a trigger of physical exercise were able to have this reproduced, and in none of the 26 patients reporting a visual trigger had this reproduced.

The authors appropriately suggest that future studies of migraine triggers should not be accepted merely based on the patient’s history. These findings have implications for treatment as well. It makes no sense to have a patient avoid exercise if the exercise is not really triggering the migraine. This article reminds us of bias in reporting clinical history and is reminiscent of what we hear from patients “I’m sure the migraine is only in my right eye” without having occluded either eye to test if it’s true.

—Mark L. Moster, MD

The authors acknowledge that migraines triggered by physical exercise in 17% of their patients could have been coincidental. They should have rechallenged those 17% to see if they could trigger another migraine. Interestingly, light could not induce a migraine when patients clearly identify it as a trigger. Perhaps, they needed a different light source or perhaps it really isn’t a trigger.

—Michael S. Lee, MD

Conclusions: Experimental provocation using self-reported natural trigger factors causes MA only in a small subgroup of patients with MA. Prospective confirmation is important for future studies of migraine trigger factors and in the clinical management of patients with migraine.

In this study, professional driving evaluators assessed hemianopic drivers in a dual-control car around a busy city. They found more satisfactory responses to unexpected hazards on the blind hemianopic side using real prisms compared with sham prisms. None of the patients had an accident, but an intervention (braking, steering) occurred in 29 instances. I have seen 2 patients who did not meet minimum field requirements for licensure in Minnesota. Using these prisms, they experienced sufficient visual field expansion to qualify for a license. Obviously, this doesn’t make them safe. I think it is important to realize that this study did not assess whether hemianopic patients using prisms were safe drivers. This was a pilot study to assess the feasibility of performing on-road driving evaluations in preparation for a larger clinical trial.

—Michael S. Lee, MD

This study is quite important. By placing a hemianopic prism obliquely, it allows for expansion of the visual field (VF) near the horizontal meridian without inducing diplopia. The study also points out that determining safety and legality of driving by a strict rule of VF in the horizontal meridian (e.g., 120 degrees) does not make a lot of sense. Other factors contribute to the relative safety of the driver. These include visual neglect and tendency to scan into the impaired VF and a host of nonvisual issues. Information from such studies will contribute to more valid assessments of driving safety in hemianopic patients in the future.

—Mark L. Moster, MD


Aims: Homonymous hemianopia (HH), a severe visual consequence of stroke, causes difficulties in detecting obstacles on the nonseeing (blind) side. We conducted a pilot study to evaluate the effects of oblique peripheral prisms, a novel development in optical treatments for HH, on detection of unexpected hazards when driving.

Methods: Twelve people with complete HH (median 49 years, range 29–68) completed road tests with sham oblique prism glasses (SP) and real oblique prism glasses (RP). A masked evaluator rated driving performance along the 25-km routes on busy streets in Ghent, Belgium.

Results: The proportion of satisfactory responses to unexpected hazards on the blind side was higher in the RP than the SP drive (80% versus 30%; P = 0.001), but similar for unexpected hazards on the seeing side.

Conclusions: These pilot data suggest that oblique peripheral prisms may improve responses of people with HH to blindside hazards when driving and provide the basis for a future, larger-sample clinical trial. Testing responses to unexpected hazards in areas of heavy vehicle and pedestrian traffic appears promising as a real-world outcome measure for future evaluations of HH rehabilitation interventions aimed at improving detection when driving.


Purpose: To evaluate the thickness of the inner retinal layers in the macula using frequency-domain optical coherence tomography (fd-OCT) in patients with demyelinating diseases.

Design: Cross-sectional study.

Participants: A total of 301 eyes of 176 subjects were evaluated. Subjects were divided in 5 different groups: controls, neuromyelitis optica (NMO), longitudinally extensive transverse myelitis (LETM), multiple sclerosis with a history of optic neuritis (MS-ON), and multiple sclerosis without a history of optic neuritis (MS non-ON).
Methods: The individual layers from macular fd-OCT cube scans were segmented with an automated algorithm and then manually hand-corrected. For each scan, we determined the thickness of the retinal nerve fiber layer (RNFL), the combined retinal ganglion cell and inner plexiform layers (RGCL+), and the inner nuclear layer (INL).

Main Outcome Measures: Macular RNFL, RGCL+, and INL thickness.

Results: The RNFL was significantly thinner than in controls for all patient groups ($P \leq 0.01$). Macular RGCL+ thickness was significantly thinner than in controls for the NMO, MS-ON, and MS non-ON groups ($P < 0.001$ for the 3 groups). The INL thickness was significantly thicker than in controls for the patients with NMO ($P = 0.003$) and LETM ($P = 0.006$) but not for those with MS-ON or MS non-ON. Although the RNFL and RGCL+ were not significantly different between the NMO and MS-ON groups, the patients with NMO had a significantly thicker INL than the patients with MS-ON ($P = 0.02$).

Conclusions: Macular RNFL and RGCL+ demonstrate axonal and neural loss in patients with MS, either with or without ON, and in patients with NMO. In addition, the INL thickening occurs in patients with NMO and patients with LETM, and study of this layer may hold promise for differentiating between NMO and MS.

