Tigers and Snakes in Neuro-Ophthalmology

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In her book *Eyes Wide Open: How to Make Smart Decisions in a Confusing World*, Noreena Hertz tells the story of an experiment conducted by cognitive psychologists in which subjects were asked to view a variety of scenes and report what they saw (1,2). One of the scenes was of a tiger in a forest with a snake hidden in the background. Some subjects concentrated mainly on the tiger in the foreground and failed to see the snake. Others focused on the entire scene and did see the snake. Using this study as an analogy, Hertz emphasized that to make the best possible decisions, we need to see beyond the obvious, to see the snakes as well as the tigers. In the complex world of neuro-ophthalmology, we have our own versions of tigers and snakes. Consider the following cases.

Case 1
An 89-year-old woman developed headaches. Her family informally asked a neurosurgeon for advice. Magnetic resonance imaging (MRI) of the brain was recommended, and it showed a mass in the right cavernous sinus characteristic of a meningioma (Fig. 1). Three weeks later, she experienced sudden loss of vision in her right eye, followed in 5 days by loss of vision in her left eye. She was referred for neuro-ophthalmologic evaluation and a history of malaise and jaw claudication was elicited. Examination revealed finger counting vision bilaterally, ropy temporal arteries, poorly reactive pupils, and bilateral optic disc swelling with hemorrhages (Fig. 2). Erythrocyte sedimentation rate was 121 mm/hr. A diagnosis of bilateral arteritic anterior ischemic optic neuropathy due to giant cell arteritis was made, and corticosteroid therapy was initiated. Her constitutional symptoms improved, but her vision remained unchanged, and she developed bilateral optic atrophy. Her intracranial meningioma remained stable until her death 2 years later from unrelated causes.

Comment
The finding of a brain tumor in this patient seemed to explain her headaches. Only when she lost vision in both eyes was she referred for neuro-ophthalmologic evaluation. Her headaches and other symptoms were then recognized to be manifestations of giant cell arteritis. Delayed diagnosis resulted in bilateral blindness. Her cavernous sinus meningioma was an incidental finding and never became symptomatic.
Case 2

A 66-year-old man with slowly progressive bilateral loss of vision was referred for neuro-ophthalmologic evaluation. He had a history of heavy smoking, daily alcohol consumption, and a poor diet for many years. Examination revealed visual acuity of 20/400, right eye and 20/70, left eye, mild bilateral optic disc pallor, and bilateral cecocentral scotomas (Fig. 3). A diagnosis of nutritional optic neuropathy was made. Smoking cessation, alcohol abstinence, and improved nutrition were recommended, and he was treated with a daily multivitamin and weekly intramuscular injections of hydroxocobalamin. Over the next several months, his visual acuity progressively improved to 20/40, right eye and 20/60, left eye. Follow-up visual field testing unexpectedly showed worsening field defects bilaterally (Fig. 4). Carotid angiography demonstrated a giant suprachinoid internal carotid artery aneurysm (Fig. 5).
internal carotid artery aneurysm (Fig. 5). He underwent left extracranial–intracranial bypass surgery with clipping of the aneurysm that was complicated postoperatively by a stroke. The patient was left with a complete right homonymous hemianopia. However, visual acuity improved to 20/25 in each eye and remained stable thereafter.

Comment
This patient had classic findings of nutritional optic neuropathy. So certain was the diagnosis that initially neuroimaging was not ordered. Had it been, his aneurysm would have been the focus of concern, and his nutritional amblyopia might not have received the attention that it deserved. The first diagnosis was correct, but it did not tell the whole story. Follow-up visual field testing identified changes that led to the diagnosis and treatment of his intracranial aneurysm.

Case 3
A 69-year-old woman had sensorineural hearing loss in her left ear and decreased peripheral vision in her right eye. Brain MRI revealed left cerebellopontine angle and right medial sphenoid lesions consistent with meningiomas (Fig. 6A, B). Her medical history was significant for systemic hypertension, atrial fibrillation, anemia, and migraine. Her mother and 2 sisters had glaucoma. On neuro-ophthalmologic examination, visual acuity was 20/25, right eye and 20/20, left eye. In her right eye, she had mild dyschromatopsia, a relative afferent pupillary defect, and a predominantly inferior nerve fiber bundle visual field defect (Fig. 7). Intraocular pressures were 16 mm Hg in the right eye and 15 mm Hg in the left eye. Ophthalmoscopy showed prominent optic disc cupping bilaterally with focal thinning of the superotemporal neural rim of the right optic disc. Corresponding superotemporal retinal nerve fiber layer thinning was demonstrated by optical coherence tomography (Fig. 8). The patient had radiation treatment for her meningiomas, and she was treated as a normal tension glaucoma suspect with latanoprost ophthalmic drops. One year later, her visual function was unchanged.

Comment
This patient had intracranial meningiomas, one of which compressed her right optic nerve. She also had findings consistent with normal tension glaucoma. Missing that diagnosis could have resulted in insidious loss of vision mistakenly attributed to compressive optic neuropathy. This case illustrates the potential dilemmas and pitfalls associated with the diagnosis and management of concurrent conditions.

Occam’s razor is a precept that states: “Entities should not be multiplied beyond necessity” (3). This principle has been expressed in various ways by Aristotle, Ptolemy, Maimonides, Thomas Aquinas, and others, including 14th century English philosopher and theologian William of Ockham (or Occam), who wrote: “Pluralitas non est ponenda sine necessitate,” translated to “plurality should not be posited without necessity” (3–7). In 1852, centuries after Ockham’s death, this principle of parsimony was referred to in the works of Scottish metaphysical philosopher William Hamilton as Occam’s razor (3,6).
In medical practice, Occam’s razor is a useful heuristic that pertains to diagnostic parsimony. For any given illness, a unifying diagnosis to explain a patient’s symptoms is preferable to multiple diagnoses—do not make 2 diagnoses when one will do. Noble David, MD, succinctly described Occam’s razor as “one disease to a customer” (8). The medical counter-argument to Occam’s razor is Hickam’s dictum. Attributed to mid-20th century Duke medicine professor John B. Hickam, it states: “Patients can have as many diseases as they damn well please” (7–9).

These counterbalancing philosophies are relevant to neuro-ophthalmology, as evidenced by the cases described above. Each patient had 2 important diseases, one of which was more obvious but not necessarily more significant, than the other. Differentiating patients who conform to Occam’s razor from those who fulfill Hickam’s dictum can be challenging and subject to cognitive biases (10–13).

Cognitive biases are predictable and recurring thinking errors that we all make when we acquire and process information (14). It is helpful to consider cognitive biases in the context of a dual thinking system that has intuitive (System 1) and analytical (System 2) components (13–15). Intuitive thinking is fast, automatic, and unconscious; analytical thinking is slow, deliberate, and conscious (13–15). Although intuitive thinking is highly effective and essential to our daily decision-making, it is in this mode that most biases and other cognitive failures occur (12). In neuro-ophthalmology, as in other disciplines, an appropriate blend of intuitive and analytical thinking would seem to provide the best foundation for optimal decision-making (13,16).

FIG. 8. Case 3. There is increased cupping of both optic discs with thinning of the superotemporal neural rim of the right optic disc. This is confirmed on optical coherence tomography.

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Of the many cognitive biases that are known, among the most important ones that affect our clinical decision-making are anchoring, availability, confirmation, framing, unpacking, and premature closure (10,11).

Anchoring bias is the tendency to rely too heavily on certain information early in the diagnostic process, to be overly influenced by first impressions, and thereby to limit consideration of alternative explanations. Availability bias is the tendency to overestimate the likelihood of events based on what we have recently seen or experienced and what we most remember. Confirmation bias is the tendency to focus on information that supports, rather than refutes, our preconceptions. Framing bias occurs when different conclusions are drawn from the same information, depending on how that information is presented. The unpacking principle refers to failure in eliciting all relevant information, which may result in other significant possibilities being overlooked. Premature closure is the tendency to suspend the decision-making process too soon, accepting a diagnosis before it has been confirmed. Said in another way, “When the diagnosis is made, the thinking stops.” In each of the cases described, various combinations of these thinking errors occurred or potentially could have occurred.

A number of strategies to eliminate or reduce the influence of cognitive biases in clinical decision-making have been proposed; chief among them are having greater appreciation and awareness of biases, improving medical education, improving critical thinking skills, and thinking about one’s own thinking, a process known as metacognition (10,12,17,18). Each of these debiasing strategies requires vigilance and sustained commitment.

In neuro-ophthalmology, we see a wide array of complex cases that are time- and resource-intensive, cognitively challenging, and beset with uncertainty. In some cases, the obvious diagnosis might not be the most important one. We always should be mindful of the thinking traps to which we are susceptible. A thorough history, meticulous examination, and conscientious follow-up are timeless, indispensible tools for the neuro-ophthalmologist. When these tools are combined with strategies to avoid thinking errors in clinical decision-making, we minimize the likelihood of misdiagnosis and improve our quality of care. We increase our chances of seeing the snakes as well as the tigers.

REFERENCES

Effect of Patient Positioning on Cerebrospinal Fluid Opening Pressure

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Background: Prone is the preferred patient position for fluoroscopic-guided lumbar puncture (LP). Normative data for cerebrospinal fluid (CSF) opening pressure (OP) exist for lateral decubitus (LD) positioning only and have not been defined for the prone position. This study compares CSF OP values in the prone and LD positions and examines the effect of body mass index (BMI) on OP.

Methods: Patients undergoing diagnostic or therapeutic fluoroscopic-guided LP were recruited prospectively at 2 tertiary care centers from 2009 to 2012. Following prone fluoroscopic-guided LP, patients were rolled to the LD position for repeat CSF OP measurement. In addition to comparing the mean OP in each position, the relationships between OP, body position, and BMI were also explored.

Results: Fifty-two patients were enrolled. A mean OP difference of 1.2 cm H₂O was observed (prone: 26.5 cm H₂O; LD: 27.7 cm H₂O; P = 0.07). No correlation between CSF OP and BMI was seen in either position.

Conclusions: No statistically or clinically significant difference between prone and LD OP was identified. BMI does not appear to affect CSF OP measurement in either position.

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Neuroradiologists increasingly perform diagnostic and therapeutic lumbar puncture (LP) under fluoroscopic guidance, especially for patients whose body habitus may obscure bony landmarks. Although the diagnostic criteria for idiopathic intracranial hypertension (IIH) specify the measurement of cerebrospinal fluid (CSF) opening pressure (OP) in the lateral decubitus (LD) position (1), most fluoroscopic-guided LPs measure OP with the patient in the prone position (2). Most neuroradiologists appropriately add the needle length to the manometer when measuring prone OP, but some do not.

While normal CSF OP in the LD position is well defined in both adults and children, (3–5) normative data for prone CSF OP do not exist. Conceivably, increased intra-abdominal or intrathoracic pressure (6) or change in respiratory rate during prone body positioning could raise CSF pressure. In 2002, Jacobson and Coppens (7) reported a prospective pilot series of 7 patients with IIH, in which they did not observe a significant difference between OP measured in the prone and LD positions. Schwartz et al (8) reported a series of 55 patients in which a statistically significant difference between prone and LD positions was observed. Several studies describe conflicting relationships between CSF OP, lower extremity position, and body mass index (BMI) (8–15). Our study prospectively compared CSF OP values in the prone and LD positions and examined the effect of BMI on CSF OP.

METHODS

Study Design
After approval from the Institutional Review Boards (IRB) of the University of Minnesota and the University of Rochester, patients undergoing fluoroscopic-guided LP with OP measurement for clinical care were recruited prospectively. Patients aged 18–89 years were included. Those who
were unable to give informed consent or requiring intravenous sedation were excluded. Six neuroradiologists at the University of Minnesota, and 2 registered and certified physician assistants from the Department of Imaging Sciences at the University of Rochester performed the LPs.

**Study Protocol**

Informed consent was obtained for study participation with fluoroscopic-guided LP including OP measurement in both the prone and LD positions. Patients undergoing fluoroscopic-guided LP at the University of Minnesota and the University of Rochester were enrolled between January 1, 2009 and May 31, 2012. Light sedation with oral diazepam was administered in the selected cases based on physician discretion and patient preference. The patients were placed in the prone position, and then prepared and draped in a sterile fashion. Fluoroscopy was used to identify the lumbar spinal puncture level before administering local anesthesia with 1% lidocaine subcutaneously. Thecal sac puncture was performed with a 5-inch Whitacre or Quincke spinal needle. Puncture level and needle gauge were recorded. A manometer was attached to the spinal needle with extension tubing and a stopcock. The tubing was extended horizontally between the spinal needle and the manometer. Zero was defined at the level of the spinal canal for all OP measurements. The patients were encouraged to relax and breathe normally while the CSF meniscus equilibrated. Elapsed time from thecal sac puncture to CSF meniscus equilibration was not recorded, but took less than 1 minute in all cases. On average, equilibration took approximately 15 seconds. The highest pressure reading during respiratory excursion was recorded. Needle length was added to the manometer reading to account for the distance between the manometer and the zero level of the spinal canal while in the prone position. The stopcock was then closed to prevent CSF loss, and the patients were repositioned in the LD position with legs extended and the patient relaxed. The extension tubing was then reoriented to maintain a horizontal connection between the spinal needle hub and the manometer. If there was any obliquity of the spinal needle with respect to the spinal column, the manometer was positioned at the level of the spinous processes nearest the needle to best approximate the level of the spinal canal. The stopcock was then reopened, and the CSF meniscus was again allowed to equilibrate. Again, this took approximately 15 seconds depending on the pressure. The highest OP measurement during respiratory excursions was then recorded.

Each patient’s age, gender, self-identified ethnicity, BMI, LP indication, spinal level of thecal sac puncture, needle gauge, and OP in the prone and LD positions were recorded. Post-procedure symptoms and the ultimate diagnosis were recorded when available. All complications were reported to the IRB.

**Statistical Methods**

The paired *t* test was used to compare OP measured in the prone and LD positions. Unpaired *t* tests were used to assess both the effect of needle gauge and the use of sedation on OP. One-way analysis of variance was used to assess the effect of the level of spinal puncture on OP. The relationship between OP and BMI was investigated with linear regression modeling. Bland–Altman analysis was used to evaluate the agreement between OP measurements in the 2 positions. Data were analyzed using commercially available software (GraphPad Prism 6; GraphPad Software, Inc, San Diego, CA). A *P*-value <0.05 was considered statistically significant.

**RESULTS**

Fifty-two patients were enrolled. One patient was excluded because OP was not ordered by the referring physician. The demographic and clinical data of our patient cohort are summarized in Table 1.

<table>
<thead>
<tr>
<th>LP indication</th>
<th>No. Patients</th>
<th>Characteristics of patients undergoing lumbar puncture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected papilledema</td>
<td>32 (63%)</td>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>IIH</td>
<td>8 (16%)</td>
<td>18.7–64.0; mean 35</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (14%)</td>
<td></td>
</tr>
<tr>
<td>Vision loss/optic neuritis</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>1 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; IIH, idiopathic intracranial hypertension; LP, lumbar puncture.
Of the 39 patients undergoing LP for suspected papilledema or IIH workup, 6 (15%) crossed the 25 cm H$_2$O threshold to elevated CSF OP in the prone position only. Two additional patients (1 undergoing workup for headache and 1 for optic neuritis) also crossed the 25 cm H$_2$O threshold while prone.

Four patients (8%) were sedated with oral diazepam before LP. A significantly larger OP differential (prone-LD) was seen in sedated patients (95% CI, 0.55–10.1; \( P = 0.04 \)). Thirty-seven (73%) LPs were performed with a 22-gauge needle. Fourteen (27%) were performed with a 20-gauge needle. There was no significant difference between the OP differential (prone-LD) with either needle gauge (\( P = 0.30 \)). Twenty-eight (55%) LPs were performed in the L2/L3 intervertebral space, 16 (31%) in the L3/L4 intervertebral space, and 7 (14%) in the L4/L5 intervertebral space. The lumbar spinal level puncture had no significant effect on the OP difference measured in the 2 positions (\( P = 0.69 \)).

Following LP, 8 (16%) patients complained of new or persistent headache. Four (8%) patients required epidural blood patch. One (2%) patient complained of persistent fever, and 1 (2%) complained of localized pain and transient lower extremity paresthesias, which resolved spontaneously. There were no complications related to study participation.

**DISCUSSION**

In cases of suspected IIH, spontaneous intracranial hypotension, shunt malfunction, and normal pressure hydrocephalus, the accuracy of OP measurement is critical. Specifically for IIH, the diagnostic criteria require a CSF OP \( > 25 \text{ cm H}_2\text{O} \) measured in the LD position with legs extended and the patient relaxed (1). While nearly 90% of neuroradiologists perform fluoroscopic-guided thecal sac puncture in the prone position, less than one-third of neuroradiologists rotate the patient to measure OP in the LD position (2). Consequently, prone OP measurements direct clinical decision making, despite the absence of established OP norms in the prone position.

The small observed difference between CSF OP measured in the prone and LD positions of 1.2 cm H$_2$O was not statistically significant. In our opinion, we believe that difference also is clinically insignificant and likely falls within the margin of error for the measure. Cautious comparison is warranted between our study and that of Schwartz et al (8), which found a 2.7 cm H$_2$O difference between the prone and LD positions. The patient populations between the studies were very different. Most patients (56%) in Schwartz’s study had myelograms, whereas all our patients had diagnostic or therapeutic LPs. Moreover, the patients in Schwartz’s study had lower OPs, with 27% of patients’ OP \( < 10 \text{ cm H}_2\text{O} \) (average: 12.6 cm H$_2$O LD, 15.3 cm H$_2$O prone). The average OP in our study was considerably higher (average: 26.5 cm H$_2$O, 27.7 prone). Regardless, we disagree with Schwartz’s conclusion that 2.7 cm H$_2$O is clinically significant. A study population with even higher average OP (\( > 30 \text{ cm H}_2\text{O} \)) would be useful. There may be a greater difference observed among patients with a normal or low OP.

We found a statistically significant higher OP differential between the prone and LD position in patients sedated with oral diazepam. This finding indicates that sedation may induce an artifact when measuring OP in the prone position. Given the small number (8%) of sedated patients, further studies are needed to determine whether the effect of sedation is clinically significant.

The relationship between CSF OP and BMI is controversial. We did not find a correlation between BMI and CSF OP in either position. Although 1 retrospective study (15) reported a linear relationship between BMI and CSF pressure among patients with OP \( < 25 \text{ cm H}_2\text{O} \), 5 other prospective studies found this relationship to be clinically insignificant (8,12–14,16). Avery et al (5) found a small, positive correlation between CSF OP and BMI in children. Others have suggested that increased intra-abdominal or intrathoracic pressure can increase CSF OP (6,16). This is of particular concern in IIH, given its prevalence among obese women.

According to published diagnostic criteria for IIH, 25 cm H$_2$O is the threshold needed to diagnose IIH (1). Our 8 patients, who crossed the 25 cm H$_2$O threshold only while prone, deserve closer examination. The LP indication for these “threshold-crossing” patients was suspected papilledema (\( n = 4 \)), IIH workup (\( n = 2 \)), headache (\( n = 1 \)), and vision loss/optic neuritis (\( n = 1 \)) (Table 1). Six of these 8 “threshold-crossers” had borderline-elevated OP (21–24 cm H$_2$O) in the LD position, whereas, only 2 had LD OP within the normal range. The average BMI for these 8 threshold-crossers was 36.9 kg/m$^2$, which was not statistically significantly different from the rest of the patients (\( P = 0.16 \)), further supporting our conclusion that BMI does not affect CSF OP.

Sugerman et al (16) postulated that excess intra-abdominal fat increases intra-abdominal pressure, thereby raising pleural...
and cardiac filling pressures, and ultimately increasing CSF OP by impeding venous return from the brain. If Sugerman’s theory is correct, one would expect that the pressure from the abdominal contents would elevate CSF pressure when the patient is prone. According to Pascal’s principle, pressure applied to an enclosed fluid under equilibrium conditions is transmitted equally and undiminished throughout the fluid. Therefore, if increased intra-abdominal or intrathoracic pressure were transmitted at any point along the dural sac, CSF OP would increase. However, we did not observe a correlation between BMI and CSF OP. Our findings argue against Sugerman’s theory that central obesity causes IIH by impeding venous return from the brain. Although the average BMI of our patients was 35.5 kg/m² and that of Sugerman’s patients was 45 kg/m², we suggest that the vector forces transmitted from central obesity to the thecal sac during OP measurement are minimal, as long as the patient lies down and relaxes (no Valsalva) with the base of the manometer level with the spinal canal.

As obesity increases in the United States, the incidence of IIH will also likely rise, which may lead to an increase in fluoroscopic-guided LPs performed in the prone position. Based on this study’s data, it seems reasonable to interpret prone OP measurements with the established normal range defined for OP in the LD position (8–25 cm H₂O). An accurate prone OP must have the needle length added to the final manometer reading unless flexible tubing is used to bring zero to the level of the spinal canal. When OP is needed to certify a clinical diagnosis as in IIH, the trend toward higher OP in the prone position that we identified should be considered, especially when the measurement is borderline. If a clinical diagnosis is questionable because of an OP near the 25 cm H₂O threshold, we think it is reasonable to roll the patient to the LD position or repeat the LP with OP measurement in the LD position.

Limitations of this study include the relatively small sample size and homogenous study population. Most patients were obese women undergoing diagnostic LP for suspected papilledema or IIH workup. This selection bias likely exists because only patients who were specifically referred for LP with measurement of OP were recruited. Many physicians do not specifically order OP, so hundreds of eligible patients were potentially missed. Although this potentially limits the clinical application of our results, we have no reason to believe that the difference in OP measurements should vary with age or gender. This lack of heterogeneity, however, could potentially confound our BMI vs OP analysis. Another limitation of this study is that the clinician cannot be masked to patient positioning during OP measurement. In an attempt to minimize potential bias, the OP measurement technique was standardized to the highest manometric reading during respiratory excursion after equilibration of the CSF meniscus in the manometer. This method is widely accepted as the most accurate OP measurement technique. Despite this strict protocol, variability could potentially exist among the 8 practitioners performing the LPs. However, we believe that this approximates the variability seen in routine clinical practice and, therefore, argues in favor of supporting the generalizability of our data.

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REFERENCES

Ventriculoperitoneal Shunt as a Treatment of Visual Loss in Idiopathic Intracranial Hypertension

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Background: The aims of this study were to evaluate visual function outcomes in idiopathic intracranial hypertension (IIH) patients who underwent ventriculoperitoneal (VP) shunt for visual loss and to determine a VP shunt survival curve over time.

Methods: A retrospective medical record review was performed of all new IIH patients first evaluated at our institution who underwent VP shunt placement over a 7-year period (2004–2010). There were 2 primary outcome measures: the first being visual acuity (VA) and the second being shunt survival. Patients who received VP shunt for visual loss were included in the visual outcome analysis, and all patients who received VP shunt for any reason were included in the shunt survival analysis.

Results: Of the 338 new patients with IIH, 19 patients (6%) met the inclusion criteria and 17 underwent VP shunt for visual loss and 2 for headaches. Average follow-up was 21.2 months (range, 5–1,342 days). Of the 17 patients who had VP shunt for visual loss, 5 patients had optic nerve sheath fenestration (ONSF) surgery before VP shunt, and 1 patient had bilateral ONSF surgery after VP shunt. Median VA before shunt was 20/200 in the worse eye (range, 20/20 to NLP) and 20/40 in the better eye (20/20 to HM). Median VA after shunt was 20/60 in the worse eye (20/20 to lumbo-peritoneal) and 20/30 in the better eye (20/20 to 20/800).