This study compared the thickness of 3 macular segments (retinal nerve fiber layer [RNFL], retinal ganglion cell layer and inner plexiform layer [RGCL+], and inner nuclear layer [INL]) in multiple sclerosis (MS) and neuromyelitis optica (NMO) patients. There were 4 groups—MS with and without optic neuritis, NMO, and longitudinally extensive transverse myelitis (LETM). LETM is a disorder on the NMO spectrum, which the authors are considering a possible equivalent of NMO without a previous episode of optic neuritis.

The findings of RNFL thinning in all 4 patient groups are consistent with previous reports on MS and symptomatic NMO patients. However, it is slightly surprising for LETM, as NMO spectrum patients have been felt not to have subclinical loss of RNFL in the past, the RNFL loss only occurring after a clinical episode of optic neuritis. However, in support of the previous thinking on this issue was the finding that macular RGCL+ was thinner for all groups except the LETM group. This is consistent with retrograde axonal degeneration and ganglion cell death in previous demyelinated optic nerve.

What is even more unexpected is the finding that INL was significantly thicker in NMO and LETM patients than in controls or MS patients. The authors speculate that this may be due to intracellular edema with Müller cell dysfunction by virtue of the fact that these cells have Aquaporin4, the target of the NMO antibody. Although this may be a finding that will become clinically useful and helpful in distinguishing differences between MS and NMO, further verification of these findings is necessary. Additionally, although there was a statistically significant difference in INL, the total difference between the NMO/LETM patients and the MS/control patients was less than 2 μm.

—Mark L. Moster, MD

The RGCL+ and INL are the new hot topics in neurological diseases. Thankfully, there are only 10 layers of the retina, so we are almost finished segmenting them all and we can move on to something other than optical coherence tomography (OCT), right? But seriously, I look forward to the day when we can have fully automated segmentation with age-matched controls for the retinal layers. Until then, it can be tedious to hand-correct each OCT for segmentation purposes.

My criticism of this study is that we are not given any comparative statistics on how well matched the groups were with regards to age, gender, duration of disease, and time from last attack of optic neuritis. With the small but statistically significant differences, we definitely cannot distinguish NMO from MS based on INL thickness, especially in the acute phase (none of these patients had acute visual loss), which would be of great benefit.

—Michael S. Lee, MD


Background/Aims: To investigate the causes of isolated fourth nerve palsy (IFNP) and the association among etiology, prognosis and ocular deviation.

Methods: A total of 126 consecutive cases of IFNP was retrospectively reviewed. According to etiologies, all patients were classified into five groups: microvascular, congenital, decompensated of congenital, traumatic, and others. We investigated the recovery rate of IFNP patients who could be followed for more than 6 months or until they recovered completely. Patients also had the magnitude of vertical and horizontal ocular deviations (prism dipter) measured in the primary eye position on the first visit.

Results: Major causes of IFNP were microvascular (47%) and decompensated (33%). The rate of recovery was significantly different between microvascular IFNP and decompensated IFNP (92% vs. 55%, $P < 0.001$). There were no differences in both age of onset or mean vertical deviation between the two etiologies (68.6 ± 9.8 vs. 65.4 ± 13.3, 5.7 ± 3.3 vs. 7.8 ± 7.9). However, for mean horizontal deviation, there was a significant difference between microvascular and decompensated IFNP (0.4 ± 3.0 vs. 4.9 ± 5.6, $P < 0.001$). Although the fourth nerve abducts the eyeball, 69 of 126 cases (55%) showed exotropia. The microvascular IFNP group included more cases of exodeviation, while the decompensated IFNP group included more cases of esodeviation ($P < 0.001$).

Conclusions: Contrary to previous thinking, the horizontal deviation of IFNP mainly showed exodeviation, and the degree of horizontal deviation is useful for making a determination between vasculopathic and decompensated IFNP. This differentiation could be critical for predicting the outcome.

The authors retrospectively identified patients with isolated fourth nerve palsy (IFNP), categorized the etiology, and compared the clinical characteristics.

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I have problems with this study beginning with many of the authors’ definitions. 1) They define an IFNP by the 3-step test but do not mention how they distinguished these patients from skew deviation, myasthenia, or thyroid eye disease. 2) The only criterion for microvascular IFNP was if the patient had a vascular risk factor. 3) Decompensated IFNP was defined if the patient had a longstanding head tilt. There was no comment about vertical fusional amplitudes or other diagnostic criteria. Although the authors found that significantly more patients with decompensated IFNP (73%) had an exotropia compared with microvascular IFNP (37%), I do not agree with the conclusion that the degree of horizontal deviation is useful to differentiate the two (mainly because the definitions are weak).

—Michael S. Lee, MD

Michael, I agree with all your concerns. I also have some additional issues with this article. First, the authors don’t define how they measured the deviation. For instance, if by alternate cover test, they may merely be measuring a congenital exophoria or esophoria, and if it is with near fixation, perhaps measuring some convergence insufficiency. Additionally, with IFNP, there is not necessarily a specific exotropia or esotropia, rather a mild V pattern, with relative esotropia in down gaze, where the superior oblique is maximally active and where we lose it’s tertiary action of abduction in patients with IFNP.

—Mark L. Moster, MD


Objective: To determine whether childhood obesity is a risk factor for developing pediatric multiple sclerosis (MS) or clinically isolated syndrome (CIS).

Methods: Cases were identified through the Kaiser Permanente Southern California (KPSC) Pediatric Acquired Demyelinating Diseases Cohort between 2004 and 2010. For cases, body mass index (BMI) was obtained prior to symptom onset, for the underlying cohort BMI was obtained through the KPSC Children’s health study (n = 913,097). Weight classes of normal weight, overweight, moderate obesity, and extreme obesity were assigned based on BMI specific for age and sex.

Results: We identified 75 newly diagnosed pediatric cases of MS or CIS, the majority of which were in girls (n = 41, 55%), age 11–18 years (n = 54, 72%). Obesity was associated with a significantly increased risk of MS/CIS in girls (P = 0.005 for trend) but not in boys (P = 0.93). The adjusted odds ratio and 95% confidence intervals for CIS/MS among girls was 1.58 (0.71–3.50) for overweight compared to normal weight (reference category), 1.78 (0.70–4.49) for moderately obese, and 3.76 (1.54–9.16) for extremely obese. Moderately and extremely obese cases were more likely to present with transverse myelitis compared with normal/overweight children (P = 0.003).

Conclusion: Our findings suggest the childhood obesity epidemic is likely to lead to increased morbidity from MS/CIS, particularly in adolescent girls.

Two previous studies have suggested an increased risk of MS in young adults with obesity. This population-based study in children found an increased risk of clinically isolated syndrome (CIS) or multiple sclerosis (MS) in obese girls older than 11 years but not in boys or younger girls. The adjusted odds ratio was 1.58 (0.71–3.50) for overweight up to 3.76 (1.54–9.16) for extremely obese teenage girls. Additionally, moderate or severe obesity was associated with a presentation of transverse myelitis compared with normal/overweight children (P = 0.003). The authors suggest that the increase risk of MS may be related to the combination of a low-grade inflammatory state associated with obesity and the hormonal changes that occur with puberty.

According to a recent report in Lancet (1), obesity has overtaken hunger as a global health crisis. In addition to the many known health-related issues with obesity, we may have to add MS to the growing list.

—Mark L. Moster, MD

We cannot assume causality based on inference or association. When looking at the entire cohort, there was no clear association with BMI. The authors then “arbitrarily” (I say arbitrarily because boys and girls do not reach puberty at the same age) divided patients into younger (2–11 years old) and older (12–18 years old) groups. BMI was not associated with MS/CIS in the younger group. In the older group, there were a total of 54 cases, and only 8 of them were extremely obese. Extreme obesity was associated with an increased odds ratio of MS/CIS in this older group overall and especially for girls but not for boys. Although the adjusted odds ratio among girls seemed to rise with increasing BMI (overweight 1.58, moderate obesity 1.78, extreme obesity 3.76), the confidence intervals in the overweight and moderate obesity groups crossed over 1.00, indicating that they were not statistically significant. Therefore, the obesity association was really based on 8 extremely obese teenage girls.

Although obesity is associated with a number of health issues, I don’t know that this study clearly identifies an increase in the odds ratio of MS/CIS among these individuals. The cohort was very small and the authors created too many subgroups for my liking.

—Michael S. Lee, MD

REFERENCE

Reversible Vertical Gaze Palsy in Sodium Valproate Toxicity

W e read with interest the report on corticobasal syndrome by Rajagopal et al (1). At times, this neurodegenerative disorder may lead to vertical gaze palsy. We evaluated a patient with valproate toxicity and hyperammonemia and reversible vertical gaze palsy.

A 56-year-old man presented with progressive unsteadiness, drowsiness, and cognitive decline for the past 6 months. Twenty-five years previously, he was involved in a traffic accident and was in coma for 2 weeks. Subsequently, he made partial recovery with recurrent nocturnal generalized tonic-clonic seizures. He was changed to monotherapy with 400 mg of sodium valproate twice daily for 6 months. The patient’s relatives noted progressive drowsiness and decline in cognition since the treatment was started. His general health was otherwise excellent, and his last seizure occurred 3 weeks before our evaluation.

On physical examination, the patient needed support to stand and walk. He was drowsy with hypophonic and dysarthric speech. Extraocular movements revealed marked limitation of upward and downward gaze for both saccades and pursuit with preserved horizontal gaze (see Video 1, Supplemental Digital Content 1, http://links.lww.com/WNO/A64). Vestibulo-ocular reflex was preserved, but convergence was absent. Pupils were of normal size and reactive to light. Motor examination showed bradykinesia, rigidity, bilateral postural tremors of hands, and positive pull test. He walked with short steps, moderate stoop, and wide-based gait. His tendon reflexes were brisk, and plantar responses were flexor. Sensory examination was normal.