The improvement in VA was not significant (P = 0.27, P = 0.26, respectively). Independent masked record reviews by 3 neuro-ophthalmologists showed that 9 (53%) patients improved, 5 (29%) unchanged, 1 (6%) worsened, and 2 (12%) were indeterminate. Kaplan–Meier analysis showed a persistent steady decrease of functioning VP shunts over the entire period of 36 months with 80%, 65%, and 48% of VP shunts functioning without replacement, removal, or revision at 12, 24, and 36 months, respectively.

Conclusion: VP shunts improve or stabilize most IIH patients presenting with severe progressive visual loss or those with visual loss refractory to medical treatment and ONSF. Survival analysis shows persistent decrease of functioning shunts over time.

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Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is a disorder caused by increased intracranial pressure (ICP) of unknown cause. (1,2) The condition affects overweight women of childbearing age, and its incidence is rising in the United States paralleling the obesity epidemic. (3) Severe visual loss from papilledema occurs in 10% of IIH patients (2). Surgical interventions including optic nerve sheath fenestration (ONSF) and cerebrospinal fluid (CSF) shunting procedures are aimed to decrease papilledema and/or lower the ICP. The efficacy of these treatments is not established in clinical trials and are usually considered when visual loss is refractory to medical treatment. High rates of complications from lumbo-peritoneal (LP) and ventriculoperitoneal (VP) shunting are well documented even with stereotactic placement (4–8). Outcome studies evaluating shunt procedures often include alleviation of headaches and generalized descriptions of visual function. Quantitative visual acuity (VA) and visual field measures often are not provided (Table 1) (5–7,13–15).

At our institution, VP shunt for IIH-associated visual loss typically is reserved for cases refractory to medical
### TABLE 1. Ventriculoperitoneal shunting for idiopathic intracranial hypertension: visual outcomes and shunt survival

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Sex (F)</th>
<th>Age (Mean)</th>
<th>Design</th>
<th>Shunt Mechanism</th>
<th>Revision/Fail Rate</th>
<th>Follow-up (Mean)</th>
<th>Ophthalmic Exam</th>
<th>Prior Surgical Treatment</th>
<th>Vision Improvement</th>
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<tbody>
<tr>
<td>Kandasamy et al (6)</td>
<td>17</td>
<td>70%</td>
<td>24.2</td>
<td>Retro</td>
<td>Stereotactic</td>
<td>29%</td>
<td>22 mo</td>
<td>Pap, VFD</td>
<td>LP shunt (23%)</td>
<td>100% of patients, symptoms, and findings</td>
</tr>
<tr>
<td>Maher et al (7)</td>
<td>13</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Stereotactic</td>
<td>23%</td>
<td>15.1 mo</td>
<td>Blurred vision</td>
<td>54% (ONSF)</td>
<td>38%, subjective</td>
</tr>
<tr>
<td>Tamaris et al (9)</td>
<td>34</td>
<td>94%</td>
<td>35</td>
<td>—</td>
<td>LP vs VP</td>
<td>35%</td>
<td>28.9 mo</td>
<td>Pap, ON atrophy, VA</td>
<td>15% (ONSF)</td>
<td>41% “improved VA based on clinic letters”</td>
</tr>
<tr>
<td>Abubaker et al (10)</td>
<td>25</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>LP vs VP</td>
<td>LP 60%, VP 30%</td>
<td>—</td>
<td>VA, VFD, Pap</td>
<td>—</td>
<td>Not reported</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Literature review</td>
<td>LP vs VP vs ONSF</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Feldon (12)</td>
<td>344</td>
<td>74%</td>
<td>32.4</td>
<td>Literature review</td>
<td>LP vs VP vs stent vs ONSF</td>
<td>—</td>
<td>48.3 mo</td>
<td>—</td>
<td>—</td>
<td>38.7%</td>
</tr>
<tr>
<td>Abu-Serieh et al (13)</td>
<td>9</td>
<td>55%</td>
<td>26.4</td>
<td>—</td>
<td>Stereotactic</td>
<td>50% at 12 mo</td>
<td>44.3 mo</td>
<td>Pap, VA, VFD, ON atrophy (none quantitative)</td>
<td>Not reported</td>
<td>33%</td>
</tr>
<tr>
<td>Woodworth et al (14)</td>
<td>21</td>
<td>—</td>
<td>—</td>
<td>Retro</td>
<td>VP vs VA vs V-pleural; Stereotactic</td>
<td>10% at 3 mo</td>
<td>24 mo</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>McGirt et al (5)</td>
<td>42</td>
<td>—</td>
<td>—</td>
<td>Retro</td>
<td>LP vs VP</td>
<td>44%</td>
<td>36 mo</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Byrke et al (15)</td>
<td>17</td>
<td>70%</td>
<td>34</td>
<td>—</td>
<td>No guidance</td>
<td>41% (all within 1.9 yrs)</td>
<td>6.5 yrs</td>
<td>Pap, VA, VFD (VFD not quantitative)</td>
<td>—</td>
<td>18% (acuity in M units); 65% VFD (including enlarged blind spot)</td>
</tr>
<tr>
<td>Groh and Jünemann (16)</td>
<td>1</td>
<td>100%</td>
<td>30</td>
<td>Case report</td>
<td>VP shunt</td>
<td>—</td>
<td>30 mo</td>
<td>VA 20/500 OU, constricted fields</td>
<td>No</td>
<td>100%</td>
</tr>
<tr>
<td>Tulipan et al (17)</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>Retro</td>
<td>Stereotactic</td>
<td>0%</td>
<td>9 mo</td>
<td>Pap</td>
<td>28% (1 LP, 1 ONSF)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rosenberg et al (18)</td>
<td>37</td>
<td>30%</td>
<td>—</td>
<td>Retro</td>
<td>LP vs VP, atrial, jugular</td>
<td>37%</td>
<td>30.9 mo</td>
<td>VA, VFD (not quantitative)</td>
<td>—</td>
<td>35%</td>
</tr>
</tbody>
</table>

Age is mean age in years.
F, female; LP, lumboperitoneal; ON, optic nerve; Pap, papilledema; Retro, retrospective study design; VA, visual acuity; VFD, visual field defect; VP, ventriculoperitoneal.
treatment and ONSF or for cases who present with fulminant progressive severe bilateral visual loss. The purpose of our study was to evaluate visual function including VA and field outcomes in IIH patients who underwent VP shunt for visual loss with a secondary goal of determining a VP shunt survival curve over time.

**METHODS**

After institutional review board approval, a retrospective medical record review was performed of all new patients who met modified Dandy criteria for the diagnosis of IIH and were initially evaluated at our eye institute from January 2004 to December 2010. Patients who underwent VP shunt at our medical center for IIH with or without ONSF were included. Patients were excluded if the medical/surgical record was not available, VP shunt was performed elsewhere or performed for headache only, or if no post-VP shunt follow-up at our eye institute was available.

The best-corrected Snellen VA and automated visual fields (AVF) of qualified patients were used. The visual fields that were selected as “visual field before shunt” were those with the shortest time interval before the shunt and were reliable (≥25% fixation loss, false positives, and false negatives). Visual fields selected for “visual field after shunt” were those on the latest follow-up visit after the fields had stabilized. In one case, the follow-up was <1 month, and in this patient, the last available visual field after shunt was selected. VAs recorded on the same day as the selected visual fields were designated as “visual acuities before shunt” and “visual acuities after shunt,” respectively. If no visual fields were available, VA was selected from the examination closest before the shunt and nearest to 3 months after the shunt. Visual fields were performed using an automated perimeter (Humphrey) using the SITA standard algorithm with a 30-2 program and a Size III target. One patient underwent 24-2 visual field testing. In 4 subjects, poor VA levels warranted kinetic visual fields (Goldmann) (Table 2).

Medical records were reviewed independently in a masked fashion by 3 neuro-ophthalmologists to determine whether the visual function improved, remained unchanged, worsened, or was indeterminate after VP shunt.

VP shunt survival was monitored in all patients by 3 neuro-ophthalmologists to determine whether the visual function improved, remained unchanged, worsened, or was indeterminate after VP shunt.

A literature review was performed to compare visual outcomes and shunt survival rates of VP shunting for IIH (Table 1). A PubMed search was performed in September 2013 with the keywords “idiopathic intracranial hypertension,” “pseudotumor cerebri,” and “ventriculoperitoneal shunt.” This returned 103 results, and of these, 13 articles were selected that mentioned visual outcome and specifically evaluated the surgical outcome of VP shunts alone or in comparison with LP shunting. Articles concentrating exclusively on LP shunting were eliminated as were those focused on pediatric populations.

**RESULTS**

Of the 338 new patients with IIH evaluated during the study period, 19 (6%) patients met the inclusion criteria. The mean age was 29 ± 13 years, and only 1 (5%) patient was male. Of the 19 qualified patients, 17 patients had VP shunt for visual loss and 2 patients had VP shunt for headaches. The 2 patients who had VP shunt for headaches were excluded from the visual function analysis but were included in the shunt survival analysis.

Table 2 summarizes the visual function data for the 17 patients who had VP shunt for visual loss. Five patients had ONSF surgeries before VP shunt, and another patient had bilateral ONSF surgeries after VP shunt. Median VA before shunt was 20/200 in the worse eye (range, 20/20 to NLP) and 20/40 in the better eye (20/20 to HM). Median VA after shunt was 20/60 in the worse eye (20/20 to LP) and 20/30 in the better eye (20/20 to 20/800). The improvement in VA was statistically significant in both worse eyes (P = 0.002, Wilcoxon signed-rank test) and better eyes (P = 0.028).

The mean AVF mean deviation (MD) of available AVFs before shunt was 223.36 dB (range, 233.38 to 27.01 dB) for the worse eye (n = 11) and 219.66 dB (230.11 to 25.91 dB) for the better eye (n = 11). The mean AVF MD of available AVFs after shunt was 220.68 dB (232.13 to 23.97 dB) for the worse eye (n = 11) and 216.35 dB (232.13 to 21.00 dB) for the better eye (n = 11). There were only 9 patients who had both pre- and post-shunt AVF MDs. The improvements of 2.1 dB in the worse eye and of 2.4 dB in the better eye were not statistically significant (P = 0.27, P = 0.26 paired t test, respectively). However, there was a trend toward visual field improvement. Figure 1 shows a plot of AVF MD before shunt against MD after compared with a 1:1 line, showing that most points fall above the line, demonstrating improvement in MD. The available AVFs were taken 7 ± 4 (mean ± SD: range, 3–15) days before shunt (N = 9), and the AVFs after shunt were taken 96 ± 118 (range, 5–341) days after shunt (N = 9).

Independent review of the medical records by 3 neuro-ophthalmologists were in agreement and showed 9 (53%) patients improved (of which 2 required shunt revision or adjustment), 5 (29%) patients unchanged, 1 (6%) patient worsened, and 2 (12%) patients were indeterminate because of unavailable or fluctuating visual fields. The one patient who worsened required ONSF bilaterally approximately 1 year after shunt placement. With VA improvement defined as 1 eye improving by at least 1 line of Snellen VA and the fellow eye either stable or improved, 12/17 (71%) patients improved. With visual field improvement defined similarly as at least 1 eye showing improvement in
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age**</th>
<th>ONSF (Months Before Shunt)</th>
<th>Visual Acuity† Before Shunt</th>
<th>Visual Acuity‡ After Shunt</th>
<th>AVF 30-2 Before Shunt</th>
<th>AVF 30-2 After Shunt</th>
<th>Length Follow-up After Shunt (mo)</th>
<th>Complications and Failure (Months After Shunt)§</th>
<th>Visual Outcome After Shunt Based on Record Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>34</td>
<td>None</td>
<td>20/20</td>
<td>20/20</td>
<td>1.00</td>
<td>3.97</td>
<td>11.57</td>
<td>13</td>
<td>Improved</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>12</td>
<td>None</td>
<td>20/40</td>
<td>20/40</td>
<td>20.26</td>
<td>17.11</td>
<td>54</td>
<td>6</td>
<td>Improved (2020)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>46</td>
<td>None</td>
<td>20/40</td>
<td>20/200</td>
<td>29.72</td>
<td>NA</td>
<td>29</td>
<td>KVF (100)</td>
<td>Worsened</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>14</td>
<td>None</td>
<td>2/200</td>
<td>2/200</td>
<td>-0.33</td>
<td>-0.26</td>
<td>341</td>
<td>34</td>
<td>Stable</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>42</td>
<td>None</td>
<td>20/40</td>
<td>2/200</td>
<td>30.11</td>
<td>33.38</td>
<td>54</td>
<td>40</td>
<td>Improved (2020)</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>22</td>
<td>None</td>
<td>20/20</td>
<td>20/20</td>
<td>20.71</td>
<td>20.17</td>
<td>54</td>
<td>15</td>
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</tr>
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<td>20/20</td>
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<td>112</td>
<td>22</td>
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<td>8</td>
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<td>4/200</td>
<td>6/200</td>
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<td>14.83</td>
<td>30</td>
<td>27</td>
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<td>9</td>
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<td>27</td>
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<td>20/40</td>
<td>20/40</td>
<td>27.19</td>
<td>29.69</td>
<td>159</td>
<td>15</td>
<td>Improved (2020)</td>
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<td>F</td>
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<td>20/60</td>
<td>20/50</td>
<td>27.19</td>
<td>29.69</td>
<td>235</td>
<td>31</td>
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<tr>
<td>11</td>
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<td>31</td>
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<td>20/20</td>
<td>20/20</td>
<td>27.19</td>
<td>29.69</td>
<td>235</td>
<td>31</td>
<td>Improved (2020)</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>20</td>
<td>None</td>
<td>20/40</td>
<td>20/25</td>
<td>20.71</td>
<td>20.17</td>
<td>54</td>
<td>15</td>
<td>Improved (2020)</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>25</td>
<td>OS (0.25)</td>
<td>20/20</td>
<td>20/25</td>
<td>-0.33</td>
<td>-0.26</td>
<td>341</td>
<td>34</td>
<td>Stable</td>
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<tr>
<td>14</td>
<td>F</td>
<td>40</td>
<td>OS (0.25)</td>
<td>20/20</td>
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<td>-0.33</td>
<td>-0.26</td>
<td>20.71</td>
<td>20.17</td>
<td>Improved (2020)</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>40</td>
<td>OS (0.11)</td>
<td>20/20</td>
<td>20/25</td>
<td>-0.33</td>
<td>-0.26</td>
<td>20.71</td>
<td>20.17</td>
<td>Improved (2020)</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>40</td>
<td>OS (0.11)</td>
<td>20/20</td>
<td>20/25</td>
<td>-0.33</td>
<td>-0.26</td>
<td>20.71</td>
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<td>Improved (2020)</td>
</tr>
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<td>17</td>
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<td>61</td>
<td>ONSF</td>
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<td>20/20</td>
<td>1.00</td>
<td>3.97</td>
<td>11.57</td>
<td>13</td>
<td>Improved</td>
</tr>
</tbody>
</table>

**Age at VP shunt:** Age at first ONSF or AVF if not within 3 months before shunt and enrolled in 3 month after shunt. Patient 11 with post-shunt VA at 3 years because vision was lost to follow-up.

†Visual acuity on same day as AVF or KVF, if no VF, acuity on date closest before shunt date and nearest to 3 month after shunt. Patient 11 with post-shunt VA at 3 years because vision was lost to follow-up.

‡All 30-2 Humphrey SITA standard size III visual fields except for 24-2 in subject 6. KVF days before and after shunt in parentheses for those without AVF.

§Shunt failure = replacement, removal, or revision.

kBased on independent review of records from 3 neuro-ophthalmologists.

¶Number of months following VP shunt.

AVF, automated visual fields; CF, count fingers; HM, hand motion; KVF, kinetic visual fields; NA, not applicable; NLP, no light perception; OD, right eye; ONSF, optic nerve sheath fenestration; OS, left eye; VP, ventriculoperitoneal.
MD whereas the fellow eye either stable or improved, 5/9 (55%) showed improvement (only 9 patients had pre- and post-shunt visual fields).

All 19 patients had VP shunts placed between October 2006 to August 2011, with an average follow-up of 21 months (range, 5–1,342 days). Kaplan–Meier analysis showed a persistent steady decrease of functioning VP shunts. Figure 2 shows 80% of VP shunts were functioning without replacement, removal, or revision at 12 months, 65% at 18 and 24 months, and 48% at 36 months. During this period, 3 patients required revision (at 1, 18, and 27 months after shunt), 2 required replacement (at 7 and 14 months), and 1 required removal (at 8 months). Additionally, 1 patient required a replacement at 38 months.

**DISCUSSION**

We found that VP shunting improved or stabilized VA and visual field analysis in most of our IIH patients who either presented with rapidly worsening vision or who had progressive visual loss despite medical treatment and ONSF. One patient worsened after VP shunt and required ONSF in both eyes. This is consistent with previous reports of the potential benefit of ONSF for those who worsen after VP shunt (19,20). Five of our patients had ONSF before VP shunt, of which, 2 showed improvement after VP shunt, 2 were unchanged, and 1 was indeterminate. There are reports of IIH patients with visual loss after ONSF who benefited from subsequent VP shunt (6,7).

Visual acuity changes for worse eye and best eye were both statistically significant demonstrating that patients with both mildly decreased and poor VA may improve after VP shunt. Visual field analysis was not statically significant, but there was a trend toward less field constriction after VP shunt (Fig. 1). The lack of significance may be due to the small sample size because only 9 patients had quantifiable fields before and after surgery.

The second outcome of our study was shunt survival. For a variety of reasons, VP shunting is the preferred method of CSF diversion at our institution. Kaplan–Meier survival analysis of our patients showed a persistent steady decrease in functioning VP shunt over time. Our failure rates of 20% at 1 year, 35% at 2 years, and 52% at 3 years are in line with other series that report shunt complication/revision rates between 23% and 64% in the first 1–4 years (Table 1) (6,13,15).

In our literature search, the closest study to ours was conducted by Bynke et al (15). In evaluating 17 IIH patients, they reported a shunt revision rate of 41%, an 18% improvement in VA and a 65% improvement in visual field defects, compared with the 70% in our study based on VA and 55% based on visual field MD. Bynke et al included enlarged blind spot in their descriptive nonquantitative visual field analysis, which may, in part, explain the high percentage of improvement reported.

We recognized the limitations of our study. The first is the retrospective design, leading to gaps in data collection, variation in baseline clinical characteristics, and lack of standardization of visual field testing and follow-up. Another limitation is the sample size. Although our sample size is similar to other studies looking at shunting procedures for IIH, it is small which limits statistical significance, making it difficult to compare outcomes directly in a paired fashion. Of the 17 patients included in the visual outcome analysis, only 9 had both a pre- and post-surgical visual field results that were suitable for analysis. Of those, 4 had previous ONSF.

FIG. 1. Mean deviation (MD) of visual fields before and after shunt placement plotted with 1:1 line. Points above the line indicate improvement in MD after surgery. ONSF, optic nerve sheath fenestration.

FIG. 2. Kaplan–Meier survival plot of the probability of ventriculoperitoneal shunt success, defined as no replacement, removal, or revision over time.
causing additional bias because patients who have failed medical treatment and ONSF may be less likely to respond to a shunt procedure.

REFERENCES


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Inpatient and Emergency Service Utilization in Patients With Idiopathic Intracranial Hypertension

Jagger C. Koerner, BS, Deborah I. Friedman, MD, MPH

Background: Many patients with idiopathic intracranial hypertension (IIH) are diagnosed in the emergency department (ED) or visit the ED during the course of their illness. We studied the use of inpatient and emergency services, determined what procedures and tests were provided at those encounters, evaluated how these variables changed over the study period and examined the coding validity of the International Classification of Diseases (ICD)-9 code for IIH (348.2) for adult patients seen in our affiliated EDs and inpatient services.


Results: We were able to analyze 137 encounters from 51 patients. Sixty-eight percent of encounters were to the ED and 40% of those patients were subsequently admitted to the hospital. The most common symptoms were headaches (96%), vision change (53%), and photophobia (27%). Recurrent symptoms accounted for 43% of encounters, followed by surgical complications (26%) and initial presentation (12%). Four patients (25% of the patients who received a diagnosis in the ED) were misdiagnosed at their initial presentation and correctly diagnosed on a subsequent ED visit. The number of ED visits more than doubled over the study period. The ICD-9 code had a low positive predictive value (55%) for identifying patients with IIH.

Conclusions: The ED was commonly used by patients with IIH, with a mean of 2.7 visits per patient. The rate of a missed diagnosis was similar to another published series and is concerning for potentially permanent visual loss in undiagnosed patients. In our experience, the ICD-9 code vastly overestimated the number of ED and inpatient encounters attributable to IIH. This has important implications for research studies, particularly those relying on national inpatient databases.


Many patients with idiopathic intracranial hypertension (IIH), particularly those with the most severe symptoms, are initially diagnosed and treated in an emergency department (ED) or inpatient setting. If surgery is required to control the intracranial pressure or treat visual loss, it is almost always performed on an inpatient basis (shunt procedure) or in an ambulatory surgery center (optic nerve sheath fenestration). Inpatient shunting procedures for IIH increased by 350% between 1988 and 2002 (1). However, the use of inpatient and emergency services by patients with IIH previously has not been examined. The purpose of this study was to determine the coding validity of the International Classification of Diseases (ICD)-9 code (348.2) for IIH, record the use of inpatient and emergency services, determine what procedures and tests were provided at those encounters, and evaluate how these variables changed over the study period.

METHODS

Our protocol was approved by the Research Subjects Review Board at the University of Rochester (RSRB# 15754). Strong Memorial Hospital, Rochester, NY, inpatient and ED patient charts coded with a diagnosis of IIH, optic nerve sheath fenestration, or lumbo-peritoneal (L-P) shunting, from August 1, 2000, to July 31, 2011, were selected for review. Children younger than 18 years were excluded.

The ICD-9 code (348.2) for IIH identified 92 adult patients seen in the ED or inpatient setting over the search period. The procedure codes for optic nerve fenestration, and L-P shunting did not identify any additional IIH patients. Twenty-seven (30%) of the charts were initially excluded from further review. Of these, 15 charts (55%) were excluded...
because there was no evidence of an IIH diagnosis or workup, 7 (26%) mentioned IIH in the medical history but provided no evidence of diagnosis or workup, and 5 (19%) were incomplete.

There were 65 charts with evidence of IIH in adult patients seen in the ED or the inpatient setting. Of these, 14 did not meet our criteria for inclusion in the study. Patients presenting to the ED were included in the study when documentation supported the diagnosis of IIH consistent with the Friedman and Jacobson criteria (2). This included lumbar puncture (LP) pressure greater than 25 cm of cerebrospinal fluid (CSF) with normal CSF composition, negative magnetic resonance imaging (MRI) or computed tomography (CT), and no other explanation for intracranial hypertension. Surgical patients were included when they had IIH in their medical history, surgery to treat IIH, or medical/surgical visits to treat complications.

The 51 patients identified averaged 2.7 encounters (ED or inpatient) each over the study period. Only encounters related to IIH were included in the study. ED patient visits were included when presenting symptoms, diagnosis, workup, and discharge information were consistent with IIH. The “possible initial presentation” category (see below) is an exception for patients who presented with IIH symptoms, were not diagnosed or assessed for IIH, and at a subsequent encounter were evaluated and diagnosed with IIH. All surgery visits to treat IIH or complications from past surgeries were included. The total number of ED and inpatient encounters was 137.

The following data were recorded: date of birth, age, race/ethnicity, gender, date of encounter, body mass index (BMI), setting of encounter (ED, inpatient), presenting symptoms (headache, vision changes, syncope, emesis), length of stay, neuroimaging procedures [CT, MRI, magnetic resonance angiography, and magnetic resonance venography], surgical procedures (L-P shunt placement, removal, revision, optic nerve sheath fenestration), LP data (with or without fluoroscopy, opening pressure, amount of CSF removed), suspected cause, and possible undiagnosed initial encounter.

**RESULTS**

Patient data are summarized in Table 1. The female-to-male ratio was 25:1 (96% female). The average age was 33 years with a range of 19–59 years. The racial/ethnic breakdown of patients was generally consistent with the geographic area in which they lived, with 69% of the patients being Caucasian, 16% black, 6% Hispanic, and 10% unknown. The average BMI was 43.03 kg/m² (n = 29). The BMI could not be calculated but obesity was noted in the chart in an additional 12 patients. Ten patients had no data regarding body habitus. The average LP opening pressure was 32.4 cm of CSF and a mean of 16.8 mL of CSF was removed.

The majority (68%) of the 137 patient encounters were in the ED. Patients presented to the ED most commonly with headache (94%), vision changes (53%), photophobia (27%), emesis (17%), and syncope (9%). Three patients sought care in the ED for a post–lumbar puncture headache. A physician referral, most frequently from an ophthalmologist, prompted 11 of the 93 ED visits. Of the ED visits, 40% resulted in hospital admission. Most patient encounters were the result of recurrent symptoms from IIH (43%), followed by surgical complications (26%) and initial presentation (12%). ED visits increased over the study period with a minimum of zero visits in 2001 and a maximum of 18 in 2009 (Fig. 1).

Of the 3 patients only seen in the inpatient setting, 1 was admitted for elective LP shunt and 2 for headache symptoms. Shunt revision was the most common surgery, followed by LP shunt placement. Over the study period, 8 L-P shunts were placed, 2 removed, and 10 revised.

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**TABLE 1. Patient and demographic data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>35 (68)</td>
</tr>
<tr>
<td>Black</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (6)</td>
</tr>
<tr>
<td><strong>Age, yr</strong></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>33.3</td>
</tr>
<tr>
<td>Maximum</td>
<td>59</td>
</tr>
<tr>
<td>Minimum</td>
<td>19</td>
</tr>
<tr>
<td><strong>Sex, n</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>49 (96)</td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td><strong>Body habitus</strong></td>
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<tr>
<td>Average BMI, kg/m²</td>
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<tr>
<td>Obese</td>
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<tr>
<td><strong>LP pressure, cm of CSF</strong></td>
<td></td>
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<tr>
<td>Average opening</td>
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</tbody>
</table>

*2011 census data estimated the population in the greater Rochester New York area (Monroe County) to be 78% Caucasian, 16% black, and 7.5% Hispanic. CSF, cerebrospinal fluid; LP, lumbar puncture.

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**FIG. 1.** Emergency department visits for patients with idiopathic intracranial hypertension. Asterisk indicates that only full calendar years are included.
The positive predictive value (PPV) using our criteria for the diagnosis code 348.2 was 55% (51 of 92 patients were positively identified). IIH was recorded in 70% of patient encounters, and the average length of stay for inpatients was 3.9 days.

The most common procedures followed by MRI were CT and LP. The use of CT, LP, and MRI (including magnetic resonance angiography and venography) did not increase on a per ED visit basis throughout the study, although the absolute number of the procedures increased as the number of ED visits rose. The number of these procedures and imaging studies per ED visit by year ranged from 0.9 to 2.3 with an average of 1.6 (Table 2).

**DISCUSSION**

The ICD-9 code for IIH had a low PPV (55%) in our study. This could partly be explained by the charts that mentioned IIH but lacked workup, possibly being incomplete, and the several patients who left before the workup was complete. The largest group of charts excluded, however, did not mention IIH at all. Patients who were incorrectly coded with IIH had evidence in their chart of traumatic brain injury following motor vehicle accident, subdural hematoma, hydrocephalus, and neuroleptic malignant syndrome, among others. This suggests that the IIH code often is incorrectly used and is being assigned when intracranial hypertension is not idiopathic. This apparent overapplication of the code makes it difficult to compare data across institutions, and further research is needed to examine variability in coding validity. Assuming that the coding inaccuracies found at our institution are not unique to the University of Rochester, this has implications regarding research relying solely on national inpatient databases to study the impact of IIH (3).

**TABLE 2.** Frequency of neuroimaging studies and lumbar punctures, during the study period

<table>
<thead>
<tr>
<th>Year</th>
<th>CT</th>
<th>LP*</th>
<th>MRI†</th>
<th>Total</th>
<th>ED Visits</th>
<th>Ratio‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>14</td>
<td>6</td>
<td>2.3</td>
</tr>
<tr>
<td>2003</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>10</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td>2004</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td>2005</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>12</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>2006</td>
<td>6</td>
<td>9</td>
<td>2</td>
<td>17</td>
<td>13</td>
<td>1.3</td>
</tr>
<tr>
<td>2007</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>13</td>
<td>8</td>
<td>1.6</td>
</tr>
<tr>
<td>2008</td>
<td>11</td>
<td>8</td>
<td>8</td>
<td>27</td>
<td>12</td>
<td>2.3</td>
</tr>
<tr>
<td>2009</td>
<td>12</td>
<td>12</td>
<td>4</td>
<td>28</td>
<td>18</td>
<td>1.6</td>
</tr>
<tr>
<td>2010</td>
<td>5</td>
<td>11</td>
<td>10</td>
<td>26</td>
<td>13</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*LP and LP under fluoroscopy.
†Includes MRI, MVA, and MRV.
‡Number of procedures and imaging studies per ED visit.
CT, computed tomography; ED, emergency department; LP, lumbar puncture; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography.

Patients previously diagnosed with IIH presenting with recurrent symptoms or complications from surgical procedures are a significant majority of IIH patients seen in the ED. Only 16 patients over the study period were newly diagnosed with IIH in the ED, making this a relatively rare occurrence given the 11-year study period. This study did not review outpatient data or data from other hospitals, and possibly, a subset of IIH patients only used outpatient services. Suspected cases of misdiagnosis in the ED are difficult to determine in a retrospective chart review study. Of the 16 patients initially diagnosed in the ED, 4 previously had presented with typical IIH symptoms and were diagnosed with IIH on a subsequent visit giving a misdiagnosis rate of 25%. This is similar to a previous study of the initial IIH presentation in the ED that demonstrated a 27% misdiagnosis rate (4). Our misdiagnosis rate could be inaccurate as patients who presented to the hospital and received an alternative diagnosis may have sought care and subsequently been diagnosed with IIH as an outpatient or at another institution.

Nearly all the patients who underwent surgery were also seen in the ED with complications from surgical procedures being the second greatest reason for an encounter (26%). Shunt malfunction or infection was noted as a suspected diagnosis in 11 of the 93 ED patient encounters. These visits resulted in 3 admissions for shunt revision and 1 recommendation to have the shunt revised at a later time, although in the remainder no evidence of shunt malfunction was found. None of the surgical procedure codes revealed any patients that were improperly coded.

Use of the ED increased over the study period. Given our study limitations, it is difficult to explore why this occurred and the increase could have been due to a variety of factors, including change in local referral patterns, increasing incidence of IIH, increased use of the ED generally, and growth driven by increased numbers of shunts placed over time (1).

Our study is limited because it was performed in a single center. It is possible that some ED and inpatient visits were missed by our methods, as the search terms were selected to identify patients having encounters related to IIH. We were unable to verify whether our patients also sought care in nonaffiliated hospitals. Nonetheless, our findings suggest that the ED is frequently used by patients with recurring symptoms and complications from surgery. Many surgery patients use the ED at some point, and patients who use the ED typically presented multiple times. Initial diagnosis of IIH in the ED was infrequent and misdiagnosis of IIH occurred in approximately 25% of patients in our series, emphasizing the importance of fundoscopy and a high index of suspicion to prevent delays in treatment and possible irreversible visual loss. Many patients with IIH presenting to the ED subsequently are admitted to hospital and suspected complications from surgery is the second most common reason for presentation to the ED. Lumbo-peritoneal shunts were performed more frequently for IIH...
in the Rochester area at the time our study, and L-P shunts are more prone to failure than ventriculoperitoneal shunts (5). It is possible that shunt-related admissions may be lower in hospitals where ventriculoperitoneal shunts are the preferred CSF diversion procedure. The ICD code 348.2 does not reliably identify patients with IIH, and using this code in isolation without a chart review likely overestimates the number of encounters for IIH in the ED and inpatient settings.

REFERENCES
A Direct Comparison of OnabotulinumtoxinA (Botox) and IncobotulinumtoxinA (Xeomin) in the Treatment of Benign Essential Blepharospasm: A Split-face Technique

Julien Saad, BSc, MD, Alain Gourdeau, MD, FRCSC

Background: Benign essential blepharospasm (BEB) is characterized by progressive involuntary contractions of the protractor muscles, sometimes leading to a debilitating closure of the lids. It is currently treated with the injection of botulinum neurotoxin A (BoNT/A). The purpose of this study was to compare 2 BoNT/A preparations (i.e., Xeomin and Botox) in the treatment of BEB.

Methods: This was a prospective, randomized, double-blinded split-face technique in 48 patients already treated by Botox for BEB. Patients received the same medication to either side of the face for 4 injections, and were then evaluated using subjective and objective measures. Blepharospasm Disability Index (BSDI) and Jankovic Rating Scale (JRS) were assessed using a repeated-measures analysis of variance (ANOVA) and paired t test. Patient preference and objective comparison of residual orbicularis strength and spasm were compared using a multinomial logistic regression model, a repeated-measures ANOVA, and a paired t test.

Results: A paired t test showed no preference between Xeomin and Botox (P = 0.7205) and demonstrated a tendency toward not having a preference for either medication (P = 0.0301 vs Botox and P = 0.0039 vs Xeomin). The regression model showed no effect of time on patient preference (P = 0.4217). The ANOVA for BSDI scores did not reveal any difference between the 2 medications as compared with baseline (P = 0.8161), nor did it demonstrate an effect of time on BSDI scores (P = 0.6108). A paired t test found no difference between the 2 scores (P = 0.1909) at baseline. There was no difference in JRS scores for either medication when compared with baseline (P = 0.2314), nor was there an effect of time on such scores (P = 0.4951). There was also no difference between the 2 medications according to paired t test (P = 0.3224) at baseline. Baseline residual orbicularis strength was similar between the 2 medications (paired t test; P = 0.3228). ANOVA shows an effect of time on orbicularis strength (P = 0.0055), but no difference was seen at any of the 5 visits (P > 0.05). Baseline spasm scores were similar between Botox and Xeomin (paired Student t test; P = 0.3228). The ANOVA shows no difference between both medications at any point in time (P = 0.4408), and that time had no effect on the efficacy of either treatment (P = 0.3268).

Conclusion: No difference between Xeomin and Botox was detected in either subjective or objective measures for the treatment of BEB.

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Benign essential blepharospasm (BEB) is characterized by involuntary progressive contractions involving the principal protractors of the lids, and when severe, can lead to complete occlusion of the eye (1). Symptoms typically begin between the fifth and seventh decade, with females being more affected than males in a 3:1 ratio (2). The neurological circuit controlling the eye blink includes a sensory and a motor pathway, with BEB possessing numerous possible triggers, and a likely multifactorial etiology (3).

Spontaneous remission of BEB is rare, with most patients requiring treatment for many years. Treatment consists of reducing involuntary contractions, primarily with botulinum neurotoxin A (BoNT/A) injections (4,5).

BoNT/A inhibits the fusion of cholinergic vesicles in the presynaptic membranes of the neuromuscular junctions, which causes a temporary focal muscle paralysis (6). One of the most commonly used neurotoxins is Botox (Vistabel, onabotulinumtoxinA; Allergan Inc). Botox preparations are accompanied by complexing proteins, which allow for greater stability in the digestive tract and increased absorption (7). These proteins do not improve storage life, nor do they affect the diffusion of the medication once injected (8).
TABLE 1. Demographic and treatment data of patients injected with Botox vs Xeomin

<table>
<thead>
<tr>
<th></th>
<th>All Enrolled Patients (n = 48)</th>
<th>Excluding Deceased Patient (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>24/24</td>
<td>24/23</td>
</tr>
<tr>
<td>Age at enrollment, years</td>
<td>70.2 ± 12.1 44.5–92</td>
<td>69.7 ± 11.8 44.5–88.2</td>
</tr>
<tr>
<td>Age at onset of symptoms, years</td>
<td>56.8 ± 15.0 6.0–80.6</td>
<td>56.7 ± 15.1 6.0–80.6</td>
</tr>
<tr>
<td>Duration of treatment before study, years</td>
<td>17.0 ± 10.5 3.0–42.3</td>
<td>16.6 ± 10.3 3.0–42.3</td>
</tr>
<tr>
<td>Units used per side</td>
<td>19.9 ± 4.9 7.5–30</td>
<td>20.0 ± 4.9 7.5–30</td>
</tr>
</tbody>
</table>

Some studies have demonstrated that neutralizing antibodies to these complexing proteins are found in the circulation, which may lead to a secondary resistance (8).

Xeomin (Bocouture, incobotulinumtoxinA; Merz Pharmaceuticals GmbH) is the first BoNT/A not associated with complexing proteins. It also has a long shelf life of 4 years, is stable at room temperature, and possesses the same diffusion pattern as Botox (9). Many studies have demonstrated a noninferiority of Xeomin to Botox for BEB (10,11), and also for many other pathologies including focal dystonia, spasticity, hemifacial spasm, and hypersalivation (12). To the best of our knowledge, there has not been a prospective, randomized split-face comparison of these 2 medications for the treatment of BEB.

The purpose of this study was to evaluate and compare Botox with Xeomin in the treatment of BEB in the same population, using a split-face technique in patients with bilateral symmetric BEB.

METHODS

Study Design

A randomized, double-blind prospective study in which 48 patients treated for bilateral, symmetrical BEB were enrolled between February and March 2012. All patients were previously treated and controlled with Botox at the Neuro-Ophthalmology Clinic at Hôpital de l’Enfant-Jésus in Quebec City, Quebec. The patients were randomized so that half received Xeomin on the right side and Botox on the left side of their faces, and vice versa for the other half. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board and ethics committee of the Hôpital de l’Enfant-Jésus. Written consent was obtained from all patients before enrollment.

Study Protocol

Patients were examined and treated by a single investigator (A.G.) and questioned by either the research nurse or medical resident. All were masked to the randomization. At each visit, the patient would answer the Blepharospasm Disability Index (BSDI) and choose a preferred treatment side based on better control of spasms or lesser side effects.

After the questionnaire, the patients then underwent a slit-lamp examination, an assessment of orbicularis strength and spasm, as well as an evaluation using the Jankovic Rating Scale (JRS) by the same investigator (A.G.). The patients were then injected with Xeomin to either the right or left side of the face, with Botox to the other side for 4 consecutive treatments. There was no washout period before enrollment in this study; any residual effect of Botox was thought to have worn off after the first injection of Xeomin. The medications were dispensed by the hospital’s pharmacy department in syringes labeled with the patient’s ID number and the side to be injected. The patients were interviewed and assessed at each of 4 treatment visits, as well as the first appointment after their last injection of Xeomin.

Dosage

The patients enrolled in this study had previously found stability and control with Botox, using the same number of units during the previous 2 visits, and having a steady interval between visits. Many studies that compared the efficacy of Xeomin with Botox have found that a substitution of 1:1 was sufficient (9,11), therefore the same number of units and interval of treatment were continued throughout the study, substituting 1 unit of Botox for 1 unit of Xeomin.

Statistical Methods

All analyses have been performed using SAS software (SAS Inst, NC, release 9.3, 2012). Side preference, residual orbicularis strength, and an objective comparison of spasm were assessed by evaluating the probability of each of the 3 possible answers; Xeomin being more effective, Botox being more effective, or equal efficacy. The effect of time on preference was evaluated using a repeated-measures multinomial logistic regression model.

The JRS was scored objectively on a scale of 0–4 for both severity and frequency of spasms. This was performed by the principle investigator for each side of the face, and at each of the 5 visits. The sum of the 2 scores (0–8) were then tabulated, with a higher score correlating to poorer control of spasms.

The BSDI assesses functional impairment while performing 6 daily activities ("driving a vehicle", "reading", "watching TV", "shopping", "walking", "doing everyday activities")...
Each activity was rated on a scale of 0–4 with the possibility of rating an activity as “nonapplicable”. The sum of all scores were added and then divided by the number of applicable activities. The mean BSDI and JRS scores for each side of the face were compared at the first visit (i.e., before receiving the first Xeomin injection) using a paired t test. The scores from subsequent visits were then compared with baseline scores looking for a difference between the 2 medications at any of the visits, as well as for an effect of time on the efficacy of either medication using a repeated-measures analysis of variance (ANOVA). The baseline score served as a covariable, and the medication and visit served as the repeated measures for these analyses.

The residual orbicularis strength and spasm were assessed at each visit using a Likert scale of 5 points (0 to +4 for strength). The means of each score were calculated for each medication at each of the 5 visits. Baseline scores (i.e., before the first Xeomin injection) were compared using a paired Student t test, and subsequent visits were compared with baseline using a repeated-measures ANOVA looking for difference between the 2 medications and for an effect of time on treatment. Baseline scores served as a covariable, and the medication and visit were used as the repeated measures.

The probability of a patient preferring either medication or having no preference at all were as follows: $P_{\text{Botox}} = 0.2549$ (confidence interval [CI], 0.1602–0.3495), $P_{\text{Xeomin}} = 0.1652$ (CI, 0.1652–0.2731), and $P_{\text{no preference}} = 0.5799$ (CI, 0.4454–0.7144). When comparing the probability of each occurrence, we found a significant trend toward having no preference as compared with preferring Botox ($P = 0.0301$) or Xeomin ($P = 0.0039$), but no preference between the 2 medications ($P = 0.7205$). There was also no effect of time on the patients’ preference ($P = 0.4217$).

Comparing the BSDI scores for both medications, we averaged the sums for each patient at each of the 5 visits and calculated a mean score for each medication at each visit (Table 2). Xeomin scores tended to be lower than the Botox score, but baseline scores were not significantly different ($P = 0.1909$). Furthermore, there was no difference detected with respect to baseline scores for either medication ($P = 0.8161$), nor was there an effect of time ($P = 0.6108$).

The mean JRS scores were calculated at each of 5 visits for Xeomin and Botox (Table 2). There was no significant difference between the 2 medications at baseline ($P = 0.3224$). The ANOVA showed no difference between the 2 treatments as compared with baseline ($P = 0.2314$) and showed no effect of time on JRS scores ($P = 0.4951$).

The mean scores for residual orbicularis strength at each visit were determined (Table 2). The paired Student t test indicates no significant difference between the 2 medications at the initial visit ($P = 0.3228$). However, the ANOVA shows a significant difference in strength between the 2 medications, which varied from one visit to the other ($P = 0.0055$). Further analyses found no significant difference at any of the visits using a paired t tests ($P = 0.1590$ at Visit 3 and $P = 0.0706$ at Visit 4).

The mean scores for spasms on a rating scale from 0 to +4 at each visit are shown in Table 2. The paired Student t test showed no significant difference between the 2 medications at the initial visit ($P = 0.3228$). There was also no difference between both medications at any point in time ($P = 0.4408$), nor did time have an effect on the efficacy of both treatments ($P = 0.3268$).

Furthermore, there were instances where the investigator noted a slight difference between the 2 sides, but not enough to attribute a different score on the predetermined scale. A multinomial logistic regression model, much like that used for patient preference, was used to determine whether a slight difference exists. No difference was noted between the 2 medications for orbicularis strength ($P = 0.2960$) or spasms ($P = 0.5181$).

### RESULTS

Forty-five of the 48 enrolled patients completed the study (Table 1). One patient died after the first injection, unrelated to the medication, and the other 2 withdrew from the study after the third injection. Missing data were imputed using the “Hot Deck” method.

The probability of a patient preferring either medication or having no preference at all were as follows: $P_{\text{Botox}} = 0.2549$ (confidence interval [CI], 0.1602–0.3495), $P_{\text{Xeomin}} = 0.1652$ (CI, 0.1652–0.2731), and $P_{\text{no preference}} = 0.5799$ (CI, 0.4454–0.7144). When comparing the probability of each occurrence, we found a significant trend toward having no preference as compared with preferring Botox ($P = 0.0301$) or Xeomin ($P = 0.0039$), but no preference between the 2 medications ($P = 0.7205$). There was also no effect of time on the patients’ preference ($P = 0.4217$).

### DISCUSSION

BEB can be a debilitating disease, with up to two-thirds of patients becoming functionally blind (13). The purpose of
this study was to determine whether there was a difference in efficacy and patient preference between Xeomin and Botox. To the best of our knowledge, this study is the first using a prospective, randomized, double-blinded split-face technique for the comparison of these 2 medications. Furthermore, using 4 injections of the same medication to either side, we eliminated any potential residual effect of Botox received before the study at Visits 2 to 4.

Subjectively, no significant difference was noted. Using the BSDI, we were unable to detect any difference between the 2 medications. A possible explanation for the lack of difference on the BSDI is that although the index is sensitive enough when comparing BONT/A with placebo, it may be less useful when comparing the 2 agents (14). A 1-point improvement on this scale constitutes a 25% difference in symptoms, which may be too great to be noted by the patient. It also does not take into account the importance of each activity in an individual’s daily life. However, in our study, we asked the patients about their preference, if any, between the two, and no preference was found.

Using objective measures, the JRS results failed to demonstrate any difference between Xeomin and Botox, as did the global scores for spasms. Once again, the JRS may not be sensitive enough to demonstrate a difference between the 2 agents, as opposed to comparing with placebo (14). However, a different scale used to assess for spasms also indicated that no significant difference exists between the 2 medications. Using the regression model, we eliminated the possibility of there being a subtle difference in spasm, not detected by the JRS.

The residual orbicularis strength as assessed by the investigator did show some difference over time, likely because of the differences seen in Visits 3 and 4. This difference went in opposite directions (i.e., Botox was more effective at Visit 3, but Xeomin was more effective at Visit 4) and with a posteriori analyses, no difference was seen at any single visit. We cannot explain this difference. In addition, the use of the regression model confirmed that there was no difference, however subtle, between the 2 medications.

Our study failed to find any difference between Xeomin and Botox in the treatment of BEB. We consider both medications equally efficacious in the treatment of this disorder.

ACKNOWLEDGMENTS

The authors thank Mr Paul-Marie Bernard and Mr Gaetan Daigle for their statistical analyses; Mrs Jocelyne Boivin, research nurse, for her help in data collection; Mrs Marcelle Giasson for her assistance in project coordination; and Dr Patrick J. Rochette for his review of the article.

REFERENCES

Homonymous Hemianopia Due to Erdheim–Chester Disease

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Abstract: Erdheim–Chester disease (ECD) is a rare non-Langerhans cell histiocytosis typically affecting multiple organ systems. We report 2 patients who presented with homonymous hemianopia and were ultimately diagnosed with biopsy-confirmed ECD. We review the spectrum of ECD and its treatment as well as histopathological and immunohistochemical differentiation from other histiocytic disorders.

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Erdheim–Chester disease (ECD) is a rare non–Langerhans cell histiocytosis (NLCH) first described by Jakob Erdheim and William Chester in 1930 (1). It is a multisystem disorder, characterized by xanthogranulomatous infiltration, most commonly affecting appendicular bones but also may involve the heart, lung, liver, kidneys, retroperitoneum, brain, and orbits (2). Central nervous system involvement is seen in less than 50% of patients and has been found to be an independent predictor of death (3). Visual loss usually is due to anterior visual pathway compressive lesions within the orbit and parasellar region (4–8). We report 2 biopsy-confirmed ECD cases found to have homonymous hemianopia on presentation because of posterior visual pathway lesions. Our first patient is the third known case of ECD with isolated intracranial involvement (9,10).

CASE REPORT

Case 1

A 45-year-old woman with a history of migraine headaches preceded by bilateral peripheral scintillating lights for 25–35 minutes was evaluated for atypical visual aura of 3-day duration without headache. She described seeing distorted shapes and buildings as if she was in “Toon Town” (Disneyland, CA) in the right half of her visual fields. She reported left leg and hip weakness and pain that was attributed to a fall on icy stairs 2 years previously. She rarely drank alcohol and had never smoked cigarettes. Although born in the United States, she spent her first 2.5 years of life in Japan and traveled extensively throughout Europe and Asia. She denied any preceding illnesses, new animal exposures, or insect bites.