Complete blood count, renal function tests, profiles of glucose, sodium, potassium, calcium, and thyroid, thyroid antibodies, and B12 levels were normal. Venereal disease research laboratory testing and HIV testing were normal. Brain magnetic resonance imaging showed diffuse cerebral atrophy and bifrontal gliosis. There were no imaging signs of atypical Parkinson syndromes. Electroencephalography showed diffuse mild slowing of background activity of 6–7 Hz theta suggestive of mild diffuse encephalopathy.

His plasma ammonia level was 194 μmol/L (normal, 11–32 μmol/L) with valproic acid level of 109 μg/mL (therapeutic range, 50–100 μg/mL). Sodium valproate was discontinued, and 1,000 mg of levetiracetam twice a day was started. Four days later, vertical gaze for both saccadic and pursuit eye movements had markedly improved (see Video 2, Supplemental Digital Content 2, http://links.lww.com/WNO/A65). Significant improvement also was noted in his rigidity, bradykinesia, and postural imbalance. One week later, he was walking independently.

Partial or total gaze palsy has been described with exposure to phenytoin (2), phenobarbitone (3), and carbamazepine (4). Selective upward gaze palsy has also been described in phenobarbitone poisoning (3). To our knowledge, vertical gaze palsy in valproate intoxication has not been reported. In our patient, complete recovery of upward gaze palsy within few days of stopping valproate strongly suggests a causal relationship. Our patient also had features of parkinsonism, which showed a significant improvement after stopping the medication (5). We did not rechallenge the patient with valproate.

The centers for control of vertical gaze are located in the premotor structures of the midbrain, namely, the rostral interstitial nucleus of the medial longitudinal fasciculus and the interstitial nucleus of Cajal. These areas have abundant gamma-aminobutyric acid (GABA) receptors (6). In the interstitial nucleus of Cajal in macaque monkey, medium-sized and large GABAergic neurons have been identified projecting contralaterally to the superior oblique and inferior rectus motoneurons and presumably the contralateral interstitial nucleus of Cajal as well. These commissural GABAergic projections are well suited to inhibit the superior oblique and inferior rectus motoneurons and premotor down-burst-tonic neurons during upward eye movements (7).

Valproate is a well-known GABAergic drug that facilitates glutamic acid decarboxylase, an enzyme responsible for GABA synthesis. At high concentrations, valproate also blocks GABA transaminase in the brain, preventing degradation of GABA. The deactivation of vertical burst neurons by the GABA agonist action of valproate may explain the selective vertical gaze palsy as a result of valproate toxicity (8).

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16 Syndrome in a Patient With Multiple Sclerosis

We read with interest the report of Connors et al (1) of a case of 16 syndrome with complete horizontal gaze paralysis and facial diplegia caused by a pontine hemorrhage. We describe a patient with multiple sclerosis (MS) who experienced an evolving eye movement disorder, which included internuclear ophthalmoplegia, one-and-a-half syndrome, eight-and-a-half syndrome, fifteen-and-a-half syndrome, and finally 16 syndrome.

A 44-year-old man with a history of hypertension, heavy smoking, and a positive family history of cardiovascular disease complained of double vision upon awakening. Neurological examination revealed bilateral internuclear ophthalmoplegia (INO), which was attributed to a brainstem infarction given the sudden onset and patient’s vascular risk factors. Magnetic resonance imaging (MRI) of the brain and the intracranial vessels revealed several periventricular white matter lesions but no brainstem abnormality. Three days later, the patient developed drooping of the right corner of his mouth and complained of drooling. Examination revealed a right lower motor neuron facial nerve paresis in addition to bilateral INO. Repeat MRI revealed a nonenhancing lesion in the midline of the dorsal pons (Fig. 1). Two days later, he developed a complete right conjugate horizontal gaze palsy which, coupled with his left INO, produced a one-and-a-half syndrome. Concurrently, he also experienced bilateral facial paresis.

Evaluation for stroke including extensive hematological tests, Holter cardiac monitoring, and transesophageal echocardiography was normal. Cerebrospinal fluid analysis for IgG, oligoclonal bands, and aquaporin-4 antibodies as well as visual evoked responses were normal. MRI of the cervical spinal cord revealed no lesions.

On the 11th day of hospitalization, the patient developed bilateral horizontal gaze palsies with worsening of his facial diplegia. His clinical course in combination with the periventricular white matter lesions was highly suggestive of demyelinating disease. Treatment with methylprednisolone...
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FIG. 1. Axial fluid-attenuated inversion recovery (A) and sagittal T2 (B) MRI show an area of high signal (arrows) in the dorsal pons ventral to the fourth ventricle.
was begun, and 3 weeks later, he had recovered completely. Several follow-up MRIs were performed. The most recent MRI, 1.5 years after the onset of symptoms, revealed an increase in number and extent of the white matter hyperintensities (Fig. 2). Glatiramer acetate therapy was initiated.

On occasion, a one-and-a-half syndrome can be accompanied by a facial paresis if the fascicle or nucleus of the seventh cranial nerve in the lower part of the dorsal pontine tegmentum is also affected. Eggenberger (2) designated this as eight-and-a-half (1.5 + 7) syndrome. As mentioned by Connors et al (1), variations of this syndrome caused by pathology of the dorsal pontine tegmentum have since been described including a combination of a one-and-a-half syndrome and a bilateral peripheral facial paresis which Bae and Song (3) designated fifteen-and-a-half (1.5 + 7 + 7) syndrome.