Brain magnetic resonance imaging (MRI) revealed multiple intra- and extra-axial enhancing masses involving brain parenchyma, pituitary infundibulum, and corpus callosum (Fig. 1). Visual acuity was 20/20, right eye and 20/30, left eye. Color vision was normal in the right eye and diminished in the left eye. There was no relative afferent pupillary defect. Ocular motility and funduscopy were unremarkable. Visual field testing demonstrated an incomplete right homonymous hemianopia (Fig. 2A).
Complete blood count, metabolic panel, angiotensin-converting enzyme (ACE), and free T4 were normal with a mildly elevated thyroid stimulating hormone. Serum antibody testing was negative for rapid plasma reagin, HIV-1 and -2, Lyme, cysticercosis, and coccidioides. Cerebrospinal fluid analysis, including flow cytometry, was negative for malignant cells. Oligoclonal bands, venereal disease research laboratory tests, ACE, acid-fast stains, mycobacterium tuberculosis complex polymerase chain reaction (PCR), Lyme immunoglobulin G (IgG)/IgM Western blot, Borrelia DNA PCR, and Cryptococcus antibodies and IgG synthesis rate were normal.

Brain needle biopsy of the right temporal lobe mass revealed “granulomatous cerebritis.” Tertiary center review concluded the biopsy was nonspecific without evidence of granulomatous disease. After administering 1 mg/kg of prednisone daily for 6 weeks, there was no change in the clinical examination and brain MRI. Computed tomography (CT) of chest and abdomen showed no evidence of hilar or mediastinal lymphadenopathy or interstitial lung disease. Despite continuing prednisone, visual acuity of the left eye deteriorated to counting fingers, and right homonymous hemianopia worsened (Fig. 2B). Funduscopic examination showed right bow-tie optic atrophy and left optic disc pallor. Her left-sided hemiparesis continued to worsen. A craniotomy with resection of the right temporal lobe mass was performed 6 months after presentation.

Immunohistochemical examination of the brain specimen showed S-100 negative lipid-laden histiocytes, positive for CD68 and CD163 and arranged in sheets with collagen deposition. There was subtle S-100 immunoreactivity of microglia. The large histiocytic cells were CD1a negative and factor XIIIa positive. Touton giant cells were identified without evidence of emperipolesis (Fig. 3). Microbial DNA PCR was negative. No acid-fast bacilli, mycobacterium tuberculosis, or avium complex DNA was detected. Non-caseating granulomas were not present. After consultation with the University of California (San Francisco) and the National Cancer Institute, the histiocyte population was deemed consistent with ECD.

No extracranial involvement was found with CT of chest and abdomen, transthoracic echocardiogram, long bone x-rays, and whole-body positron emission tomography.

The patient remained off steroids, and surveillance MRIs were performed at 6-month intervals. Subsequent imaging found decreasing size of enhancing intracranial lesions.

**FIG. 1.** Case 1: Brain magnetic resonance imaging. Precontrast T1 coronal (A) and following contrast (B, coronal; C, axial) show multiple enhancing lesions involving the suprasellar region, corpus callosum, and both cerebral hemispheres including the left occipital lobe. D. Axial fluid-attenuated inversion recovery image confirms widespread cerebral involvement.
However, the suprasellar lesion began to increase in size and 18 months after presentation, the patient developed galactorrhea without signs or symptoms of diabetes insipidus. Six months later, visual acuity in the right eye decreased to 20/60. She was given 1,000 mg of intravenous methylprednisolone daily for 3 days with plans to start pegylated interferon-α.

**Case 2**

A 44-year-old man was seen in neuro-ophthalmologic consultation for intermittent attacks of blurred vision in the temporal portion of his right eye lasting 15–20 minutes. He was unaware of whether this was monocular or binocular. He had a history of headache and sinus symptoms 2 years previously and was found to have an ethmoid mucocele and pituitary mass without visual pathway involvement. Brain CT and MRI showed multiple tentorial masses, most likely multiple meningiomas. Ethmoid biopsy at that time revealed NLCH consistent with Rosai–Dorfman disease. His medical history included diabetes mellitus, hypertension and hyperlipidemia.

On neuro-ophthalmologic examination, the patient had visual acuity of 20/20 in both eyes. Color vision, pupillary testing, and extraocular movements were normal. Automated visual fields demonstrated a right homonymous hemianopia (Fig. 4). Funduscopic examination revealed mild bilateral optic disc pallor.

Brain MRI revealed multiple tentorial-based lesions (Fig. 5). Biopsy and partial resection was performed of a lesion at the junction of the tentorium and posterior falx cerebri. Histopathologic examination showed sheets of large foamy histiocytes without anaplastic features. Ki-67 proliferation index was 3.8%. Emperipolesis was
not seen. The foamy histiocytes exhibited positive immunohistochemical staining for CD68, CD163, and CD45 (Fig. 6). The cells were negative for CD1a and S-100. Review of the previous ethmoidal biopsy did not demonstrate emperipolesis or immunoreactivity to S-100 as would be expected in Rosai-Dorfman disease. Rather, the findings were similar to the intracranial mass, most consistent with ECD.

DISCUSSION

Our patients developed homonymous hemianopic visual field defects because of the unusual occurrence of ECD involving the posterior visual pathways. In both patients, the diagnosis was delayed because of the unusual presentation and initial nondiagnostic biopsy results. Our first patient is the third known case of isolated intracranial ECD, as extensive evaluation failed to detect evidence of extracranial disease.

ECD is a rare nonfamilial NLCH proliferative disorder characterized by tissue infiltration. The clinical presentation, course, and severity of disease varies according to the organs involved. Mild nonspecific lower extremity bone pain typically occurs in the fifth to sixth decades (2,3,10–13). Osteosclerosis and pulmonary fibrosis may also be seen. Periorbital xanthelasma and orbital infiltration are seen in approximately 25% (2,11–13). Pathologically, ECD is characterized by the infiltration of various tissues by large foamy lipid-laden histiocytes (Touton giant cells) arranged within sheets of inflammation with collagen deposition (2,10). ECD lesions are immunoreactive to CD68 and CD163, both markers of macrophages. Lipid-laden cells are not immunoreactive to S-100 (Table 1). Haroche et al (14) found 54% of patients with ECD harbored a BRAFV600E mutation, an activating mutation of the proto-oncogene.
BRAF. This mutation is also seen in Langerhans cell histiocytosis but in none of the other histiocytoses.

Central nervous system (CNS) involvement can be seen in up to 50% of affected patients (2,15). The majority of reported CNS lesions are hypothalamic–sellar masses, followed by dural lesions. Rarely intra-axial lesions occur including brainstem, cerebellum, and cerebral hemispheres (10,15–17). CNS lesions on MRI typically are isointense on T1 sequences with prolonged avid postcontrast enhancement (greater than 24 hours) thought to be specific for ECD lesions (15,17,18). Less commonly, spinal meninges and vertebral column lesions may occur.

Visual loss in patients with ECD typically is due to anterior visual pathway compression either in the orbit or sellar region (4–8). It is estimated that 25% of patients have orbital involvement with painless proptosis with or without compressive optic neuropathy (2,19–22). Parasellar lesions also may cause anterior visual pathway compression. Our 2 patients presented with visual field loss because of posterior visual pathway lesions; patient 1 with an intra-axial inferior occipital lobe lesion and patient 2 was found to have an extra-axial tentorial mass with medial left occipital lobe compression.

Intracranial ECD without other organ system involvement at presentation, as occurred in our first patient, has been reported twice previously. Rushing et al (9) evaluated a 26-year-old man who experienced a seizure and was found to have a solitary cortical lesion consistent with ECD. Shortly after diagnosis, he developed wrist pain, found to have an elevated alkaline phosphatase, and bone scan revealed multiple foci of abnormal increased signal in the upper thoracic costovertebral junctions. Conley et al (10) described a 58-year-old woman with progressive cognitive dysfunction, polydipsia, and polyuria. She had normal visual acuity, visual fields, and funduscopic examination, despite a large heterogeneously enhancing suprasellar mass found on MRI. CT of the thorax, abdomen, and pelvis as well as bone and gallium scans did not find additional lesions. Biopsy of the suprasellar mass confirmed ECD.

Corticosteroids have been the traditional first-line treatment in ECD, often with temporary or little effect. Bisphosphonates have been used for bone involvement. Chemotherapeutic or cytotoxic agents have also shown little or temporary effectiveness (2,3,11,12). In 2005, Braiteh et al (23) reported 3 cases of biopsy-proven ECD who responded to interferon-α. The mechanisms of interferon are thought to be due to its effects on dendritic maturation and activation, immune-mediated destruction of histiocytes (through natural killer cells), or direct antiproliferative effects (23). Subsequent reports of interferon-α including high doses in patients unresponsive to standard doses or with severe multisystem involvement have shown encouraging results (24). Before interferon-α therapy, 60% of patients with ECD died within 3 years (11). Survival analysis with the use of interferon-α has decreased mortality to 26% and increased 5-year survival to 68% (3). The optimal duration of treatment with interferon-α is yet to be determined. Haroche et al (25) reported dramatic efficacy treating both

![FIG. 5. Case 2: Postcontrast T1 axial magnetic resonance imaging shows multiple tentorial-based masses.](image)

![FIG. 6. Case 2: Biopsy of dural-based lesion. A. There are sheets of large macrophages with foamy cytoplasm (hematoxylin and eosin, ×400), Macrophages show positive immunohistochemical staining for CD68 (B) and CD163 (C) (×400). Staining for S-100 and CD1a were negative (not shown).](image)
multisystemic and refractory ECD with vemurafenib in patients harboring the BRAFV600E mutation. The BRAFV600E mutation results in activation of the mitogen-activated protein kinase signaling pathway, which ultimately regulates cell proliferation, survival, and differentiation (26). Vemurafenib is a protein kinase inhibitor targeted at the BRAF mutation, thus interfering histiocyte proliferation and survival. If patients are refractory to interferon treatment, vemurafenib should be considered in patients with the BRAFV600E mutation especially if the condition is life threatening.

**ACKNOWLEDGMENTS**

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**REFERENCES**

Third Nerve Palsy as the Initial Manifestation of Giant Cell Arteritis

Matthew J. Thurtell, MBBS, FRACP, Reid A. Longmuir, MD

Objective: Giant cell arteritis (GCA) is rarely reported as a cause of third nerve palsy. We describe the presentation and course of patients with third nerve palsy as the sole initial ocular manifestation of GCA.

Methods: Retrospective chart review of patients with third nerve palsy as the presenting sign of GCA. Symptoms, signs, and inflammatory marker levels at presentation and on follow-up were analyzed. All patients had imaging of the brain and circle of Willis, to exclude a compressive or inflammatory lesion, and had a temporal artery biopsy showing granulomatous arteritis.

Results: Four patients (aged 63–82) were identified and included. One patient had a complete third nerve palsy with pupil involvement, whereas the other 3 had third nerve palsies without pupil involvement. Three patients had ipsilateral periorbital/brow pain, and the other patient had temporal headache. Two patients reported no systemic symptoms of GCA but had elevated inflammatory markers. One patient had normal inflammatory markers but reported systemic symptoms of GCA. All patients had rapid improvement in symptoms and signs after high-dose oral prednisone was started with all showing complete recovery within weeks.

Conclusions: GCA can rarely present with acute painful third nerve palsy, mimicking the presentation of a microvascular cause. The third nerve palsy often improves rapidly after steroid treatment is started. The presence of GCA symptoms or elevated inflammatory markers in a patient older than 50 years with an acute third nerve palsy should prompt initiation of high-dose steroid treatment and temporal artery biopsy.

When third nerve palsy develops acutely with associated pain or headache in a middle-aged or elderly patient with risk factors for vascular disease, it is often secondary to microvascular ischemia (1). However, alternative possibilities, such as third nerve compression by an aneurysmal, neoplastic, or inflammatory lesion must also be considered, especially when there is pupil involvement (2). Imaging of the brain (e.g., magnetic resonance imaging [MRI] with contrast) and circle of Willis (e.g., magnetic resonance angiography [MRA] or computed tomographic angiography [CTA]) generally is obtained to exclude compression or enhancement of the third nerve (2,3). Because other causes of acute painful third nerve palsy are less common (1), other investigations, such as laboratory studies, initially may be deferred. We report 4 patients in whom third nerve palsy was the sole initial ocular manifestation of giant cell arteritis (GCA). We discuss the implications for the work-up of patients with acute third nerve palsy and the prognosis for recovery when GCA causes third nerve palsy.

METHODS

We retrospectively reviewed the charts of 4 patients presenting to our institution with third nerve palsy as the only ocular manifestation of GCA. All patients had been assessed in a standardized fashion, with a structured history and neuro-ophthalmic examination. Symptoms and signs at presentation and on subsequent follow-up were documented. All patients had undergone imaging of the brain and circle of Willis (with either MR or CT), to exclude third nerve compression and enhancement, and all had blood drawn to determine the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. The diagnosis of GCA was confirmed on the basis of a temporal artery biopsy showing granulomatous arteritis.

CASE REPORTS

Patient 1

An 82-year-old woman reported a 1-week history of binocular diagonal diplopia and left-sided ptosis. She had developed
severe left-sided brow and periorbital pain about 12 hours before the ocular symptoms began. Her medical history was remarkable for Type 2 diabetes, hypertension, and dyslipidemia. Review of systems was positive for malaise, weight loss, and proximal myalgias, but she denied scalp tenderness and jaw claudication. Visual acuity was 20/20, right eye and 20/50, left eye. Confrontation visual fields were full in both eyes. There was a left pupil-involving third nerve palsy with marked limitation of adduction, elevation, and depression, complete ptosis, and a dilated unreactive pupil. There was no relative afferent pupillary defect. Slit-lamp examination showed nuclear sclerotic cataract in both eyes but was otherwise unremarkable. Intraocular pressures were 12 mm Hg in both eyes. Funduscopic examination revealed an epiptelinal membrane in the left eye but was otherwise unremarkable. Postcontrast MRI showed chronic small vessel ischemic changes in the white matter, and CT angiogram of the circle of Willis was unremarkable. ESR was 37 mm/hr and CRP was <0.5 mg/dL (normal <0.5 mg/dL). Although her third nerve palsy was thought to be secondary to microvascular ischemia, she was started on 80 mg of oral prednisone daily because of her systemic symptoms. Temporal artery biopsy showed granulomatous inflammation consistent with GCA. Prednisone was continued and her symptoms rapidly improved. When she returned for follow-up 18 days after presentation, her motility, lid, and pupil abnormalities had significantly improved. Her motility, lids, and pupils were normal at subsequent visits.

**Patient 2**

A 70-year-old woman experienced binocular, diagonal diplopia and right-sided ptosis for 2 days and a severe right-sided brow and periorbital ache 3 days before ocular symptoms began. Her medical history was remarkable for morbid obesity. Review of systems was negative; she denied having scalp tenderness, jaw claudication, or constitutional symptoms. Visual acuity was 20/25, right eye and 20/20, left eye. Confrontation visual fields were full bilaterally. There was a partial right-sided third nerve palsy, with moderate adduction, elevation, and depression deficits and partial ptosis. The pupils were equal and briskly reactive to light without a relative afferent pupillary defect. Slit-lamp examination showed nuclear sclerotic cataracts, and intraocular pressures were 22 mm Hg in both eyes. Funduscopic examination was unremarkable in both eyes. Brain MRI showed chronic small vessel ischemic white matter changes and a pituitary macroadenoma without extension into the cavernous sinus. MRA was unremarkable. ESR was 75 mm/hr and CRP was 2.6 mg/dL (normal <0.5 mg/dL). The patient was started on oral prednisone, 80 mg daily, and temporal artery biopsy was consistent with GCA. Prednisone was continued and her symptoms rapidly improved. When she returned for follow-up 21 days after presentation, examination revealed full ductions and that the ptosis on the right had improved. The ptosis had completely resolved 1 month later.

**Patient 3**

A 65-year-old woman described a 2-week history of increasing left-sided ptosis associated with severe left-sided brow and periorbital pain. Her medical history was remarkable for dyslipidemia and tobacco smoking. Her ophthalmic history was remarkable for anisometropic amblyopia of the left eye and longstanding mild left-sided ptosis. Review of systems was unremarkable; she denied scalp tenderness, jaw claudication, and constitutional symptoms. Visual acuity was 20/20, right eye and counting fingers at 1 foot, left eye (unchanged from previous examinations). Confrontation visual fields were full in both eyes. Pupils were equal and reactive to light with 1.2–1.5 log unit relative afferent pupillary defect in the left eye. There was a partial left third nerve palsy, with a severe elevation deficit, moderate adduction and depression deficits, and moderate ptosis. Slit-lamp examination was unremarkable, and intraocular pressures were 16 mm Hg, right eye, and 14 mm Hg, left eye. Funduscopic examination revealed myopic degeneration with a posterior pole staphyloma and tilted optic disc in the left eye but was normal in the right eye. Brain MRI and MRA were within normal limits. ESR was 33 mm/hr and CRP was 2.2 mg/dL (normal <0.5 mg/dL). Because of her symptoms and elevated inflammatory markers, she was started on oral prednisone, 80 mg daily. Temporal artery biopsy showed granulomatous arteritis. Prednisone was continued and her symptoms rapidly resolved. When she returned for follow-up 10 days after presentation, examination revealed full ductions and mild left-sided ptosis that was back to her baseline.

**Patient 4**

A 63-year-old man was evaluated for a 3-week history of binocular diplopia and right-sided ptosis. He had developed a severe right temporal headache 10 days before ocular symptoms began. Both the headache and right ptosis had spontaneously improved before presentation. Medical history was remarkable for hypertension. Review of systems was positive for scalp tenderness; he denied jaw claudication or constitutional symptoms. Visual acuity was 20/20 bilaterally, and confrontation visual fields were intact. There was a partial right third nerve palsy, with moderate adduction and depression deficits, and partial ptosis. The pupils were equal in size and briskly reactive to light without a relative afferent pupillary defect. Slit-lamp examination showed mild cataracts, and intraocular pressures were 18 mm Hg in both eyes. Funduscopic examination was unremarkable. Brain MRI and MRA were within normal limits. ESR was 35 mm/hr and CRP was 2.2 mg/dL (normal <0.5 mg/dL). Because of his symptoms and elevated inflammatory markers, he was started on oral prednisone, 80 mg daily. Temporal artery biopsy showed granulomatous arteritis. The prednisone was continued and his
symptoms rapidly resolved. When he returned for follow-up 10 days after presentation, examination revealed full ductions and complete resolution of ptosis.

**DISCUSSION**

GCA is infrequently reported as a cause of acute painful third nerve palsy (4–12). In a recent prospective, multi-center, observational case series of patients aged 50 years or older presenting with isolated oculomotor cranial nerve palsies, GCA was not found as a cause of any third nerve palsies but was reported as the cause of 3/62 sixth nerve palsies (13). In most reported cases of third nerve palsy due to GCA, the presentation was similar to microvascular ischemia with pain and isocoric pupils. However, cases with pupill involvement have been reported (5,7,12). One of our 4 patients had a complete pupil-involving third nerve palsy, whereas the other 3 had pupils of equal size. Three of our patients reported severe ipsilateral periorbital and brow pain that began either concomitantly with ocular symptoms or up to 3 days prior. The characteristics and timing of the pain were similar to that reported with microvascular third nerve palsy (14). Our findings confirm that the presentation can mimic that of a microvascular third nerve palsy.

The mechanism of third nerve palsy because of GCA is presumably similar to that of microvascular ischemia, in which there is ischemic demyelination of the nerve (15–17). It has been hypothesized that the ischemia arises due to vasculitis affecting branches of the posterior cerebral artery, which supply the third nerve (4). A notable finding in our series was that all patients showed rapid improvement in their symptoms and signs, often over days, after the initiation of steroids. This is significantly quicker than would be expected for a microvascular third nerve palsy, which often takes about 3–4 months to recover (18). This rapid recovery in patients with GCA has been reported previously (6–9). Although some reports suggest that recovery of third nerve palsy due to GCA is incomplete (5), our patients experienced complete resolution of their cranial neuropathy. We considered the possibility of orbital ischemia as a cause of our patients’ ophthalmoplegia (19), but this seemed unlikely given the pattern of the motility deficits and lack of involvement of the superior oblique and lateral rectus muscles.

Three of our 4 patients had elevated inflammatory markers, and 2 had no symptoms to suggest GCA. The 1 patient with normal inflammatory markers did have other symptoms of GCA. Given the potential for severe irreversible vision loss in untreated GCA (20,21), we propose that all patients older than 50 years with an acute onset third nerve palsy be questioned for symptoms of GCA and have laboratory testing to determine the ESR and CRP level. This should be done even if the patient has risk factors for vascular disease.

**REFERENCES**

Do the Clinical Features in Infantile-Onset Saccade Initiation Delay (Congenital Ocular Motor Apraxia) Correlate With Brain Magnetic Resonance Imaging Findings?

Michael S. Salman, BSc, MBBS, MRCP, MSc, PhD, Kristin M. Ikeda, MD

**Background:** Infantile-onset saccade initiation delay (ISID) is a defect in saccade initiation. Other features may include impaired smooth ocular pursuit, developmental delay, hypotonia, and ataxia. Brain magnetic resonance imaging (MRI) can be normal or show supratentorial or infratentorial abnormalities. Our aim was to correlate the clinical features of ISID with brain MRI findings.

**Methods:** Detailed review of the English medical literature between 1952 and 2012 revealed 67 studies with possible ISID. Patients without a brain MRI or with inadequate information, Joubert syndrome, neurodegenerative disorders, and acquired saccade initiation delay were excluded. Ninety-one patients (age range, 3 months to 45 years) met the inclusion criteria and were divided into 3 groups based on their brain MRI findings: normal (n = 55), supratentorial abnormalities (n = 17), and infratentorial abnormalities (n = 19). The patients’ clinical features including the direction of head thrusts, smooth pursuit, optokinetic response (OKR), tone, development, and coordination were compared and analyzed among the MRI groups using $\chi^2$ test.

**Results:** Horizontal head thrusts were significantly more common in patients with infratentorial abnormalities or normal brain MRI, whereas vertical head thrusts were more common among patients with supratentorial abnormalities ($P < 0.0001$). The slow phases of the OKR were significantly more likely to be impaired in patients with supratentorial or infratentorial abnormalities than in those with a normal MRI ($P = 0.011$). Other neuro-ophthalmological, neurological, and developmental features were similar among patients in the 3 neuro-imaging groups.

**Conclusion:** The direction of head thrust and the integrity of the slow phases of the OKR are useful clinical indicators of possible sites of abnormality on brain MRI in patients with ISID.

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Patients with infantile-onset saccade initiation delay (ISID), also known as congenital ocular motor apraxia, are unable to initiate voluntary saccadic eye movements and usually present with head thrusts. Random small-amplitude saccadic eye movements may be present (1,2). The clinical features reported in patients with ISID are variable and may include abnormalities in smooth ocular pursuit and the slow phases of the optokinetic response (OKR) (3). In addition to the neuro-ophthalmological findings, other deficits have been described, including developmental or cognitive delay and speech or language deficits (2–6). Tone is typically decreased, and clumsiness or ataxia is reported frequently (2–4,7).

A normal brain magnetic resonance imaging (MRI) is common in patients with ISID (3,4). In addition, there are a variety of neuroradiological findings associated with ISID, most frequently involving the cerebellum, particularly the inferior vermis (2–4,7,8). Other abnormalities have been reported in the corpus callosum, thalamus, brainstem, and cerebral cortex (2–4,9,10).

We are unaware of any studies attempting to correlate the clinical features with neuroradiological findings among patients with ISID. We reviewed the reported cases of ISID to determine if there are any associations between their clinical features and neuroradiological findings.
METHODS

Search Strategy and Selection Criteria
We performed a detailed search of the English medical literature using PubMed for publications relating to ISID or congenital ocular motor apraxia between 1952, when the condition was first described (11), and December 2012. Each author (M.S.S. and K.M.I.) performed the search independently and compiled the results. Titles and abstracts were screened and, if appropriate, were included for review. References of relevant studies were also searched for additional cases.

Inclusion criteria were studies with patients who had 1) a diagnosis of ISID with a clinical description consistent with the disorder, 2) brain MRI, and 3) adequate description of eye movements, other neuro-ophthalmological findings, and/or developmental outcomes. Exclusion criteria were studies in which patients had acquired saccade initiation delay, Joubert syndrome, ataxia telangiectasia, ataxia with ocular motor apraxia types 1 and 2, Niemann-Pick disease, spinocerebellar degeneration, and other neurodegenerative conditions because the clinical findings and pathology in these disorders are not typical of ISID (12). Patients with both supratentorial and infratentorial abnormalities on MRI were also excluded.

Data Extraction
Once studies were selected for inclusion, the patients were divided into 1 of 3 groups based on their brain MRI findings: normal, supratentorial abnormalities, or infratentorial abnormalities. The patients’ clinical features were extracted, and the frequency of their findings was calculated for each MRI group. The clinical features were divided into 4 categories: neuro-ophthalmological, other ophthalmological, developmental, and motor outcomes. Neuro-ophthalmological findings included the presence and direction of head thrusts, direction of eye movements during head thrusts, use of blinks during or independent of head thrusts to initiate saccades, smooth ocular pursuit, slow and fast phases of both the vestibular ocular reflex and OKR. Other ophthalmological abnormalities included the presence of strabismus and pigmentary retinopathy. Developmental outcomes collected included global, cognitive, and speech or language delays, and reading and behavioral difficulties. Motor outcomes included tone, motor delay, and the presence or absence of ataxia or clumsiness. Demographic information collected included age at diagnosis, gender, and familial cases.

Statistical Analysis
Statistical analyses were performed using a Statistical Package for Social Sciences (version 22.0; SPSS, Inc, Chicago, IL). The data were compared and analyzed among the 3 MRI groups using Pearson χ² test or Fisher exact test. Statistical significance was set at P ≤ 0.05. Variables that reached statistical significance were further analyzed for specific differences among the 3 groups (post hoc analyses). We assumed that the nonreported variables in the studies analyzed were randomly distributed among the 3 MRI groups.

RESULTS
Sixty-seven studies were identified as having patients with possible ISID through a PubMed search. There were 91 patients from 26 studies (1,2,4–10,13–29), who met the inclusion criteria. The age range at diagnosis was 3 months to 45 years. The 91 patients were subsequently divided into 3 groups according to their brain MRI findings: normal (n = 55), supratentorial abnormalities (n = 17), and infratentorial abnormalities (n = 19). There were 4 familial cases, all of whom were in the normal MRI group.

Supratentorial abnormalities (frequency) included abnormalities in the thalamus (7), basal ganglia (2), and cerebral white matter (2), heterotopia (2), periventricular encephalomalacia (2), corpus callosum hypoplasia (1), bilateral occipital infarcts (1), leukodystrophy (1), encephalomalacia (1), temporal lobe asymmetry (1), left hemispheric subependymal hemorrhage (1), and multiple infarcts (1) (4,6,9,10,14–16,18,21,27). Infratentorial abnormalities included hypoplastic or absent cerebellar vermis (10), other cerebellar abnormalities (5), midbrain abnormalities (2), pontine abnormalities (2), and thin intercollicular commissure (1) (2,4,7–9,13,15,17,18,24,28,29). Some patients had more than 1 abnormal MRI finding within their respective MRI group.

The neuro-ophthalmological features did not differ significantly among the 3 MRI groups with the exception of the direction of head thrusts and the slow phases of the OKR (see Table 1). Post hoc analyses revealed that the direction of head thrusts was significantly different in patients with a normal MRI in comparison with those with supratentorial abnormalities (P = 0.001) but similar to those with infratentorial abnormalities (P = 0.417). Horizontal head thrusts were frequently reported in patients with normal MRI or patients with infratentorial abnormalities, whereas vertical head thrusts occurred more commonly in patients with supratentorial abnormalities. Within the supratentorial MRI group, 4 (80%) of 5 patients with vertical head thrusts had lesions in their thalami, while 3 (37.5%) of 8 patients with horizontal head thrusts had lesions in their thalami; however, the difference was not statistically significant (P = 0.266).

Post hoc analyses of the OKR slow phases revealed that patients in the normal MRI group had significantly different OKR slow phases than those in the groups with supratentorial (P = 0.025) and infratentorial abnormalities (P = 0.012). The latter 2 groups showed similar OKR slow phases. Patients with normal MRIs frequently had normal slow phases of the OKR, whereas patients with abnormal
### TABLE 1. Clinical features in reported patients with infantile-onset saccade initiation delay in relation to their brain MRI findings

<table>
<thead>
<tr>
<th>Feature</th>
<th>Normal MRI (n = 55)</th>
<th>Supratentorial MRI Abnormalities (n = 17)</th>
<th>Infratentorial MRI Abnormalities (n = 19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>6</td>
<td>6</td>
<td>9</td>
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</tr>
<tr>
<td>Women</td>
<td>9</td>
<td>6</td>
<td>2</td>
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</tr>
<tr>
<td><strong>Neuro-ophthalmological findings</strong></td>
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<td></td>
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<tr>
<td>Head thrusts presence</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50</td>
<td>13</td>
<td>15</td>
<td>0.532</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
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<td>2</td>
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</tr>
<tr>
<td>Head thrusts direction</td>
<td></td>
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<tr>
<td>Horizontal</td>
<td>48</td>
<td>8</td>
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<td>&lt;0.0001</td>
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<tr>
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<td>1</td>
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<td>1</td>
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<tr>
<td><strong>Direction of eye movements during head thrust</strong></td>
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<td>Same</td>
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<td>Smooth ocular pursuit</td>
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<tr>
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<td>Impaired OKR fast phases</td>
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MRI (i.e., supratentorial or infratentorial abnormalities) more commonly had impaired slow phases of the OKR.

The following variables could not be analyzed among the MRI groups due to the absence of clearly dichotomized data in the articles analyzed (i.e., whether a variable was present/absent or normal/impaired): the presence of blinks without head thrusts to initiate saccades, blinks during head thrusts, spontaneous saccades, oculocephalic maneuver response, and fast phases of both the vestibulo-ocular reflex and OKR. Other neuro-ophthalmological, motor, and developmental outcomes were similar among the 3 MRI groups (Table 1).

**DISCUSSION**

ISID is associated with a variable clinical phenotype and diverse neuroimaging findings (3). The etiology of ISID is unknown (12). Whether the clinical features, including head thrusts and slow phases of the OKR, and neuroradiological abnormalities are correlated has not been explored previously. The results of this study show that there remains significant clinical and neuroradiological heterogeneity among patients with ISID; however, there are 2 clinical features, head thrusts and slow phases of the OKR, that are associated with certain brain MRI findings.

Horizontal head thrusts were one of the cardinal features of ISID when it was first described by Cogan in 1952 (11). Although not present in all patients, horizontal head thrusts remain a hallmark feature and correlate with brain MRI findings. In contrast, vertical head thrusts are a rare feature of ISID (10,14,21). The overwhelming majority of patients with ISID who have normal neuroimaging or infratentorial abnormalities display horizontal head thrusts, while vertical head thrusts are more commonly reported in patients with supratentorial abnormalities. The reason for this is not clear. The neural substrate for eye and head saccades is thought to be similar (30). Multiple brain structures located both supratentorially and infratentorially are involved in processing head movements and both horizontal and vertical saccades (30). We speculate that neural projections between supratentorial structures and rostral brainstem structures specifically involved in processing vertical saccades were affected by lesions in the patients with vertical head thrusts and supratentorial abnormalities.

Abnormalities in the slow phases of the OKR, as well as smooth ocular pursuit, have been increasingly recognized as part of the spectrum of ISID (3,15). Our results indicate that patients with MRI abnormalities, either supratentorially or infratentorially, are more likely to have impaired slow phases of the OKR. Our findings are consistent with the neuroanatomical pathways and structures involved in processing the OKR, which include cerebral, brainstem, and cerebellar projections (31,32). However, only 3 studies of patients with ISID have used a large-field visual stimulus to examine the OKR (1,7,15). The rest of the studies either used the optokinetic drum (2,13,20,28) or did not report how the OKR was examined. Examining the OKR using the rotating handheld optokinetic drum may in fact be stimulating the smooth ocular pursuit system because global large-field visual motion is needed to elicit the OKR (30,32). Therefore, the data on OKR slow phases extracted from the studies analyzed in our study may, in fact, reflect smooth ocular pursuit. However, such proposition contradicts our finding of similar smooth ocular pursuit impairment among patients in the 3 MRI groups. Such discrepancy may be explained by the relatively small power of our study to detect differences in smooth ocular pursuit response among patients in the 3 MRI groups, nonrandom biases in reporting neuro-ophthalmological findings among patients in the publications included, and the different methods used to examine the OKR.

The large variety of clinical features reported in ISID that were not significantly different among the 3 MRI groups likely reflects the widespread central nervous system dysfunction in patients with ISID.

Interestingly, although ataxia or clumsiness is frequently reported in ISID, there was no significant association of patients with ataxia and infratentorial abnormalities. Although patients with cerebellar abnormalities were not analyzed separately due to small numbers, the majority of the patients with infratentorial abnormalities had cerebellar abnormalities (15/19 patients). This finding also suggests a more widespread dysfunction in patients with ISID than is appreciable on brain MRI. This dysfunction may reflect the involvement of a variety of cerebellar inflow and outflow tracts outside the cerebellum that play an important role in the coordination of movement.
One of the limitations of this investigation is that data were gathered from published cases, which did not always have all the information we included in the analysis. This may have resulted in an underrepresentation of the frequency of abnormalities associated with ISID and potentially biased the results, especially if the unreported data were not randomly distributed among the 3 MRI groups. In addition, the number of published cases of ISID with MRI findings is relatively small, which may have decreased the statistical power needed to find clinical-neuroradiological associations. Selecting patients with a brain MRI was necessary because brain computed tomography has a lower spatial resolution in general, and it is not ideal for imaging infratentorial structures.

REFERENCES
Idiopathic Opticochiasmatic Arachnoiditis

Simmons Lessell, MD, Andrzej E. Grzybowski, MD

Abstract: A critical review of the literature indicates that idiopathic opticochiasmatic arachnoiditis, once considered an important consideration in patients with otherwise unexplained optic atrophy, is not a valid disease entity.

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Why do diseases disappear? Prevention can be credited for the disappearance in the developed world of such once prevalent disorders as poliomyelitis, rheumatic heart disease, and smallpox, and treatment accounts for the markedly reduced incidence of many other diseases. However, the disappearance of some disorders remains enigmatic; one of the particular interests to neuro-ophthalmologists is the idiopathic opticochiasmatic arachnoiditis (IOCA). Although specific causes of opticochiasmatic arachnoiditis are recognized (see below), the idiopathic form seems to have vanished. Until the middle of the 20th century, it was a prominent consideration in the differential diagnosis of neurogenic visual impairment, but IOCA rarely is mentioned in current neuro-ophthalmic texts and is only referred to obliquely in the 6th edition of Walsh and Hoyt’s encyclopedic Clinical Neuro-Ophthalmology (1). The exact incidence of this disorder (or more exactly the frequency with which it was diagnosed) at various times will never be known. However, a review of the medical literature provides some inferences. That IOCA was the subject of a plethora of publications between 1929 and 1980 but few, if any subsequently, suggests that in recent decades IOCA is rarely, if ever, diagnosed. How can this remarkable change be explained?

The anatomy of the structures implicated in IOCA, the optic chiasm and prechiasmal segments of the optic nerves, are immersed in cerebrospinal fluid. The arachnoid under the chiasm consists of 2 thin concentric layers. In some areas, trabeculae connect the inner layer to the pia that closely invests the chiasm and nerves (2). Although it is generally assumed that the suprasellar cistern communicates freely with the rest of the subarachnoid space, this is not universally true. In many healthy individuals, the subarachnoid space is septated not only over the intraorbital portion of the optic nerve but also under the chiasm (3–5). Cysts may develop if cerebrospinal fluid becomes immured in the chiasmatic cistern, and these may become symptomatic. Contamination of the cerebrospinal fluid in the perichiasmatic subarachnoid space by blood, chemicals, foreign materials, and infectious microorganisms can cause inflammation and fibrosis on the surface of the optic chiasm. Similar changes can occur after closed head injuries and in proximity to brain tumors (6,7). The existence of these non-idiopathic instances of opticochiasmatic arachnoiditis is well accepted.

Schlesinger (8) in 1898 was the first to show that localized arachnoiditis could cause focal neurological dysfunction. In the 1920s, clinicians proposed that idiopathic arachnoiditis covering the optic chiasm and the intracranial segment of the optic nerves could cause visual loss. At that time, although pneumoencephalography had very recently been invented, it was not widely used. Plain radiographs were the most commonly used means of imaging the head. However, plain skull radiographs were of very limited diagnostic value because one can infer the presence of brain disorders only if there is intracranial calcification or bony abnormalities. In light of this limitation, it was considered acceptable in the 1920s to explore the chiasm and intracranial segments of the optic nerves when a patient with normal plain skull radiographs had otherwise unexplained progressive optic atrophy. This practice continued well into the 1930s and 1940s, even after large centers had adopted more informative neuroimaging tests such as arteriography,
He then cites "Cogan (6) wrote that the signiﬁcant report omitted information fl..."
to be a process concomitant with the process going on in the visual pathways themselves. I would suggest that those cases in which surgery uncovers only minimal adhesions and collections of fluid about the chiasm and in which prompt visual improvement does not occur after surgery be referred to as opticochiasmatic neuritis [italics ours] with or without associated arachnoiditis.”

In 1969, Walsh and Hoyt (18), obviously skeptical, wrote “That such cases are observed relatively frequently in other parts of the world, and remain rare in Baltimore and San Francisco does seem remarkable, but possibly there are reasons for this that we do not know.” “As an entity its occurrence has been very infrequent in our experience and the vision of 1 or both eyes may be affected. The fact that in some cases breaking down a few filmy adhesions seems to be responsible for the recovery of vision and fields remains mysterious.” “The treatment is surgical and merely consists of freeing adhesions and liberating excess amounts of fluid. The benefits which have been described are difficult to understand since one would anticipate reformation of the adhesions in a majority of cases.” In 1974, Lowes et al (19) commented that “...... it is still not fully understood how thickening of the arachnoid in the chiasmal region can produce defects in the visual field.”

What then could account for the disappearance of IOCA? As mentioned above, it is often difficult to distinguish normal from diseased arachnoid during surgical exploration. This could lead to misinterpretation of the findings at craniotomy. The most likely explanation is that it really was not a distinct and separate disease entity. In some cases, the lesion was probably, in retrospect, an arachnoid cyst. Cushing pointed out that in one of his patients presumed to have IOCA, a third ventricular tumor was subsequently discovered. There are also cases in which the patient was later recognized to have Leber hereditary optic neuropathy or multiple sclerosis. Only a few of the reports of IOCA provide the reader with adequate details of the history, the family history, and the course subsequent to the exploration. No report providing the long-term follow-up of a series of IOCA cases has, to the best of our knowledge, been published. Information on the later course of IOCA patients could help to recognize that the patients had such diseases as multiple sclerosis, Leber hereditary optic neuropathy, or a brain tumor; all disorders in which arachnodial abnormalities have been encountered.

The modern era of neuroradiology might be dated from the introduction of computed tomography (CT) in the early 1970s. The decline of IOCA cases coincides with the advent of this technology, a decline that has continued after the introduction of magnetic resonance imaging (MRI). MRI is capable of detecting the type of abnormalities said to be present in the perichiasmatic region in IOCA, but such abnormalities are not encountered even in busy neuroradiology departments. It is notable that IOCA is not included in current neuroradiology textbooks. CT and MRI can also demonstrate the presence of the vision-limiting lesions within the nerves that were the true source of the impaired visual function in IOCA but which went unrecognized until these Technologies became available. Glaser (20) commenting on IOCA wrote that “this vague diagnostic category is shrinking as a result of advances in neuroimaging and cerebrospinal fluid analysis.”

IOCA is not the only neuro-ophthalmic disorder once considered an established clinical entity but that which is (or should be) no longer recognized as such. Tobacco–alcohol optic neuropathy was, as the name implies, blamed on the combined toxic effects of tobacco and alcohol (21–23). Now, it is recognized that tobacco and alcohol do not act synergistically as optic nerve toxins. There is ample evidence that the patients have a nutritional disorder, and in some cases pipe or cigar smoking is an independent cause.

We are persuaded that, based on the available evidence, IOCA did not and does not exist as a separate and distinct clinical entity. In some patients, the appearance of the arachnoid, while within the range of normal variation, was misinterpreted as abnormal. In others, there were indeed abnormalities of the arachnoid but they were associated with, or consequent to, an unrecognized primary disorder of the chiasm and optic nerves. Idiopathic chiasmatic arachnoiditis need not be included in the differential diagnosis of disorders of the anterior visual pathway. The disease disappeared because it never existed.

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Visual Recovery After Surgical Decompression of an Occipital Intraventricular Cyst

Aditya Vedantam, MD, Daniel Yoshor, MD, Rod Foroozan, MD

Abstract: A 62-year-old woman presented with a chronic left homonymous visual field defect because of a right occipital cyst. Serial visual field examination documented stable visual fields for 12 months, after which there was worsening of visual fields associated with enlargement of the cyst. Surgical decompression of the occipital cyst resulted in marked improvement of the visual field defect over 9 months. This case demonstrates that surgical decompression of cystic lesions adjacent to posterior visual pathways can result in recovery of chronic visual field loss.

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A 62-year-old woman was found to have a nonenhancing right occipital cyst after undergoing computed

FIG. 1. Automated perimetry and corresponding axial fluid attenuated inversion recovery images of the brain. A. At initial presentation, an incomplete left homonymous hemianopia is present with a right occipital intraventricular cyst. B. Fourteen months after the first visit, perimetry shows a complete left homonymous hemianopia associated with enlargement of the cyst. Surgical decompression was performed, and postoperative axial computed tomography reveals reduction in size of the cyst. C. At 9 months after surgery, there is near complete resolution of visual field defects. MRI performed 24 months after surgery shows continued resolution of the cyst.
tomography (CT) for headaches and dizziness. Her neurologist found that she had a visual field defect on confrontation testing and referred for neuro-ophthalmic evaluation. She denied any visual symptoms and was not aware of any previous vision problems. She had previously undergone surgery for pterygium on the right eye and blepharoplasty of the upper lids.

Visual acuity was 20/20 in both eyes. Automated perimetry showed an incomplete left homonymous hemianopia (Fig. 1A). Pupils, extraocular movements, intraocular pressures and funduscopic examination were normal. No immediate intervention was advised for her field defect. She subsequently underwent magnetic resonance imaging (MRI), and 3 months later, her visual field defects were stable. She was followed at 3 month intervals, and at 14 months after initial presentation, the patient reported worsening visual fields. Testing now revealed a complete left homonymous hemianopia (Fig. 1B). We advised her to see a neurosurgeon for possible surgical treatment of her intracranial cyst.

The patient underwent endoscopic fenestration of her intracranial cyst, resulting in reduction in size. She reported subjective improvement in her visual fields and automated perimetry 3 months after surgery demonstrated marked improvement (Fig. 1C). She has remained stable over 2 years of follow-up.

Reversibility of visual field defects following surgical decompression of parieto-occipital lesions is variable. Approximately one-third of patients with homonymous defects due to occipital lobe lesions show some improvement after surgical intervention (1,2). In 2 previous reports, substantial visual field recovery was documented after surgical decompression of occipital arachnoid cysts (3,4). Similar to these lesions, intraventricular cysts are well-circumscribed and do not infiltrate the adjacent brain parenchyma. Such findings appear to predict good visual outcome after surgical decompression. Therefore, surgical intervention may be considered initially in these patients and not just with worsening of the visual fields.

The physiological basis of visual improvement in our patient is unclear. Possible mechanisms include postoperative restitution of synaptic transmission and increased synaptic efficiency in the posterior visual pathways (5). Studies of patients with spontaneous recovery of visual fields indicate a contribution of neuronal plasticity, which is greater in partially affected areas bordering the field defect. On visual field testing, patients may show inconsistent and variable responses to stimuli in these areas. The moderate success of visual rehabilitation in these patients suggests that partially damaged neurons can adapt even after a considerable time interval since initial injury (5).

Intraventricular cysts include neuroenteric cysts, which are rare, slow growing congenital lesions lined by secretory epithelium that bears a resemblance to gastrointestinal and respiratory epithelium. The radiologic appearance of neuroenteric cysts can closely resemble arachnoid cysts. Although epidermoid and dermoid cysts can show a similar appearance, these lesions usually are found in more lateral locations and show restricted diffusion on diffusion-weighted imaging. Definitive diagnosis of these intraventricular cystic lesions requires pathologic examination. Although rare in the supratentorial compartment, intraventricular cysts can exert a mass effect on adjacent neural structures (6). Affected patients often exhibit symptoms of raised intracranial pressure and cortical dysfunction attributable to adjacent parenchymal compression.

Treatment is primarily surgical, although recurrence is reported even after total resection (7). In our patient, cyst expansion was associated with visual field deterioration. The surgical approach was planned using neuronavigation, and the cyst was entered on its postero-lateral aspect, thereby avoiding the optic radiations and visual cortex.

REFERENCES

Optochiasmatic and Peripheral Neuropathy Due to Ethambutol Overtreatment

Howard L. Geyer, MD, PhD, Steven Herskovitz, MD, Thomas L. Slamovits, MD, Herbert H. Schaumburg, MD

Abstract: Ethambutol is known to cause optic neuropathy and, more rarely, axonal polyneuropathy. We characterize the clinical, neurophysiological, and neuroimaging findings in a 72-year-old man who developed visual loss and paresthesias after 11 weeks of exposure to a supratherapeutic dose of ethambutol. This case demonstrates the selective vulnerability of the anterior visual pathways and peripheral nerves to ethambutol toxicity.

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A 72-year-old smoker developed cough, hemoptysis, night sweats, weight loss, and fever. Culture of bronchoscopic specimens revealed an atypical mycobacterium. Treatment was initiated with ethambutol, mistakenly prescribed as 1,600 mg for 4 times a day (usual maximum dose for this 70-kg

FIG. 1. Temporal profile of visual recovery from ethambutol toxicity (A-D), and magnetic resonance imaging findings. Axial fluid-attenuated inversion recovery image and coronal T2 images demonstrate increased signal (arrows) in the optic chiasm and optic tracts (B) with subsequent resolution (C).

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The authors report no conflicts of interest.

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man should have been 1,200 mg daily), along with azithromycin and moxifloxacin. At that time, the patient had no visual symptoms, and baseline ophthalmologic examination, including perimetry, was normal. Renal function also was normal.

Eleven weeks later, the patient developed blurry vision and visual “rippling” in the superotemporal visual field of the left eye. Ethambutol overdose was recognized, and ethambutol, moxifloxacin, and azithromycin were discontinued. The patient developed tingling in his feet, a squeezing sensation in his feet and calves, and gait unsteadiness.

Visual acuity was counting fingers in each eye, without a relative afferent pupillary defect, and he was unable to recognize any of the Ishihara color plates. Automated perimetry showed bitemporal visual field loss with central depression bilaterally (Fig. 1A). The remainder of the examination, including ophthalmoscopy, was normal. Neurologic testing demonstrated diminished vibration sensation in both feet, with intact light touch and proprioception, negative Romberg sign, normal gait and station, and silent plantar responses. Deep tendon reflexes (DTRs) were 1+ in the upper extremities, trace at the knees, and absent at the ankles. Nerve conduction studies (NCS) were normal. Visual evoked potentials showed markedly prolonged latency bilaterally. Magnetic resonance imaging (MRI) showed no abnormalities of the anterior visual pathways.