Only 3 cases of isolated eight-and-a-half syndrome caused by MS have been described in the literature (4,5). In one of these cases (4), the eight-and-a-half syndrome was, as in our patient, the initial symptom of MS. A 16 syndrome caused by MS has not been reported previously.

The authors report no conflicts of interest.

REFERENCES

Optic Disc Edema and Optic Nerve Head Drusen

We are concerned about the conclusions reported by Sarac et al (1) in their article entitled “Differentiation of optic disc edema from optic nerve head drusen with spectral-domain optical coherence tomography” and the application of these conclusions to clinical practice.

Sarac et al seek to answer an old and important neuro-ophthalmic question: How can one distinguish between optic disc edema and optic nerve head drusen? Most clinicians have no trouble diagnosing advanced optic disc edema, such as Frisen Stages 3, 4, and 5 (2). Most clinicians have no trouble diagnosing optic nerve head drusen that are visible on ophthalmoscopy (“visible drusen”). Where clinicians do find themselves in a quandary is when they are asked to distinguish mild cases of optic disc edema (Frisen Stages 0, 1, and 2) from optic nerve head drusen that are not visible on ophthalmoscopy (“buried drusen”). Clinicians frequently look to new tools such as optical coherence tomography (OCT) to help sort out these difficult situations.
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Subclinical Optic Neuritis in Neuromyelitis Optica

We read with great interest the review of neuromyelitis optica (NMO) by Morrow and Wingerchuk (1). Even with proposed diagnostic criteria (2), establishing the diagnosis of NMO may be difficult. We describe a patient with white matter cerebral lesions, myelitis, and subclinical optic neuritis with negative NMO-IgG at the initial presentation. The diagnosis of NMO became certain 5 months later when the patient developed overt bilateral optic neuritis and a positive NMO-IgG antibody.

A 46-year-old woman experienced the onset of dizziness, nausea, and vomiting. Neurological examination was unremarkable except for horizontal gaze evoked nystagmus and mild weakness in her right leg. Muscle strength in the right lower extremity was at 4/5, patellar deep tendon reflexes were hypoactive, and the plantar reflex was indifferent on the right side. Vision was 20/20 bilaterally with normal color vision, funduscopy, and visual evoked potentials. Automated visual fields demonstrated mild generalized depression (Fig. 1).

Brain magnetic resonance imaging (MRI) revealed enhancement of the entire length of the left optic nerve (Figs. 2A and 2B) hyperintensities in the dorsal medulla, around the fourth ventricle, in the periaqueductal gray matter, mammillary bodies, the thalamus, and in the vicinity of the third ventricle (Fig. 2C). MRI of the spine

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Using time domain OCT, Karam and Hedges (3) concluded that OCT could not be used to differentiate individuals with congenitally crowded optic nerves from individuals with mild papilledema. Conversely, Johnson et al (4) argued that OCT could be used to differentiate optic disc edema from optic nerve head drusen, but these authors included subjects with disc edema that was “mild, moderate, and severe” and drusen that were both visible and buried. These authors also included subjects with papilledema, ischemic optic neuropathy, and optic neuritis in their study population. Lee et al (5) claimed that spectral domain OCT may be used to differentiate optic disc edema from optic nerve head drusen, but they also included subjects in whom the edema ranged from “subtle to severe,” and did not state the etiology of the disc edema in their subjects.

In the study by Sarac et al, the optic nerve head drusen group contained eyes with both visible and buried drusen. The optic disc edema group was also heterogeneous, containing subjects with “subtle to severe” optic nerve swelling. In addition, the optic disc edema group contained subjects with papilledema, nonarteritic anterior ischemic optic neuropathy, and optic neuritis. However, most clinicians would have no difficulty distinguishing a patient with optic nerve head drusen from a patient with anterior ischemic optic neuropathy or optic neuritis.

We do not dispute the results reported by Sarac et al. Our concern is that clinicians reading this article will inappropriately extrapolate these conclusions to clinical care. When faced with a patient in whom the differential diagnosis includes mild optic disc edema and buried optic nerve head drusen, the guidelines proposed by Sarac et al may not hold. Their study population was not relevant to the clinical question being asked.

Currently, it appears that the conclusions reached by Karam and Hedges (3) still hold. Until a study is designed with a clinically relevant population of subjects, the question of the utility of OCT in the differential diagnosis of optic disc edema and optic nerve head drusen remains unanswered.

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Subclinical Optic Neuritis in Neuromyelitis Optica

We read with great interest the review of neuromyelitis optica (NMO) by Morrow and Wingerchuk (1). Even with proposed diagnostic criteria (2), establishing the diagnosis of NMO may be difficult. We describe a patient with white matter cerebral lesions, myelitis, and subclinical optic neuritis with negative NMO-IgG at the initial presentation. The diagnosis of NMO became certain 5 months later when the patient developed overt bilateral optic neuritis and a positive NMO-IgG antibody.