Eight months after stopping ethambutol, vision was 2/200 in each eye. Visual fields were somewhat improved (Fig. 1B), and MRI showed increased signal in the optic chiasm, extending into the optic tracts (Fig. 1B). The patient had diffuse hyporeflexia, with a bilateral Hoffman sign and nonsustained clonus at the ankles, although plantar responses were flexor. NCS showed predominantly axonal sensory neuropathy. Vibration quantitative sensory testing (VQST) revealed markedly elevated threshold of 7.6 vibration units (normal <3.4 vibration units).

Six months later, visual acuity had improved to 20/60 in the right eye and 20/160 in the left eye. Automated visual field testing showed continued improvement (Fig. 1C), and MRI disclosed near-complete resolution of the hyperintensity in the anterior visual pathways (Fig. 1C). Sensory examination was unchanged, but reflexes were normal. NCS showed slight improvement, and VQST threshold had improved to 3.76 vibration units.

Twenty-six months after discontinuing ethambutol, visual acuity was 20/20 bilaterally, and there was bilateral optic disc pallor. Visual fields were near normal (Fig. 1D), and MRI was unremarkable. Acral numbness and paresthesias persisted, and NCS findings were unchanged.

Our patient received ethambutol at 5 times the usual maximum dose for 11 weeks, an overdose of greater magnitude than has been reported previously, and consequently he was affected earlier and more severely than patients in previous reports. He noted visual loss 11 weeks after beginning treatment, whereas ethambutol in standard doses produces visual loss after a mean duration of 7.31 months of treatment (1).

As is common in neurotoxicology, our patient’s findings were symmetric, and symptoms continued to worsen transiently following removal of the offending substance (“coasting”), after which symptoms and neuroimaging abnormalities gradually, but incompletely, improved. The initial examination of our patient did not show hypertreflexia or clonus, whereas subsequent examinations did. Similarly, the initial MRI was unremarkable but ultimately showed hyperintense signal abnormalities in the optic chiasm and proximal optic tracts. MRI findings within the optic chiasm have only recently been reported (2), and our report supports this observation.

In addition to anterior visual pathway involvement, our patient manifested evidence of corticospinal dysfunction including hyperactive DTRs, ankle clonus, and Hoffman sign, which subsequently resolved. Such findings are consistent with pyramidal tract demyelination, which has been observed in monkeys given high doses of ethambutol (3). The predominantly sensory axonopathy seen in our patient is typical of a polyneuropathy induced by ethambutol (4).

REFERENCES
Issues in the Diagnosis and Management of the Papilledema Shunt

Neeraj Chaudhary, MD, Julius Griauzde, MD, Joseph J. Gemmete, MD, Aditya S. Pandey, MD, Jonathan D. Trobe, MD

Background: Dural arteriovenous fistulas (DAVFs) that shunt blood into the transverse or superior sagittal venous sinuses cause papilledema by raising intracranial pressure ("the papilledema shunt"). Such fistulas pose unique diagnostic and therapeutic challenges.

Methods: Case report and literature review.

Results: In a patient presenting with papilledema, non-invasive brain vascular imaging disclosed subtle signs of a DAVF. Digital angiography delineated the DAVF and revealed cortical venous reflux. After three transarterial embolizations with ethylene vinyl alcohol, the DAVF was closed and papilledema resolved.

Conclusions: The imaging features of a DAVF that cause papilledema may be subtle on non-invasive vascular imaging. If overlooked, and lumbar puncture is performed, there is a substantial risk of brain herniation. Cortical venous reflux, which may be relatively common in these DAVFs, impels the need for endovascular closure. The transvenous route, often employed for closing cavernous sinus DAVFs, should be avoided because of the dangers of dural venous sinus thrombosis.

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Dural arteriovenous fistulas (DAVFs, arteriovenous shunts), comprised typically meningeal arteries abnormally communicating with a dural venous sinus or other cerebral veins, constitute about 10%–15% of intracranial vascular malformations (1–6). Three DAVFs have predominantly ophthalmic manifestations:

1. The "red eye" shunt, a fistula located in or near the cavernous sinus that drains primarily into the orbit. It can cause reduced visual acuity owing to retinal venous stasis or steal from optic nerve circulation, elevated intraocular pressure, periorcular pain, ptosis, and ophthalmoplegia largely due to orbital and ocular venous congestion.

2. The "white eye" shunt, a fistula also located in or near the cavernous sinus but draining posteriorly into the petrosal and pterygoid venous sinuses. Accordingly, the presentation is usually without any features of orbital venous congestion but with reduced visual acuity owing largely to vascular steal from the intracranial optic nerve and ophthalmoplegia owing to vascular steal from vasa nervorum of ocular motor cranial nerves (7).

3. The "papilledema" shunt, a fistula located in the sagittal, transverse, or sigmoid sinus. "Arterialization" of these major draining sinuses raises venous and intracranial pressure (9).

The cavernous red eye and white eye shunts are well described. The transverse and superior sagittal sinus shunts have long been recognized (9), but the fact that they can give rise to vision-threatening papilledema has largely escaped notice. An authoritative review of ophthalmic manifestations of intracranial vascular abnormalities did not mention them (10). These shunts present unique diagnostic and management challenges. To highlight those challenges, we present a typical case and describe its management.

CASE REPORT

A 35-year-old woman reported episodic bright spots in the field of vision of her right eye. They lasted less than a minute and were usually precipitated by assuming the upright posture. She had had no other medical problems but acknowledged a 20-lb weight gain over the preceding 6 months. She was taking no medications and had no pertinent family history.

The patient had a body mass index of 29 kg/m², normal vital signs, and the remainder of her physical examination...
was unremarkable. Visual acuity was 20/20 in each eye. The pupils constricted normally to light without relative afferent defect. The external ocular examination was normal, including eye movements and alignment. Biomicroscopic examination was normal, and intraocular pressures were 14 mm Hg in each eye. Automated visual field testing showed mean deviations of −2.4 dB in the right eye and −1.7 dB in the left eye without clusters of high threshold points. Ophthalmoscopy disclosed bilateral optic disc edema (Fig. 1).

Although a diagnosis of idiopathic intracranial hypertension (IIH) was believed likely, brain magnetic resonance imaging (MRI) unexpectedly showed subtle findings of a vascular anomaly centered on the right transverse–sigmoid sinus junction (Fig. 2A), later confirmed on computed tomographic angiography (Fig. 2B).

Catheter angiography delineated a DAVF centered on the right transverse–sigmoid sinus junction with multiple arterial feeders from branches of the right external carotid and right vertebral arteries (Fig. 3A). Cortical venous reflux (CVR) was present (Fig. 3B).

The patient underwent staged transarterial embolization of the DAVF with ethylene vinyl alcohol (EVOH or Onyx; Covidien, Mansfield, MA) until all CVR was obliterated on 6-month follow-up angiography (Fig. 4). Thirteen months after final embolization, the patient’s papilledema had resolved, and she remained free of visual symptoms. There were no procedure-related complications.

**DISCUSSION**

In the case presented here, a DAVF shunted blood into the right transverse–sigmoid sinus junction in a patient whose only clinical manifestations of headache and papilledema were attributable to increased intracranial pressure. In a previous report of 2 such DAVFs, abnormally high pressure gradients were recorded manometrically across the dural venous sinuses before embolization and normalized after obliterative embolization and disappearance of papilledema (11). Because high intracranial pressure is not uniformly reported in all such DAVFs, these authors and others (9) speculated that the presence of stenosis, thrombosis, or atresia in sinuses distal to the DAVF might be contributory factors.

The DAVF that gives rise to papilledema (herein called the papilledema shunt) is actually the most common type of intracranial dural fistula (8). Its pathogenesis remains uncertain, although head trauma or surgery, the postpartum state, and previously documented dural venous sinus thrombosis are known triggers. It is somewhat more common in women, and relatively uncommon in children. Adults of any age are at risk (8).

Our case highlights the diagnostic and management challenges of the papilledema shunt. The presumptive diagnosis before imaging was IIH. Because clinicians were not expecting a DAVF, they ordered the MRI and magnetic resonance angiography studies, standard in the evaluation of
suspected IIH. Those studies showed only a subtle vascular abnormality that was fortunately identified by an astute radiologist and confirmed with computed tomographic venography. Had the fistula not been detected, the patient might have undergone lumbar puncture as part of a standard evaluation of suspected IIH, a procedure that this setting carries the risk of life-threatening cerebellar tonsillar herniation (8,12).

As our case illustrates, initial imaging of patients with papilledema must rule out not only dural sinus thrombosis, but also DAVF. Noninvasive imaging may detect only subtle signs of the shunt, requiring special attention on the part of the radiologist. There are no clinical features that would aid the examiner in distinguishing increased intracranial pressure caused by DAVF from that caused by IIH except that patients with DAVF would less likely be young, female, and overweight.

Noninvasive vascular imaging will not adequately delineate the architecture of a DAVF. Digital subtraction angiography is necessary to show the features that allow definitive diagnosis, treatment planning, and risk stratification (13). Risk stratification is partially based on whether CVR is present.

There are critical differences in the features of cavernous and noncavernous DAVFs. The normal angioarchitecture of the cavernous sinus typically includes multiple outlets, which may explain the relatively low incidence of CVR in cavernous DAVFs as compared with noncavernous DAVFs (14). Satomi et al (15) classified cavernous DAVFs based on change in drainage pattern following thrombosis of the venous outlets. In a retrospective study of 65 cavernous DAVFs, these investigations showed that drainage initially was through the petrosal sinuses or the superior and inferior ophthalmic veins in 61 patients (Stages 1 and 2). As these outlets thrombosed, CVR became the drainage pattern (Stage 3), seen in only 4 patients. Cavernous DAVFs tend to close spontaneously more often than noncavernous DAVFs (16–18).

FIG. 3. A. Right vertebral artery angiogram in anteroposterior projection performed before embolization demonstrates enlarged posterior meningeal artery (arrow) that shunts blood into right transverse–sigmoid sinus junction. B. Right external carotid artery angiogram in lateral projection demonstrates shunting into sigmoid and transverse sinuses (arrow). Reflux into cortical venous system is present (arrowhead).

FIG. 4. A. After Stage 1 embolization, right external carotid artery (ECA) angiogram demonstrates persistent arterial feeder (white arrow), faintly seen ethylene vinyl alcohol (Onyx) cast (arrowhead), and persistent cortical venous reflux (black arrow), the reason for performing additional embolization. B. After Stage 2 embolization, right ECA angiogram demonstrates persistent cortical venous reflux (arrows), the reason for needing yet another embolization. C. After Stage 3 embolization, right ECA angiogram shows no residual arterial feeders or cortical venous reflux.
Noncavernous DAVFs are associated with significantly greater morbidity than cavernous DAVFs, perhaps because of the higher likelihood of having CVR (13,19,20). Untreated patients with DAVF associated with CVR are estimated to have a yearly incidence of 7% for hemorrhagic neurological deficit, 9%–13% for intracranial hemorrhage, and a 10% mortality rate (13,21,22). A recent report documenting the natural history of 75 DAVFs with a 90-year follow-up (pooled data of total patient cohort) showed a doubling of the risk of hemorrhage if venous ectasia were added to CVR (14% with CVR alone and 27% with CVR and venous ectasia) (21).

The strategy used in endovascular embolization of cavernous sinus and noncavernous sinus DAVFs differs. Fistulas of the cavernous sinus are typically fed by multiple arteries, including branches of the meningohypophyseal and ascending pharyngeal arteries. Embolization of these branches carries a substantial risk of cranial nerve palsies due to inadvertent occlusion of vasa nervorum (19,23,24). Because of their strong dural lining, DAVFs of the cavernous sinus can be approached transvenously, the preferred route. Transvenous embolization is performed effectively in DAVFs with coils (25,26). Liquid embolic agents such as EVOH are avoided because the inflammatory reaction generated could result in cranial nerve damage.

By contrast, the dural lining of the sagittal and transverse sinuses, the site of the papilledema shunt, is fragile enough to predispose to venous thrombosis if the shunting vein is approached endovascularly. The middle meningeal artery, the typical feeder of DAVFs located in the region of the transverse and sigmoid sinuses, can be readily cannulated with relatively low risk of cranial nerve damage and is the preferred route for treatment (23,27,28). Occluding the multiple feeding arterial branches often takes several hours. The duration of each embolization session must be limited to avoid overexposure to x-ray and contrast agents. Staged embolization is therefore employed when there are multiple feeders, as illustrated by our case. Treatment is considered successful when angiography shows complete elimination of all CVR. There are some reported small series of successful transvenous embolization (26,29), but we believe that the venous approach is hazardous because of the possibility of vessel rupture and extensive uncontrolled venous thrombosis. Moreover, arterial embolization helps to maintain normal venous drainage through cortical veins into the large venous sinuses after shunt occlusion.

Arterial embolization of noncavernous DAVFs with EVOH produces generally favorable outcomes. One series reported a 92% occlusion rate in patients not previously embolized (23). Carlson et al (28) reported continued occlusion of EVOH-treated DAVFs at angiography performed as far out as 4 months. There are also several short-term outcome reports of successful embolization of noncavernous DAVFs with EVOH (23,27–30). A total of 54 patients have been reported with angiographic obliteration.

Arterial embolization of DAVFs is not without risks. Significant complications include postembolization hemorrhage, mild hemiparesis, and cranial nerve palsies in 3%–7.5% of cases (19,23,24). In view of these risks, treatment should be undertaken only if the clinical manifestations of the DAVF are unacceptable, if there is CVR, and if the treating physicians have experience in dealing with such challenging cases.

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Optic Neuropathy Caused by *Propionibacterium acnes* Pachymeningitis

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**Abstract:** We describe a patient with vision loss from an optic neuropathy caused by *Propionibacterium acnes* pachymeningitis. The patient’s optic neuropathy was stabilized with appropriate antibiotic therapy.

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Pachymeningitis is a rare cause of vision loss (1–3). We present a case of vision loss caused by *Propionibacterium acnes* pachymeningitis. To the best of our knowledge, this is the only such case reported in the literature.

**CASE REPORT**

An 82-year-old man reported a 5-day history of visual field narrowing and “flattening” of colors in the vision of his right eye. His medical history was significant for a 10-year history of ANCA-negative hypereosinophilic Churg–Strauss disease, for which he had been taking prednisone 5 mg daily for 4 years. He also had hypertension, hyperlipidemia, chronic allergic sinusitis, nasal polyposis, and eosinophilic fasciitis confirmed by electromyography and muscle biopsy. He had experienced sequential episodes of nonarteritic anterior ischemic optic neuropathy, first in the left eye 20 years ago and in the right eye 4 months before the presentation.

Family history was unremarkable and review of systems was positive for intermittent left-sided hearing impairment and nonfocal tongue weakness that he had been experiencing for the past 4 months without a definitive etiology.

Visual acuity was 20/50 in the right eye, decreased from 20/40 at his last clinic visit 2 months previously. Vision in the left eye was 20/100 and stable. Pupils were reactive with a 1.9 log unit left relative afferent pupillary defect. Automated perimetry showed a new inferior arcuate defect in the right eye and an inferior altitudinal defect in the left eye that was unchanged from previous examination (Fig. 1). Ophthalmoscopy showed bilateral optic disc pallor.

The patient was prescribed prednisone 80 mg/d. A temporal artery biopsy showed no signs of inflammation. Magnetic resonance imaging (MRI) of the brain and orbits demonstrated diffuse, smooth pachymeningeal enhancement involving the orbital apices and intracanalicular optic nerve sheaths (Fig. 2). These imaging findings were not present on an MRI performed 4 years before. Laboratory studies including complete blood count, metabolic profile, erythrocyte sedimentation rate, C-reactive protein, syphilis serologies (RPR and VDRL), anticytoplasmic antibody, antinuclear antibody, angiotensin-converting enzyme, and anticardiolipin antibodies were normal except an elevated serum IgE that was unchanged from his baseline. Lumbar puncture revealed an opening pressure of 14 cm H₂O with a protein level of 96 mg/dL (normal: 15–45 mg/dL). CSF otherwise showed normal indices, and no infectious organisms were cultured.

The patient was given 1 g of intravenous (IV) methylprednisolone daily for 3 days without a change in his vision. A dural biopsy was obtained. Intraoperatively, a milky thickened arachnoid was noted, and features of chronic meningeal inflammation were seen histologically (Fig. 3). Dural tissue culture grew *P. acnes*, and the patient was treated with oral doxycycline 100 mg twice daily. Two days later, he developed fever and swelling at the surgical site.
MRI revealed an abscess at the biopsy site and persistent diffuse pachymeningeal enhancement. The abscess was drained, and he was treated for 5 days with IV vancomycin and meropenem. *Klebsiella oxytoca* and *P. acnes* were cultured from the abscess. He was switched to ceftriaxone 2 g twice daily IV, metronidazole 500 mg 3 times daily orally, and discharged to home in stable condition to complete a 6-week course of antibiotic therapy. One month later, MRI showed decreased inflammation at the biopsy site and resolution of pachymeningeal enhancement. Throughout his hospital course and during 10 months of follow-up, the patient’s visual acuity and fields have remained stable.

**DISCUSSION**

Pachymeningitis is an inflammatory thickening of the dura mater and is an uncommon cause of vision loss (4). Known causes of pachymeningitis include intracranial hypotension (5), idiopathic hypertrophic cranial pachymeningitis, central nervous system (CNS) infections, meningeal carcinomatosis, and autoimmune vasculitides including Churg–Strauss syndrome (6). The natural course and treatment of pachymeningitis depends on the underlying etiology. The optic nerves may be affected in the setting of infectious pachymeningitis (7) along with other cranial nerves at the skull base. Because pachymeningitis may be due to both infectious and autoimmune etiologies, we proceeded with dural biopsy in our patient to correctly identify the etiology and guide therapy.

Although pachymeningitis can be caused by Churg–Strauss syndrome, the MRI findings in this disorder generally are more focal and isolated and usually discovered on initial presentation, before institution of immunosuppressive therapy (6). Our patient had been on chronic immunosuppressive therapy before presenting with vision loss and pachymeningitis. Additionally, the lack of an eosinophilic inflammatory cell infiltrate in the dural biopsy makes it less likely that Churg–Strauss was the cause of pachymeningitis. Our patient’s pachymeningeal enhancement persisted while on high-dose oral and IV steroids, also making a vasculitic cause less likely. Although there have been rare reports of Churg–Strauss–associated ischemic optic neuropathy, vision loss generally occurs early in the disease course, before treatment with immunosuppressive therapy (8,9).

*P. acnes* is a slow-growing, anaerobic gram-positive bacillus that belongs to the human cutaneous propionibacteria. It is a saprophytic diphtheroid that is part of the normal flora of human skin, particularly the sebaceous glands. It is also an opportunistic agent that produces a number of virulence factors and is well known for its inflammatory and immunomodulatory properties (10). It is occasionally recognized as a contaminant of neurosurgical procedures and biopsies and is a known cause of postoperative CNS infections. Such infections generally are indolent, with a prolonged duration of symptoms before presentation, low to no attributable mortality, significant time lapse between the CNS procedure and presentation, and rarely causing fever or leukocytosis (11,12). There is only 1 report of pachymeningitis caused by *P. acnes*, and it did not result in an optic neuropathy (13). A 30-year-old woman developed recurrent headaches and recalcitrant partial motor seizures. MRI demonstrated thickening of the left fronto-parietal dura consistent with pachymeningitis, and anaerobic culture of dural biopsy grew *P. acnes*.

One could argue that *P. acnes* was inoculated into the biopsy site of our patient at the time of the procedure. However, this species was the only organism isolated from the biopsy, and it seems logical that if it was a contaminant, other organisms would have been recovered as well. Granulation tissue–like microvascular proliferation with a mild chronic inflammatory cell component also was seen in the patient’s dural biopsy, histopathologic features consistent with a *P. acnes* infection. Neuroimaging evidence of pachymeningeal inflammation only resolved after broad-spectrum...
antibiotic therapy, and this clinical course is most consistent with an infectious etiology.

It is important to recognize that isolation of *P. acnes* may indicate a pathologic infection and that this organism is not always a contaminant or saprophyte. Given the clinical and microbiological findings, our case represents a unique presentation of an optic neuropathy in the setting of *P. acnes* pachymeningitis and illustrates the importance of considering this organism in the differential diagnosis of pachymeningeal enhancement.

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**FIG. 2.** Brain magnetic resonance imaging. Initial postcontrast T1 axial (A) and coronal (B) scans show dural enhancement in the middle cranial fossa adjacent to both orbital apices (arrows) and thickening of the optic nerve sheaths of the intracanalicular optic nerves (arrowheads). After treatment, there is resolution of dural enhancement in both the contrasted T1 axial (C) and coronal (D) images (D was obtained with spoiled gradient-recalled sequences and the dural appearance is normal for this technique).

**FIG. 3.** Dural biopsy shows granulation tissue–like proliferation with a mild chronic inflammatory cell component (hematoxylin and eosin, ×40).


Reversal of Pupillary Atonia After Removal of an Encircling Band

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Abstract: We describe a patient who developed an atonic pupil after placement of an encircling band during retinal detachment surgery. When the band was removed 18 months later, the pupil signs showed partial recovery demonstrating a degree of reversibility of the parasympathetic paresis. We speculate that in this case mechanical deformation of the sclera by the encircling band had produced a conduction block of the short posterior ciliary nerve fibers as they pass forward in the underlying suprachoroidal space.

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A fixed dilated pupil is a recognized though rare postoperative complication of anterior segment surgery. It is classically described after penetrating keratoplasty (1) but also may occur after other anterior segment procedures including trabeculectomy (2) and cataract extraction (3). In these cases, the parasympathetic blockade is usually postreceptoral (because the pupil will not constrict with topically administered full-strength pilocarpine drops) and permanent. We describe an unusual case of a patient with a fixed dilated pupil after retinal detachment surgery in which parasympathetic function partially recovered after removal of the scleral encircling band.

CASE REPORT

A 23-year-old woman underwent surgery for a macula-off rhegmatogenous retinal detachment in her left eye. She had a moderate degree of myopia (−3D) but no other history of ocular disease. She enjoyed good general health and was taking no regular medications. The surgery, performed under general anesthetic, involved placement of a circumferential silicone explant (buckle) between the 11 o’clock and 4 o’clock meridians, a 360° encircling band (2.5 mm diameter) and transscleral cryopexy. The following day she noticed on removing the eye patch that her left pupil was dilated; ophthalmic examination confirmed successful reattachment of the retina. Postoperative recovery was unremarkable but the pupil remained dilated and nonreactive to light.

She returned 18 months, later having noticed problems focusing. Visual acuity was 20/20 in the right eye and 20/200 in the left eye. Anterior segment examination was unremarkable with normal intraocular pressures and no signs of ocular ischemia; funduscopy showed that the retina remained fully attached. Eye movements were full on the right but slightly restricted on the left both horizontally and vertically. The patient’s eyelids were symmetric and normal. The left pupil was larger than the right (Fig. 1), and there was almost no observable light response (LR) or near response (NR) of the left pupil. On slit-lamp biomicroscopy, the pupil appeared round with no visible sector palsy. Pupillometry confirmed significant attenuation of the pupillary constrictor responses (LR and NR; Fig. 2, Table 1) in the left eye, although the mydriatic response to sudden noise (the “startle reflex”) was preserved. The right pupil and deep tendon reflexes were normal.

In view of her persistent symptoms, the patient underwent surgery to remove both segmental and encircling buckles, which were found lying 2 mm posterior to the insertions of the rectus muscles. During
the surgical procedure and within minutes of cutting the encircling buckle, the left pupil became smaller. The following day the patient noticed that her left pupil was smaller than the right and when examined at her postoperative visit 2 weeks later the left pupil now reacted to light. Ten weeks after surgery, pupillometry showed that the left pupil was smaller, and the pupillary constrictions to a light stimulus and an accommodative effort were larger (Table 1; Figs. 1, 2). Pupillometry was repeated once more 4 months later and showed similar results. Topical 0.5% apraclonidine was used to test the integrity of the sympathetic innervation of the iris dilator muscle; this weak α1-agonist had no effect on the resting size of either pupil.

**DISCUSSION**

Although our patient did not have any previous pupil assessment, it is her recollection, supported by old photographs, that her pupils were normal and similar in size before retinal detachment surgery. Following this procedure, the left pupil became fixed and dilated. The lack of response to light can be partly attributed to a reduced afferent drive from the reattached retina. We did not record the pupil responses to unilocular light stimulation or look for a relative afferent pupil defect. However, this does not explain the increase in resting diameter of the left pupil or the absence of any pupil constriction with an accommodative effort. These changes suggest that surgery caused a marked efferent blockade of parasympathetic impulses to the iris sphincter muscle.

The findings in our patient’s left pupil are not similar to Adie’s tonic pupil, which include sector palsy, light-near dissociation, and slowed constriction associated with aberrant regeneration of postganglionic parasympathetic fibers after injury to the ciliary ganglion. The changes we noted are better described as atonic. It appears that this was a purely parasympathetic blockade. The normal lid position, preserved startle response, and absence of mydriatic effect from apraclonidine indicate that the sympathetic supply to the iris dilator muscle was unaffected. Also, there was no clinically apparent disturbance of corneal sensation.

Changes to the pupil and accommodation have been reported after various transscleral treatments for diabetic retinopathy or peripheral retinal degeneration—including cryotherapy (4), argon laser photocoagulation (5), and diode laser photocoagulation (6). Pupil changes have rarely been reported after retinal detachment surgery. Adler and Scheie (7) provided the first description of 2 cases of tonic pupils after “extensive (transscleral) electrocoagulation”; in patient 1, after several weeks the pupil became smaller and recovered a small degree of “tonic” responsiveness to light. Kronfeld (8) reported postoperative sector palsy in 5 eyes in which the affected meridian corresponded to the site of scleral buckling. There are a small number of additional cases published in which the pupil has become either tonic (9) or atonic (10,11) after placement of an encircling band or endolaser. In all cases, the pupil showed supersensitivity to dilute muscarinic agonists (methacholine or pilocarpine) confirming prereceptoral parasympathetic blockade and, in most cases, the pupil remained abnormal with no spontaneous recovery.

Our case is unique in documenting the effects of removing an encircling band in a patient who had developed an atonic pupil at the time of its placement. We would interpret the partial reversal of the parasympathetic paresis within minutes of removing the encircling band as evidence that the pupil changes were because of conduction block rather than loss of the short posterior
ciliary nerves (SPCN). The lack of any pupil signs that might indicate aberrant regeneration (tonic constriction to light and near, sector palsy, and light-near dissociation) further supports our view that the SPCN were preserved but nonfunctioning between her first and second operations. It is not clear whether the mechanism of this conduction block was primarily ischemic or mechanical. There were no clinical signs suggestive of ocular ischemia. The SPCN travel in the suprachoroidal space as they pass forward towards the iris and are presumably susceptible to mechanical deformation from scleral indentation. It is interesting that in our patient there was no evidence of dysfunction of the sympathetic and trigeminal nerves, which also pass in the suprachoroidal space. In the case reported by Valldeperas et al (11), a 11-year-old boy developed permanent corneal anesthesia after placement of an encircling band; however, additional trigeminal or sympathetic paresis was not described in any of the other published cases of pupil changes after retinal detachment surgery and was not detectable in our case. We speculate that the SPCN may be more susceptible to mechanical deformation than the other nerves traveling in the same anatomical compartment.

After removal of the encircling band, the left pupil became smaller than the right and remained so for months later. This raises the question of whether the larger right pupil was functioning normally. The amplitude of the LR in this eye was below the lower limit of the normal range for our laboratory (12), and it is possible that the extensive prophylactic cryotherapy to this eye had damaged some of the SPCN giving rise to a larger than normal resting pupilary diameter in this eye. However, the light reflex response of the pupil in the left eye remained smaller than in the right eye even after removal the encircling band suggesting that the SPCN function was still better in the eye with the larger pupil. Different degrees of denervation supersensitivity might have accounted for some of this reversed anisocoria; in the context of SPCN dysfunction in Holmes–Adie syndrome, it is a common finding that affected pupils become progressively miotic over time despite persisting signs of parasympathetic paresis. Unfortunately, we were not able to test this hypothesis by pharmacological means using a dilute muscarinic agonist (e.g., 0.1% pilocarpine) because the corneal surfaces of both eyes in this myopic patient were compromised by years of contact lens wear rendering such testing invalid.

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Cerebrospinal Fluid Leak Presenting as Oculorrhea After Blunt Orbitocranial Trauma

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Abstract: Cerebrospinal fluid (CSF) leak is an uncommon but well-documented occurrence after blunt head trauma, typically manifesting as otorrhea or rhinorrhea. Blunt cranio-orbital trauma also may cause CSF leak into the orbit, manifesting as orbitocele, blepharocele, chemosis, or tearing (“oculorrhea”). We report a patient who developed oculorrhea after blunt head trauma, and neuroimaging disclosed comminuted fractures of the left frontal, greater sphenoid wing, nasal, and maxillary bones. Because he also displayed chemosis and markedly reduced ocular ductions and periocular pain, carotid-cavernous fistula was suspected but appropriate vascular imaging was negative. Aspiration of subconjunctival fluid was positive for beta-2 transferrin, a specific marker for CSF. Chemosis lessened and the oculorrhea ceased spontaneously within 6 days of the trauma. This manifestation of CSF leak must not be overlooked because of the threat of meningitis.

CASE REPORT

Called to the scene of a traffic accident, a 34-year-old policeman sustained closed head trauma after being struck by an oncoming automobile as he exited the driver’s side door of his car. He briefly lost consciousness, and upon awakening, he noted left facial pain. Cranial computed tomography (CT) disclosed multiple comminuted fractures involving the left frontal, orbital, and maxillofacial bones (Fig. 1). After 3 days, before repair of his facial fractures, he experienced an episode of vomiting and suddenly developed marked swelling of soft tissues around the left eye and increased periocular pain. Ophthalmologic examination showed absent abduction and reduced supraduction, infrauction, and adduction of the left eye. Sensation over the second trigeminal division was decreased on the left side. Bullous chemosis was present in the lower fornix without conjunctival lacerations (Fig. 2). Ophthalmoscopic examination was unremarkable.

These findings were suggestive of carotid-cavernous fistula, but CT angiography was unremarkable. A neurosurgical consultant noted copious tearing coming from the left eye upon leaning the patient’s head forward, raising the possibility of a CSF leak through the orbit. The tearing ceased when he lay supine. Subconjunctival fluid aspirated with a 25-gauge needle was positive for beta-2 transferrin, confirming the presence of CSF.

Although treatment with a lumbar drain was considered, the oculorrhea and chemosis spontaneously resolved on the sixth post-trauma day. The patient’s zygomatic and inferior orbital floor fractures were repaired the next week. It was presumed that the frontal bone fracture with an associated dural laceration was the source of the CSF leak.

DISCUSSION

Skull base fractures result in CSF otorrhea when a dural tear allows CSF to flow through the temporal bone or mastoid fracture into the middle ear. CSF may also appear as rhinorrhea if it flows through a fractured cribriform plate.
and into the paranasal sinuses and nasal cavity. Otorrhea and rhinorrhea occur readily because of a relatively high-pressure gradient between the intracranial space and the external ear canal or paranasal sinuses. However, the route of CSF leak in oculorrhea is through a dural tear and a fracture in the frontal bone, lateral wall, or roof of the orbit. Orbital manifestations of CSF leak are presumably rare because the pressure gradient between the intracranial subarachnoid space and the intra-orbital space low is low (4–7). As no conjunctival tears have been demonstrated in these cases, the supposition is that the CSF exudes through intact conjunctiva. Establishing the diagnosis of cranio-orbital fistula can be challenging because of the difficulty in differentiating oculorrhea from excessive lacrimation caused by orbital soft tissue trauma or epiphora caused by lacrimal outflow obstruction (4).

To date, 10 cases of post-traumatic CSF oculorrhea have been reported (1,4–12). One patient developed increasing and pulsatile proptosis 1 week after a motor vehicle accident. CT showed orbital roof fractures. Orbital ultrasonography demonstrated an orbital cyst. Metrizamide cisternography with CT showed that the cyst communicated with the CSF space (5). In another case, an 8-month-old girl had pulsatile proptosis of the left eye noted 3 days after a motor vehicle accident. A transfemoral retrograde 4-vessel angiogram in pursuit of a diagnosis of carotid-cavernous fistula was negative. The proptosis increased and chemosis developed. Fluid with high sugar content was found escaping from the left nostril and flowing as tears. She underwent surgical exploration that showed a fracture of the left cribriform plate. The associated dural laceration was repaired (7).

Chemical analysis of CSF traditionally involved measurement of glucose concentration (13), but has been replaced by immunoanalysis for beta-2-transferrin. The protein is present in CSF but not in nasal secretions or tears (4,6,14,15). Ryall et al (14) retrospectively analyzed 11 consecutive cases of CSF leak after head injury, noting 100% sensitivity and specificity of the beta-2-transferrin test.

A CSF leak places the patient at risk for infection within the central nervous system. Regarding CSF oculorrhea, Dryden et al (6) described a 4-year-old boy with 2 years of tearing after a motor vehicle accident and basilar skull fracture. The tearing was attributed to nasolacrimal duct obstruction, and the patient underwent dacryocystorhinostomy (DCR). He had continued tearing and developed meningitis 1 week postoperatively. Maxillofacial CT showed “a bony defect in the posterior orbit, which did not communicate with the DCR ostium.” The “tears” were analyzed for glucose and found consistent with CSF.

**FIG. 1.** Maxillofacial computed tomography. A. Coronal view shows comminuted fractures involving the left frontal bone extending into the orbital roof (arrow) and maxillary sinus (arrowhead). B. Axial view shows left lateral orbital wall fracture (arrow) and fracture involving the greater wing of left sphenoid (arrowhead).

**FIG. 2.** Appearance of the left eye 3 days after head trauma. There is proptosis and lid ecchymosis with marked chemosis. Copious tearing was evident only when the patient bent forward.
Craniotomy performed 10 days later revealed an encephalocele extending through a fracture in the posterior medial orbital roof and a silastic implant placed over the defect stopped the oculorrhea. Sibony et al (5) reported a 27-year-old man with a post-traumatic CSF cyst of the orbit. Cisternography showed an orbital cyst communicating with the subarachnoid space. The patient developed a cerebral abscess, and CT showed a "large defect in the orbital roof." He was successfully treated with antibiotics.

Because orbital tissues tamponade most CSF leaks, repair of orbital fractures should be deferred so as not to disturb a recently sealed leak. Treatment options for CSF oculorrhea include observation, CSF diversion through lumbar drain placement, and surgical repair, including closure of the dural tear, repair of the fractured bones of anterior skull base, and obliteration of the epidural space with fibrin glue. Many authors recommend an initial 24-hour period of observation because an estimated 85% of fistulas will close spontaneously. The addition of lumbar drain placement results in fistula closure in 95% of patients (16). Surgical repair is recommended for extensive comminuted or displaced skull base fractures for leaks persisting more than 48 hours (1).

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Chiasmal Glioma in Spasmus Nutans: A Cautionary Note

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Abstract: We diagnosed chiasmal glioma in an 8-month-old infant who had spasmus nutans that spontaneously resolved. Magnetic resonance imaging showed no interval change in tumor size over the next 8 months. Clinical resolution of spasmus nutans does not preclude chiasmal glioma as the underlying cause.

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Spasmus nutans is a benign clinical entity characterized by the triad of nystagmus, head nodding, and an abnormal head position (1). The nystagmus is of low amplitude and high frequency and is often asymmetrical in the two eyes. It generally begins between 4 and 12 months of age (1) and is more common in the African American and Hispanic populations (2). Most cases are idiopathic, and its natural history is one of the spontaneous resolutions. In some children, however, it can signal the presence of chiasmal glioma or underlying retinal disease. We examined an infant with spasmus nutans whose unusual clinical course provides a cautionary note for the clinical management of this condition.

CASE REPORT

A healthy 8-month-old Caucasian infant with spasmus nutans was referred for evaluation of nystagmus, which was first noted at 2 months of age. The nystagmus intensified, and he began bobbing and tilting his head at 3 months of age. His head movements became more pronounced when trying to focus on objects of interest. He was born 4 weeks prematurely weighing 6 lb 11 ounces at birth. The parents had noted no photophobia or difficulty seeing in dim illumination. He had no family history of nystagmus and was neurodevelopmentally normal. On examination, he followed optokinetic stimuli and maintained fixation with either eye, and had normal pupillary responses to light with no relative afferent pupillary defect. He had fine symmetrical shimmery nystagmus, which was associated with vertical head bobbing and a chin-down head when viewing objects at near. Retinoscopy showed a mildly hyperopic refractive error. Retinal examination disclosed no optic disc swelling or pallor, and a normal retina in both eyes.

Magnetic resonance imaging showed bilobed thickening of the optic chiasm extending anteriorly to involve both intracranial optic nerves (Fig. 1). The tumor extended posteriorly to involve the optic tracts and showed additional extension into the right anterior midbrain and mesial temporal lobe. Endocrinologic testing disclosed no abnormalities. Over the next 2 months, his nystagmus and head nodding gradually resolved. Neuro-oncology evaluation was performed, and it was elected to observe him given the absence of associated neurological findings. On follow-up examination at 16 months of age, all signs of spasmus nutans were completely resolved, and repeat neuroimaging showed no change in the tumor size.

DISCUSSION

The rare association of chiasmal glioma with spasmus nutans is usually signaled by one or more of the following clinical findings: 1) a relative afferent papillary defect; 2) optic atrophy or disc swelling; 3) large head size; 4) café-au-lait spots; and 5) coexistent neurological dysfunction or emaciation (3,4). Because these clinical findings were absent in this infant, the decision was almost made to forego neuroimaging. More surprising was the finding that the spasmus nutans completely resolved on follow-up examination, although 2 subsequent neuroimaging studies
over a 10-month period showed no change in the tumor size. If we had seen the child after the spasmus nutans had resolved, neuroimaging would certainly have been deemed unnecessary.

This case history highlights 3 critical points in the clinical management of spasmus nutans. First, the early onset of spasmus nutans should raise particular concern about chiasmal glioma. Second, the absence of “red flag” systemic or neuro-ophthalmologic signs in the infant with spasmus nutans does not definitively rule out the possibility of chiasmal glioma (5,6). Finally, even the spontaneous resolution of spasmus nutans does not rule out chiasmal glioma as the underlying cause.

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Vitreous Seeding From a Large Optic Disc Melanocytoma

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Abstract: We report the case of a 17 year-old man with a large optic disc melanocytoma that underwent spontaneous rupture and seeding of the vitreous with pigmented cells. Potential pathogenic mechanisms and visual prognosis of this rare event are discussed.

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Optic disc melanocytoma (ODMC) is a rare, benign intraocular tumor that primarily occurs in the optic nerve head and manifests as a melanotic mass. It generally does not affect vision, although a small proportion of patients may experience minor visual impairment as the tumor expands. On rare occasions, it may lead to severe vision loss (1,2). Our patient developed a dramatic fundus appearance because of vitreous seeding of pigmented cells but fortunately retained normal visual acuity.

CASE REPORT

A 17-year-old man reported a “fluttering shadow” in front of his right eye for 3 weeks. Five years previously, he was found to have a melanocytoma in his right eye (Fig. 1). At that time, his visual function was normal, and he had regular follow-up examinations.

At the time of presentation, the patient’s visual acuity was 20/20, right eye and 20/15, left eye. Anterior segment examination was normal bilaterally, and intraocular pressures were 15 mmHg, right eye, and 16 mmHg, left eye. Although the left fundus was unremarkable, his right fundus showed disseminated pigmented cells into the vitreous cavity (Fig. 2A). This was confirmed with the findings on fluorescein angiography (Fig. 2B). Optical coherence tomography (Fig. 2C) and ultrasonography (Fig. 2D) demonstrated a posterior vitreous detachment in the right eye. The patient declined fine needle aspiration biopsy or vitrectomy and remained stable over 1 year of follow-up.

DISCUSSION

Although ODMC generally follows a benign clinical course, complications may occur during long-term follow-up. Approximately 4% of cases demonstrate vitreous seeding of pigmented cells (1), and various mechanisms have been proposed. One possibility is spontaneous tumor necrosis. Font et al (2) described a patient with a large ODMC, with massive dispersion of pigmented cells into the vitreous 19 years after initial evaluation. The patient developed cataract and glaucoma and ultimately lost all sight in the affected eye. The authors speculated that the pathomechanism involved phagocytosis of disseminated necrotic melanocytes and subsequent inflammation. Another potential mechanism is tumor invasion of the retina and release of pigmented cells into the vitreous. Mazzuca et al (3) reported 2 such patients, both associated with increase in size of the ODMC, and in 1 patient, there was dilation and tortuosity of the retinal venous system, suggestive of vascular compression by the tumor mass. A final potential mechanism is spontaneous vitreous detachment. This is the likely cause in our patient and is supported by the OCT and ultrasonographic findings (Figs. 2C, 2D). With disruption of the internal limit membrane, melanocyte cells disseminated into the vitreous cavity.

Shukla et al (4) described a patient with pigment dispersion from an ODMC and severe loss of vision after 33 years of follow-up. The eye was ultimately enucleated, and pathologic results revealed malignant transformation of the tumor melanocytes. Our patient
declined vitreous biopsy, but he has retained normal visual acuity and intraocular pressure with a stable appearance of the ODMC. Nevertheless, careful follow-up of our patient is warranted for this rare complication of ODMC (5).

REFERENCES


Cerebrospinal Fluid Pressure in Adults

Sarah C. M. Lee, MBBS, BSc, Christian J. Lueck, PhD, FRACP, FRCP

Background: Lumbar puncture (LP) is a widely used investigative procedure. It allows relatively non-invasive measurement of intracranial pressure (ICP) which may have a significant impact on diagnosis and/or patient management. Over the years there has been considerable discussion about various aspects of the procedure, including what constitutes a normal opening pressure, what factors might influence this, and how LP is best performed.

Evidence Acquisition: A review of the literature was carried out by searching PubMed and Medline, scanning relevant medical journals for recent publications, and carrying out secondary referencing and contacting other clinicians, where appropriate.

Results: The normal range of ICP measured by LP in adults in a typical clinical setting should now be regarded as 6 to 25 cmH2O (95% confidence intervals), with a population mean of about 18 cmH2O. There is, however, considerable variability: some normal individuals have pressures of 30 cmH2O (or, occasionally, even higher) meaning that pressure measurements must be interpreted in the clinical context.

Conclusions: This article aims to provide the practicing neuro-ophthalmologist with up-to-date information about the ways in which various factors can influence pressure measurements obtained at LP.

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Lumbar puncture (LP) is a widely used procedure in the diagnosis of infectious, inflammatory, and neoplastic conditions. It also plays a crucial role in the diagnosis and management of conditions involving elevated intracranial pressure (ICP), most notably idiopathic intracranial hypertension (IIH) (1). The procedure was first described over 100 years ago (2), and millions of patients around the world have subsequently been subjected to it. Somewhat surprisingly, there are still areas of uncertainty and confusion, most notably what constitutes the normal range of cerebrospinal fluid opening pressure (CSF-OP), and what factors (e.g., the patient’s weight or position during the procedure) might influence this.

A century of investigation has shown that normal ICP is influenced by a number of factors, both internal (e.g., arterial pressure, respiration, temperature, pCO2, and sleep) and external (e.g., gravity and position). A detailed review of these factors is beyond the scope of this article and the interested reader is referred elsewhere (3,4). This article will review recent findings related to the normal range of CSF-OP as measured clinically at LP, and then look at the technique of LP itself, specifically addressing factors such as patient positioning and choice of needle size.

CEREBROSPINAL FLUID OPENING PRESSURE: WHAT IS NORMAL?

LP was introduced into clinical practice toward the end of the nineteenth century by clinicians including Quincke, Wynter and Queckenstedt (2). During the early twentieth century, many studies looked at CSF-OP (5–8), and the reference ranges derived from these studies are still cited in the latest editions of many major textbooks defining the upper limit of the normal range of CSF-OP as 15 cmH2O (9), 18 cmH2O (10), or 20 cmH2O (4,11–13). Clinical experience suggests that these upper limits are too low (14), and, indeed, studies as early as 1974 found that between 16% and 25% of normal subjects had CSF-OPs higher than these values (15,16).

Four recent studies have looked carefully at CSF-OP (Table 1). The first was a prospective study of 242 adults undergoing LP for routine investigation of non-pressure-related neurological conditions. The authors found a median CSF-OP of 17 cmH2O with an upper 95% confidence interval (CI) of 25 cmH2O (14). A similar prospective study of 348 adult patients found a median CSF-OP of 19 cmH2O with an upper quartile of 23 cmH2O (17). A study of 197 children (aged 1–18 years) found very similar results with a median...
CSF-OP of 19 cmH₂O and an upper 95% CI of 28 cmH₂O (18). A much larger retrospective chart review of 12,118 adults found a slightly lower median pressure of 15.6 cmH₂O (19), but this result was probably artificially low because the authors excluded any subject with a CSF-OP of ≥25 cmH₂O, stating that this value represented the upper limit of normal. In fact, 25 cmH₂O refers to the upper 95% CI, not the absolute upper limit of the normal range so their study would have excluded 3%–5% of normal subjects with pressures higher than this (14,18). Taken together, these 4 studies suggest that the values quoted in many textbooks are incorrect, and that the upper limit of CSF-OP in normal adults should now be regarded as 25 cmH₂O. Indeed, some otherwise normal individuals can have pressures above this value, occasionally above 30 cmH₂O (14,17). The upper limit of 25 cmH₂O has been incorporated into the most recent definition of IIH (1), whereas a lower limit of normal of 6 cmH₂O has been incorporated into the most recent definition of headache induced by reduced ICP (20).

**BODY MASS INDEX**

IIH has a clear association with obesity (21,22). It has been suggested that obesity is associated with increased CSF-OP in otherwise normal people (23), but this is the subject of some controversy. Smaller studies of over 50 subjects have often failed to show a clear correlation between body mass index (BMI) and CSF-OP (24,25). Slightly, larger studies have shown a nonsignificant increase in mean CSF-OP in obese subjects (16), but not if patients with abnormal magnetic resonance venograms were excluded (26). Even larger studies of over 200 subjects have demonstrated a significant correlation between BMI and CSF-OP: these studies suggested that mean CSF-OP rises by about 0.3 cmH₂O for every unit increase in BMI (14,18,27). However, the correlation coefficients are low in these studies, meaning that the association is not clinically useful because of interindividual variability.

One factor which, in theory, might influence CSF-OP in “normal” individuals is as-yet undiagnosed obstructive sleep apnea (OSA). In one study, 6 patients with known OSA demonstrated significant elevations in ICP during prolonged periods of apnea while asleep (28). The authors reported ICP was also elevated while awake in these patients, but only 3 of their 6 patients had awake pressures of >25 cmH₂O. Another study of 4 patients with OSA found normal awake CSF-OP in all 4, despite the fact that they all had papilledema (29). Recent studies have suggested that there is no increase in the frequency of papilledema in patients with OSA (30,31) nor, there is a clear increase in the incidence of OSA in patients with IIH (32). These results suggest that a single measurement of CSF-OP while the patient is awake might not be adequate, and the relativity of OSA and ICP requires further study.