A 46-year-old woman experienced the onset of dizziness, nausea, and vomiting. Neurological examination was unremarkable except for horizontal gaze evoked nystagmus and mild weakness in her right leg. Muscle strength in the right lower extremity was at 4/5, patellar deep tendon reflexes were hypoactive, and the plantar reflex was indifferent on the right side. Vision was 20/20 bilaterally with normal color vision, funduscopy, and visual evoked potentials. Automated visual fields demonstrated mild generalized depression (Fig. 1).

Brain magnetic resonance imaging (MRI) revealed enhancement of the entire length of the left optic nerve (Figs. 2A and 2B) hyperintensities in the dorsal medulla, around the fourth ventricle, in the periaqueductal gray matter, mammillary bodies, the thalamus, and in the vicinity of the third ventricle (Fig. 2C). MRI of the spine...
showed T2 hyperintensity extending through cervical and thoracic spinal cord (Fig. 2D). Serum biochemistries, complete blood count, and erythrocyte sedimentation rate were normal, as were serological tests for herpes virus family, cytomegalovirus, Epstein-Barr virus, antinuclear antibody, anti-Smith antibody, anti-soluble substance-A and anti-soluble substance-B, anti-Jo-1, anti-Scl-70 antibody, anticoagulant antibodies, and NMO-IgG. Cerebrospinal fluid was acellular, without oligoclonal bands, normal glucose, and increased protein of 271 mg/dL (normal, 15–45 mg/dL).

The patient was treated intravenously with 1,000 mg of methylprednisolone/day for 7 days. She returned to our clinic 5 months later with pain in the right eye and blurred vision in both eyes. Visual acuity was 20/50 in the right eye, and 20/200 in the left eye. The right optic disc was swollen, and the left disc was pale. Visual evoked potentials were abnormal bilaterally, and NMO-IgG antibody was now found to be positive.

Our case is instructive for 2 reasons. First, patients with NMO may present with clinical and neuroimaging findings highly suggestive of NMO, yet NMO-IgG antibody may not be detected. Given that the sensitivity of this test is 73% (3), repeat testing is warranted if clinical suspicion is high and initial results are negative. Second, patients with NMO may present with subclinical optic neuropathy. At presentation, our patient only had mild visual field changes, yet MRI revealed contrast enhancement of the left optic nerve. To our knowledge, this observation has not been reported previously.

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FIG. 1. Visual fields show mild generalized loss bilaterally (mean deviation: right, −3.83 dB; left, −4.44 dB).
REFERENCES


FIG. 2. Contrast-enhanced T1 axial (A) and coronal (B) magnetic resonance imaging (MRI) shows enhancement of the left optic nerve (arrows). C. Axial fluid-attenuated inversion recovery image demonstrates an increased signal (arrows) surrounding the third ventricle. D. Sagittal T2 MRI of the spine shows a longitudinally extensive lesion from the medulla to the thoracic cord.


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**Erratum**

A Mystery Case of Proptosis, Optic Neuropathy, and Peripheral Neuropathy: Erratum

In the article that appeared on page 77 of the March 2013 issue of the *Journal of Neuro-Ophthalmology*, two hyperlinks were omitted which grant access to Supplemental Digital Content figures. To view Supplemental Digital Content 1, visit http://links.lww.com/WNO/A48; to view Supplemental Digital Content 2, visit http://links.lww.com/WNO/A49.

Additionally, a typo appeared in the footnote regarding Supplemental Digital Content on the first page of the article. The correct journal web site is http://www.jneuro-ophthalmology.com, and the Supplemental Digital Content figures can be found accompanying the article online.

**REFERENCE**

Nystagmus is commonly encountered in neuroophthalmic practice, but it remains a challenge to diagnose and treat. Patients with congenital and acquired forms of nystagmus often report visual symptoms, including blurred vision and oscillopsia, which can be disabling and have a significant impact on the quality of life. The Nystagmus Network, a UK-based charity run by individuals and families affected by nystagmus, has organized several meetings to highlight advances in nystagmus research. The 25 chapters of this book represent the proceedings from the 2nd International Nystagmus Research Workshop, which was held in Abingdon, UK, in September 2009. The book includes more than 40 authors, including many prominent authorities on nystagmus from Europe, the USA, and Australia.

The challenge of nystagmus is divided into 4 sections: 1) causes, waveforms, and mechanisms; 2) clinical and genetic issues; 3) visual consequences of nystagmus; and 4) management, treatment, and trials. The individual chapters focus on various aspects of current research and practice, highlighting recent advances in the understanding, diagnosis, and treatment of nystagmus. There are more than 400 pages of text with more than 120 figures, many of which are printed in color. Each of the 25 chapters includes a comprehensive list of references. Although there are some chapters devoted to acquired forms of nystagmus, more than half of the chapters are focused on congenital forms of nystagmus.

The Challenge of Nystagmus is one of only a few texts dedicated solely to the topic of nystagmus. It is a valuable resource for clinicians who care for patients with nystagmus, especially those with congenital forms of nystagmus. It is available directly from the Nystagmus Network (http://www.nystagmusnet.org/cms/).

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Neuro-Ophthalmology in Korea

The history of neuro-ophthalmology in Korea is rather short. Until recently, only a few ophthalmologists and neurologists were interested in neuro-ophthalmology and engaged in the management of patients with neuro-ophthalmologic disorders. In the past, the academic activities in this field were carried out only as a subspecialty in the ophthalmology or neurology societies without an independent society for neuro-ophthalmology. However, in recent years, there has been a marked progress. We now have 2 neuro-ophthalmology societies in Korea, one run by ophthalmologists and the other by neurologists.

On the ophthalmology side, Professor Bong Leen Chang (Fig. 1) was a pioneer in neuro-ophthalmology. He had neuro-ophthalmology training in 1975 under the mentorship of H. Stanley Thompson, MD, at the University of Iowa. On returning to Korea, he started a neuro-ophthalmology clinic at Seoul National University Hospital and trained many fellows who went on to practice at various university hospitals in Korea. In 2004, he also wrote the first neuro-ophthalmology textbook in Korean (Fig. 2).

Following Professor Chang, Professor Jeong-Min Hwang at Seoul National University has made significant contributions to the advancement of neuro-ophthalmology through her continuing dedication as a clinician, researcher, and teacher. Dr. Hwang studied neuro-ophthalmology at University of Southern California (Mark Borchert, MD, 1993) and at the Wilmer Eye Institute (Neil Miller, MD, 1998). In addition, Professor Hyosook Ahn at Ulsan College of Medicine is an active board member of the Asian Neuro-Ophthalmology Society.

On the neurology side, Professor Gyung-Cheon Chung (Fig. 3) was the first neurologist who specialized in neuro-ophthalmology. After neuro-ophthalmology fellowship in Case Western Reserve University Hospital from 1985 to 1987...
under the mentorship of Robert Daroff, MD, he started practicing neuro-ophthalmology in Hanyang University Hospital. In 1992, he moved to KyungHee University as the founding chairman of Department of Neurology, and continued his neuro-ophthalmologic practice. Following Professor Chung’s example, several other neurologists received specialized training in neuro-ophthalmology and neuro-otology.

Professor Jai-Il Kim, the founding chairman of Department of Neurology, Dankook University, completed fellowship training (R. John Leigh, MD) at Case Western Reserve University from 1999 to 2000. Since 1995, he has organized an annual workshop for vestibular function tests with the ENT department in Dankook University. Professor Ki Bum Sung, who developed an interest in eye movements during his residency training in Hanyang University Hospital, is also one of the pioneers in Korean neuro-ophthalmology. He began practicing in 1994 and had fellowship training at the University of Pittsburgh Eye & Ear Institute, 1997–1998 (Joseph M. Furman, MD).

After neuro-otology (1997–1998, Robert Baloh, MD) and neuro-ophthalmology (1998–2000, James Sharpe, MD) fellowships, Professor Ji-Soo Kim opened a neuro-otology/neuro-ophthalmology clinic in Cheju National University Hospital and moved to Seoul National University Bundang Hospital in 2003. Professor Kim has trained 1 or 2 neuro-otology/neuro-ophthalmology fellows every year, and now his former fellows hold faculty positions at 11 university hospitals of Korea. He also organizes a 2-day neuro-otology and neuro-

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**TABLE 2. The Korean Society of Neuro-Ophthalmology**

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ophthalmology workshop during the first weekend of July each year, attracting approximately 200 participants.

In 1999, neurologists interested in neuro-otology and neuro-ophthalmology founded the Korean Balance Society along with otolaryngologists and vestibular physiologists. The society holds meetings twice a year.

In 2009 and 2010, 2 Korean neuro-ophthalmology societies were founded by ophthalmologists and neurologists. The Korean Neuro-Ophthalmology Society (KNOS) (Table 1) was founded on September 26, 2009. Professor Bong Leen Chang was elected as the first president, and KNOS currently has 99 members. KNOS has held several academic events, including periodic symposia and case discussions, and engages in public outreach programs. Topics of the educational meetings include “Familiarize Yourself with Neuro-Ophthalmology” (2010), “Neuro-Ophthalmic Diagnoses in Patients with Decreased Visual Acuity” (2011), and “Differential Diagnoses of Eye Movement and Pupillary Abnormalities” (2012). At the beginning of June each year, KNOS sponsors an in-depth case study seminar. The current president, Professor Jong Bok Lee at Yonsei University, stated that the goal of KNOS is to develop into a society of international caliber and establish treatment guidelines for the medical community of Korea. In the spring of 2012, KNOS organized a neuro-ophthalmology program at the 27th Congress of Asia-Pacific Academy of Ophthalmology held in Busan, Korea.

The Korean Society of Neuro-ophthalmology (Table 2) (www.neuro-ophthalmology.co.kr) created by neurologists had an inaugural symposium at KyungHee University on December 18, 2010. About 60 neurologists participated and elected Professor Kyung-Cheon Chung as the founding president. Since then, the Korean Society of Neuro-ophthalmology has held biannual meetings, with more than 100 neurologists in attendance. The society also hosts neuro-ophthalmology case conferences on regular basis and began publishing its official Korean journal, *Clinical Neuro-Ophthalmology*. Recently, the society organized a committee for textbook compilation (Chair: Professor Ji-Soo Kim) with the goal of publishing a textbook of neuro-ophthalmology in Korean, to be completed by the Annual Spring Meeting in June 2013. With a generous donation by Professor Chung, the society is now planning a nationwide survey regarding evaluation and management of patients with ophthalmoplegia. Currently, the Korean Society of Neuro-Ophthalmology has 96 members.

In spite of the relatively short history, we have seen a marked progress in neuro-ophthalmology in Korea over the past decade. More Korean physicians now attend the annual NANOS meeting. Each April, both ophthalmologists and neurologists hold a joint conference to review and discuss the topics presented at the previous NANOS meeting. We believe that neuro-ophthalmology in Korea will continue to grow and Korean neuro-ophthalmologists will become more involved in international societies.

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Neuro-Ophthalmology in Malawi

Background

At the conclusion of the 2001 meeting of the European Neuro-Ophthalmological Society in Tübingen, Germany, William F. Hoyt stated, “Neuro-ophthalmology is like a harp in an orchestra: good to have but not always needed.” With this in mind, one might question the need for teaching neuro-ophthalmology in Africa. In an African Eye Hospital, cataract and ocular infection including endophthalmitis are very common and training ophthalmologists to deal with these disorders is essential. PubMed search with the terms “neuro-ophthalmology” and “developing countries” or “Africa” fails to yield any publications. But if comprehensive ophthalmic education is our goal, then training in neuro-ophthalmology must be included.

In 2005, the University Eye Hospital of Tübingen created a memorandum of understanding with the Eye Department of the College of Medicine in Blantyre, Malawi. This partnership primarily was founded to educate and train ophthalmologists in Africa.

Teaching Neuro-Ophthalmology in Malawi

In 2012, the first neuro-ophthalmological course in a developing African country was held in Blantyre, Malawi (Fig. 1). Topics included:

Day 1: Basic neuro-ophthalmologic examination; the relative afferent pupillary defect; visual field techniques; unexplained visual loss; and transient visual loss.

Day 2: Optic disc findings; optic neuritis; ischemic and other optic neuropathies; tumors of the visual pathways; stroke; and higher cortical visual disorders.

Day 3: How to handle diplopia; cranial nerve palsies; nystagmus and supranuclear ocular motility disorders; headache and ocular pain; and efferent pupillary abnormalities.

The Impact of Neuro-Ophthalmology Training

We administered a questionnaire to evaluate the neuro-ophthalmology course. Five candidates who graduated in M Med Ophthalmology in Malawi and 4 postgraduate students from Malawi, and 3 from Zambia were included. We questioned the quality of the course, its impact on daily clinical work, and the question whether this course would be of value for other students in Africa. Additionally, a SWOT (strengths, weaknesses, opportunities, threats) analysis was made by the participants.

On a scale from 1 (not at all) to 5 (very important), 75% (9/12) of the course participants considered neuro-ophthalmology a very important aspect of ophthalmology. Twenty-five percent (3/12) considered it as moderately important. Evaluation of their neuro-ophthalmological education before attendance of the course (1 = very poor; 5 = excellent) was moderate in 50% (6/12), high in 25% (3/12), and the others in the lower ranges of the scale. Eighty-three percent (10/12) affirmed that this course contributed a great deal to their knowledge of neuro-ophthalmology. Fifty percent (6/12) responded that their increased understanding of neuro-ophthalmology will influence their clinical practice “tremendously” and 30% (4/12) responded “very much.” Finally, 83% (10/12)
recommended this course serve as a basis for further neuro-ophthalmology training in Africa.

**Discussion**

Our survey showed that conducting a neuro-ophthalmology course, especially by an experienced neuro-ophthalmologist from a developed country, can greatly influence the practice of ophthalmology in Africa. All participants of this course consider neuro-ophthalmology as an essential subspecialty. This is important because ophthalmology care at a subspecialty level is not well developed in Africa. Besides the Republic of South Africa, few eye centers have pediatric ophthalmology and vitreo-retinal units. None have neuro-ophthalmology clinics.

In Malawi, neuro-ophthalmology is practiced by general ophthalmologists, who like our study participants, may have minimal neuro-ophthalmology expertise. Yet neuro-ophthalmological problems are not uncommon in Africa. Expertise in neuro-ophthalmologic examination techniques is particularly important since neuroimaging resources (x-ray, computed tomography, magnetic resonance imaging) and expertise (only 2 radiologists in Malawi, with a population of 14,000,000) are limited.

**Conclusions**

Neuro-ophthalmology will have an important role in Africa with the increasing prevalence of entities such as HIV (2) and diabetes mellitus (3). The growing neuro-surgical specialty will need neuro-ophthalmology support as well. We look forward to participating in the education of African ophthalmologists, allowing the “harp” to become part of their diagnostic and therapeutic “orchestra.”

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