**AGE AND OTHER FACTORS**

CSF-OP in children is addressed in an accompanying article, which suggests that normal children may have a CSF-OP as high as 28 cmH₂O (33). A recent study of 40 healthy older subjects aged between 60 and 82 years found a median CSF-OP of 15.8 cmH₂O (95% CI, 10.6–19.4 cmH₂O) (34), and the authors concluded that these results were similar to those found in young and middle-aged patients. However, their numbers were small. According to a very large retrospective chart review of over 12,000 patients, mean CSF-OP declines steadily after the age of 50 years. This study found the mean CSF-OP in patients aged 90–95 years to be only 11.4 ± 3.2 cmH₂O, about 27% lower than the normal range quoted above (19) (as discussed previously, however, all patients with CSF-OP above 25 cmH₂O were excluded from this study, so the absolute value of CSF-OP may have been somewhat underestimated; this would be unlikely to influence the finding of an age-related effect of lowering ICP).

On average, men may have a slightly higher mean CSF-OP than women by about 1–2 cmH₂O (17,19), but this is not clinically significant. Pain from headache may have a similar, small effect on CSF-OP (17). To the best of our knowledge, there are no studies showing a significant effect of race, mean arterial pressure, or diabetes mellitus on CSF-OP.

**POSITIONING: WHAT MATTERS?**

**Lateral Decubitus, Sitting, or Prone?**

LP has traditionally been performed in the left lateral decubitus (recumbent) position (35–37). CSF-OP being determined manometrically against a zero at the level of the needle in the spinal canal. It is technically easier to perform an LP with the patient sitting up and leaning forward because this increases the distance between lumbar spinous processes (38,39). However, a manometrically derived pressure in the sitting position is misleading, mean values being elevated by approximately 25 cmH₂O (5). Accordingly, CSF-OP should never be measured with the patient in the seated position; the patient must be horizontal so that the head (strictly speaking, the right atrium), and LP needle are level with each other.

Because LPs can be technically difficult, particularly in overweight individuals, there is an increasing tendency to ask radiologists to perform them under image guidance. In this situation, the LP needle is generally inserted with the patient in the prone position. Only a minority of radiologists rotate patients from prone to left lateral decubitus position before measuring CSF-OP (40). There are 2 issues which need consideration when measuring CSF-OP in the prone position. First, the reading from the manometer must be
### TABLE 1. Details of 4 recent studies evaluating CSF-OP at LP in normal individuals

<table>
<thead>
<tr>
<th>Study</th>
<th>Number; Gender Ratio</th>
<th>Age, yr</th>
<th>BMI; Median (range), kg/m²</th>
<th>CSF-OP; Median, cmH₂O</th>
<th>Range of CSF-OP, cmH₂O</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whiteley et al (14)</td>
<td>242; 45% M:55% F</td>
<td>45 (18–88), median (range)</td>
<td>26.0 (13.0–52.0)</td>
<td>17.0</td>
<td>9–28 (range); 10–25 (95% CI)</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Bø et al (17)</td>
<td>348; 43% M:57% F</td>
<td>46.7 ± 16.6 (mean ± SD)</td>
<td>—</td>
<td>19.0</td>
<td>15–23 (interquartile range)</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Avery et al (18)</td>
<td>197; 47% M:53% F</td>
<td>1–18 (range)</td>
<td>18.5 (12.9–49.1)</td>
<td>19.0</td>
<td>6–47 (range); 10–32 (95% CI)</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Fleischman et al (19)</td>
<td>12,118; 49% M:51% F</td>
<td>55 (20–95), median (range)</td>
<td>26.1 (10.1–49.1)*</td>
<td>15.6†</td>
<td>6.0–25.0 (range)†</td>
<td>Retrospective chart review</td>
</tr>
</tbody>
</table>

*Results quoted from 20 to 49 year age range and converted from mm Hg to cmH₂O for comparison.
†All pressures above 25 cmH₂O were excluded.

*BMI recorded in only 35.5% of subjects.

BMI, body mass index; CI, confidence interval; CSF-OP, cerebrospinal fluid opening pressure; LP, lumbar puncture.
corrected to a zero at the level of the spinal canal, either by adding the length of the spinal needle to the measurement from the manometer or by inserting a flexible rubber tube so that the position of the manometer can be adjusted (Fig. 1). Second, particularly in obese patients, abdominal compression in the prone position may elevate CSF-OP. Studies differ regarding how much this matters. In one study, CSF-OP measured in prone was elevated by about 3 cmH₂O (24) compared with the left lateral decubitus position. Another study found the difference was only 1.2 cmH₂O and, therefore, clinically insignificant (25). Interestingly, the patients in the latter study were, on average, slightly more overweight than in the former (mean BMI, 35 vs 31 kg/m²).

**Leg Extension and Valsalva Maneuver**

It is widely recommended that patients be asked to extend their legs and neck before measuring CSF-OP because that hip flexion may increase CSF-OP by increasing intra-abdominal pressure (16,41). Two earlier studies found that a tightly flexed position elevates CSF-OP by, on average, 6–8 cmH₂O (42,43), whereas more recent studies have found differences of only 1–2 cmH₂O (44,45). Occasional subjects paradoxically demonstrate increased CSF-OP with leg extension (42,44,46), so the practice of extending legs may not be that important. This is particularly relevant to performing LPs in children when it can be difficult to get the patient into an extended position (45,47).

However, the practice of extending legs does reduce the chance of Valsalva-induced increase in CSF-OP. In one study, performing a Valsalva maneuver transiently elevated CSF-OP by a mean of 17.7 cmH₂O (the maximum increase being from 16 to 47 cmH₂O in 1 subject) (48). In another study, there was a mean elevation of 14.3 ± 3.7 cmH₂O (49). Accordingly, it is appropriate to continue to ask patients to extend their legs (and relax) when possible.

**Needle Size**

The choice of needle is important. There is considerable discussion in the literature regarding the use of atraumatic needles and/or smaller needles to minimize the risk of post-LP headache (50). The issue of needle type is beyond the scope of this article, but size matters when measuring pressure. One study found that CSF-OP measured through a larger, 22-gauge, needle was slightly lower (by about 1.2 cmH₂O) than that measured through a smaller, 26-gauge, needle (15). Although this difference is probably

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**FIG. 1.** Diagram to demonstrate “zeroing” of the manometer reading when a LP is performed in the prone position. **A.** LP performed in the left lateral decubitus position. The needle is in the spinal canal (sc), and the fluid in the manometer rises so that the meniscus is at a level m. The cerebrospinal fluid opening pressure (CSF-OP) is the height of the column of CSF, h, that is, the difference between sc and m. **B.** When an LP is performed in the prone position, the hub of the needle is above the level of the spinal canal. The meniscus in the manometer will therefore give a lower reading, h'. To obtain the true CSF-OP, the length of the needle, N must be added to h'. **C.** Alternatively, the manometer tube can be separated from the needle by a flexible tube and repositioned so that the base of the manometer is at the level of the spinal canal. In this case, the height of the meniscus (h) will represent the true CSF-OP. LP indicates lumbar puncture; CSF-OP, cerebrospinal fluid opening pressure.
not clinically important (24,25), the time taken to reach equilibrium is significantly affected by needle size and this does matter: it takes 1–2 minutes for 90% of the total cerebrospinal fluid (CSF) height to be reached through most 22G needles. Equilibration time through larger (20G) needles is only 30–60 seconds (51). Smaller needles (24G or 25G) require several minutes for equilibration and are best avoided if measurement of CSF-OP is important (51).

Other Factors
Choice of intervertebral space seems to have no significant effect on CSF-OP (24,25), but pain and anxiety increase it (17). Sedation or anesthesia may increase CSF-OP (25,45), and an effect as large as 8 cmH₂O has been reported (52). This issue is particularly relevant to children and is discussed further in an accompanying article (33).

OTHER WAYS OF MEASURING CEREBROSPINAL FLUID PRESSURE
A single measurement of ICP may not, by itself, confirm or refute a diagnosis. All measurements need to be interpreted in clinical context, and it may be necessary to undertake repeated measurements to clarify the diagnosis.

On occasion, it may be necessary to consider more invasive techniques of measuring CSF pressures. The most accurate way of measuring ICP is a ventricular catheter connected to an external strain gauge (53,54). Although routinely used in neurosurgical intensive care units, particularly in patients with head trauma, such devices are inappropriate for most neuro-ophthalmic purposes. However, invasive monitoring of ICP is sometimes performed, particularly if the diagnosis is unclear, either through direct intracranial monitoring (55) or through lumbar catheter (56,57).

There are various different sites at which a pressure monitor can be located, and many different monitors are available, each with its own advantages and disadvantages (53,54). ICP measured at LP seems to correlate very well with intraventricular pressure (58).

CONCLUSIONS
LP is still the most practical and appropriate way to measure CSF-OP in neuro-ophthalmological practice. It should ideally be performed with the patient in the left lateral decubitus position and, though this is probably not crucial, patients should be asked to straighten their legs before making a measurement. Performing the LP in a prone position for the purposes of image guidance is acceptable provided the manometer reading is appropriately zeroed. For the purposes of measuring pressure, LP should be performed through a larger needle, preferably at least 20-gauge. Sedation or anesthesia is better avoided if possible.

The upper limit of normal CSF pressure in adults is 25 cmH₂O, although this probably falls slightly after the age of 50. This upper limit has been emphasized in the most recent definition of IIH (1). CSF-OP probably does increase with increasing BMI, but the correlation is poor, and most authors now suggest that this effect is not clinically relevant.


Interpretation of Lumbar Puncture Opening Pressure Measurements in Children

Robert A. Avery, DO, MSCE

Background: Understanding the reference range of cerebrospinal fluid opening pressure (CSFOP) in children is essential to the diagnosis of elevated intracranial pressure. Recent studies have highlighted several clinical elements that need to be considered when interpreting CSFOP measures.

Evidence Acquisition: This review and recommendations are based on peer-reviewed literature, primarily from the past decade, as well as the author’s clinical and research experience.

Results: CSFOP measures ≤28 cm H$_2$O can be considered “normal” for most children. The patient’s depth of sedation, body mass index, and sedation medication can sometimes result in small increases in CSFOP. Patient age and leg position (flexed vs extended) in the lateral decubitus position do not seem to significantly impact CSFOP measures.

Conclusions: The threshold of a normal CSFOP should not be interpreted in isolation, but instead, in concert with other clinical and examination findings to help the physician make a well-informed assessment of whether a child has elevated intracranial pressure.

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CASE REPORT

A 12-year-old boy presents with 3 months of unremitting holocehphal headache in the setting of an unremarkable comprehensive neuro-ophthalmologic examination without papilledema. He takes no medication, and his body mass index is 90th percentile for age. He underwent a sedated lumbar puncture (LP) using midazolam and fentanyl. The cerebrospinal fluid opening pressure (CSFOP) was 28 cm H$_2$O and, on awakening, the child stated he had relief of headache. His headache returned the next day, so he was placed on topiramate for headache prophylaxis. One month later, he underwent a second LP with a CSFOP of 27 cm H$_2$O, resulting in 1 day of headache relief. Neuro-ophthalmologic examination and magnetic resonance imaging (MRI) remain normal without any objective findings suggestive of elevated intracranial pressure (ICP). Does he have idiopathic intracranial hypertension (IIH)?

The CSFOP is a relatively noninvasive surrogate measure of ICP and an essential component of the diagnostic LP. An accurate interpretation of this commonly performed procedure is essential for the diagnosis and management of IIH (1,2). The reference range for a normal CSFOP in children has been described in the literature and seminal textbooks for over a century, despite the lack of empiric evidence to support these recommendations (2). In the past decade, a number of studies have questioned the previously recommended reference ranges for a normal CSFOP in both adults and children (3–5). These studies and others have also examined the impact of clinical factors, such as patient age, body mass index (BMI), depth of sedation, sedation medication, and body position that have long been speculated to influence the CSFOP values (3,4,6–13). This review examines the current data on CSFOP in children and attempts to provide a framework on how to interpret CSFOP.

ESTABLISHMENT OF A PEDIATRIC REFERENCE RANGE

Numerous studies and textbooks have listed a wide range of values for a normal CSFOP in infants and children (2). Rangwala and Liu (2) were the first to describe how many authors had cross referenced or incorrectly attributed their data to other articles, along with the lack of scientific rigor...
in developing these norms. It is likely that the normative values from the adult literature were adapted to pediatrics. In 1983, Corbett and Mehta (8) suggested that some normal adults may demonstrate a CSFOP as high as 25 cm H$_2$O. However, the pediatric literature did not adapt this range and continued to endorse values of 20 cm H$_2$O and lower as being normal (2,8). A decade later, Ellis (5) performed LPs on pediatric oncology patients and concluded that the normal range of CSFOP was from 10 to 28 cm H$_2$O. Unfortunately, these findings were not included in the pediatric literature, possibly due to the atypical method (i.e., counting the number of CSF drops for 21–39 seconds) of determining the CSFOP (5).

Ultimately, a large prospective study of adults confirmed the findings of Corbett and Mehta (8) and suggested that, at times, a normal CSFOP could be as high as 28 cm H$_2$O (3). This was soon followed by a large prospective study of children undergoing diagnostic LP and reported the mean CSFOP to be 19.7 cm H$_2$O and the 90th percentile being as high as 28 cm H$_2$O (4). Findings from a smaller cohort of pediatric patients also supported the fact that some children may have a CSFOP of up to 28 cm H$_2$O and can still be considered normal (14). Avery et al (15) provided additional support of their findings by reporting that 98% of children with optic nerve head edema believed to be secondary to elevated ICP demonstrated CSFOP measures $\geq$ 30 cm H$_2$O.

The recent studies mentioned above have helped guide clinicians and researchers in new directions. Specifically, the current CSFOP pressure data have been incorporated into the new diagnostic criteria for pediatric IIH (1). Second, the large adult (3) and pediatric (4) prospective studies listed above also highlighted the potential influence of clinical variables, such as BMI, age, depth of sedation, sedation medication, and body position that have long been speculated to influence the CSFOP values.

**FACTORS AFFECTING CSFOP**

**Age**

Many clinicians believe that CSFOP increases in early childhood until it reaches values similar to adults. Eight years of age has been discussed as a cutoff between pediatric and adult values (2). The study by Seiden et al (4), limited to children between 1 and 18 years old, did not find a statistically significant relationship between age and CSFOP. Even when age was dichotomized above and below 7 years old, Ellis (5) also did not find a difference in mean CSFOP (19.1 vs 19.0, respectively). If differences in CSFOP exist between younger and older children, it is likely that interpatient variability, level of sedation, sedation medication, and other yet to be discovered factors have cluttered our ability to firmly establish this relationship. Until further research can prove a reliable influence of age on CSFOP, the same normative values can be applied to all children between 1 and 18 years old.

**Body Mass Index**

A statistically significant relationship between BMI and CSFOP previously has been reported in both pediatric and adult cohorts (3,4,14,16). Yet, a recently published large prospective study of adults with IIH found that CSFOP and BMI were not correlated (17). Similar to the results of Whiteley et al (3), the large pediatric study demonstrated that CSFOP increased by approximately 3 cm H$_2$O for every 10-unit increase in BMI after adjusting for the influence of other factors, such as sedation and age (4). Despite the statistical significance, these relatively small changes in CSFOP are unlikely to be clinically significant.

**Sedation**

Given the variability in sedation algorithms both within and between institutions, understanding the influence of specific medications on CSFOP has proven to be difficult. Ketamine has long been suggested to increase ICP and the CSFOP measures in children, (9,11,18), although some investigators have published data to the contrary (19,20). To date, only 1 prospective, randomized study has specifically evaluated the effect of ketamine on CSFOP and concluded that CSFOP was higher in non-ketamine-sedated patients (9). Seiden et al (4) did not find a statistically significant relationship between ketamine and CSFOP, although this study was not specifically designed to address this question and the analysis was limited by the relatively low number of patients receiving ketamine compared with other sedative agents.

Not only is class of sedation medication relevant, but also the patient’s depth of the sedation is equally important. Pediatric patients who received moderate-to-deep sedation were found to have a CSFOP of nearly 3.5 cm H$_2$O higher than those not receiving any sedation medication (4). It is hypothesized that children deeply sedated likely experience a relative hypercapnia that contributes to elevated CSFOP (21). Lim and Lin (12) performed continuous monitoring of CSFOP while evaluating pediatric subjects’ end-tidal pCO$_2$ and demonstrated a higher pCO$_2$ resulted in elevated CSFOP. Eidlitz-Markus et al (21) also demonstrated a decrease in CSFOP as sedation was reduced and the child regained consciousness. Pediatric neurologists and neuro-ophthalmologists who perform LPs have suspected that deep sedation can result in even larger increases in CSFOP than have reported. To avoid sedating the child a second time, many LPs are performed immediately after completing a sedated MRI. Because the child has been sedated for approximately 1 hour, clinicians should be aware of the potential false elevation in CSFOP after prolonged sedation.


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Currently, there is no agreed-on sedation protocol for performing a LP. When possible, using a low dose benzodiazepine for anxiolysis or no sedation altogether is preferred to avoid the known increase in CSFOP when undergoing moderate or deep sedation (4). For children who are awake or only receive anxiolysis, they should be monitored closely for agitation, which may increase intrabdominal pressure and falsely elevate the CSFOP (22). To reduce procedural discomfort, application of topical lidocaine-based cream 45 minutes before the LP can obviate the need for a subdermal injection of lidocaine.

**Patient Position**

Most pediatric LPs are performed in the lateral recumbent position with the legs flexed. Although it was commonly believed that the legs had to be extended to obtain an accurate CSFOP, many practitioners were hesitant to move the legs of a sedated or anxious child for fear of needle displacement or arousing the child. The difference of CSFOP between flexed and extended leg position does not result in a clinically meaningful change in CSFOP measures (6,7,23,24). Therefore, it is not necessary to move the awake or sedated child from the flexed to extended position.

**CLINICAL SYMPTOMS**

Headache relief after a diagnostic LP is frequently interpreted as proof that the child has elevated ICP. To date, no study has been performed to either support or refute this interpretation. The analgesic effect of commonly used sedation medications, such as narcotics, benzodiazepines, or barbiturates should be considered when interpreting headache relief after a LP. Furthermore, greater than one third of subjects reported by Michalczyn et al (9) never reported headache or other symptoms of elevated ICP despite having a CSFOP $>$27 cm H$_2$O. Other studies have also reported CSFOP $>$28 cm H$_2$O in subjects without signs or symptoms (including headache) of elevated ICP (3,4,13,14).

**CASE FOLLOW-UP**

Despite continued therapy, the child’s headache persisted. Repeated neuro-ophthalmologic examinations and MRI/magnetic resonance venography remained normal. A third LP demonstrated a CSFOP of 28 cm H$_2$O. Given the lack of therapeutic benefit from medications, an ICP monitor was placed and revealed consistently normal ICP readings (12 cm H$_2$O) over a 48-hour period. Because the child did not meet all of the necessary criteria for IIH (1), he was diagnosed as having chronic daily headache.

**SUMMARY AND RECOMMENDATIONS FOR INTERPRETATION**

The above case highlights both the inaccuracy of CSFOP measures by LP and inherent variability of ICP (25). It further reinforces that a single CSFOP value should not be considered in isolation and as the sole determinant of elevated ICP. When the CSFOP is below 28 cm H$_2$O, the clinician should be reassured that the subject likely does not have elevated ICP, especially in the absence of other objective findings. If clinical suspicion of elevated ICP persists, a follow-up examination is recommended. In children whose CSFOP is greater than 28 cm H$_2$O, it is not recommended that the value be classified as “abnormal,” but instead the clinician should assess both the clinical findings and the circumstances of the LP (i.e., sedation, sedation medications, BMI, and patient agitation during the LP). Clinicians cannot be expected to calculate multivariable regression models in real time to interpret how 1 or more variables (i.e., sedation and BMI) have influenced their patient’s CSFOP. So although a strict cutoff above or below 28 cm H$_2$O can be useful for research purposes, it certainly will not apply to all children. Instead, the threshold of 28 cm H$_2$O should be interpreted in concert with other clinical and examination results to help the clinician make a well-informed assessment of whether a child has elevated ICP.

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Noninvasive Assessment of Cerebrospinal Fluid Pressure
Beau B. Bruce, MD, PhD

Abstract: Measurement of intracranial pressure (ICP) is critical for the evaluation and management of many neurological and neurosurgical conditions. The invasiveness of ICP measurement limits the frequency with which ICP can be evaluated, hampering the clinical care of patients with ICP disorders. Thus, there has been substantial interest in developing noninvasive methods for the assessment of ICP. Numerous approaches have been applied to the problem, although none seems to represent a complete solution. The goal of this review is to familiarize the reader with the currently available methods to noninvasively evaluate ICP.

Measurement of intracranial pressure (ICP) is critical for the evaluation and management of many neurological and neurosurgical conditions. An intraventricular catheter connected to an external pressure transducer is considered the gold standard for ICP measurement (1), but this highly invasive method is only justifiable in neurocritical care settings. Lumbar puncture (LP) typically is used in routine practice to measure ICP, and in the absence of an obstruction, LP opening pressure corresponds closely with the ventricular pressure (2). However, LP is still an invasive, and often painful, test (3) that provides only a snapshot of the ICP, a quantity which varies substantially over time, particularly in certain disease states (1). Therefore, accurate noninvasive methods of assessing ICP would be extremely valuable for monitoring disorders of ICP, although the majority of disorders require an initial sample of the cerebrospinal fluid (CSF) to evaluate its composition.

In infants, the fontanels are open and provide an easy “window” for the noninvasive evaluation of ICP. Indeed, fontanometers have been developed that provide reliable, continuous information about changes in ICP and cerebral compliance (4). In adults, the cranial cavity has very few windows for the noninvasive monitoring of ICP. The difficulty of directly accessing the intracranial contents adds “noise” to measurements and provides other challenges to the estimation of ICP in adults.

Currently, 2 general approaches are available for the noninvasive assessment of ICP: 1) qualitative markers that suggest the possibility of increased ICP and 2) quantitative measures of the patient’s specific ICP or an estimation of the change in ICP after an invasively determined pressure. Although a simple test that definitively differentiates normal from high ICP would have substantial clinical utility, quantitative measures would be even more powerful, particularly for the long-term monitoring of ICP. However, many studies suffer from a critical statistical problem: they report a significant association that exists between a given measure and the mean ICP by a modeling method such as linear regression. However, for a new quantitative marker to be clinically valuable, it must be predictive of a specific individual’s value rather than the mean. For example, one can intuitively see how much easier it would be to predict the average age of the children attending an elementary school than to predict the age of a particular child chosen at random from that school.

Beyond the common symptoms and signs of increased ICP, such as headache, diplopia, transient visual obscurations, nausea, vomiting, sixth nerve palsy, and papilledema, there are numerous qualitative and quantitative approaches to the noninvasive evaluation of ICP, which we will review in the following broad categories: neuroradiologic epiphenomena, ophthalmic, otic, electrophysiologic, and fluid dynamic (Table 1).

NEURORADIOLOGIC EPIPHENOMENA
Several neuroradiologic epiphenomena of increased ICP have been described. In severe head injury, computed
tomography (CT) is frequently used, and several findings have been associated with increased ICP, including absent or compressed basal cisterns and third ventricle, midline shift, and intracerebral hemorrhage (5,6). However, these findings have only been studied in head trauma and are unlikely to be of significant value in other settings. Furthermore, even in head trauma, the predictive value of these findings remains unclear: when Mizutani et al (7) developed a multivariate predictive model using 39 checkpoints, they were only able to predict the ICP within ±10 mm Hg (13.6 cm H₂O) in 80% of patients.

With magnetic resonance imaging (MRI), epiphenomena of increased ICP include empty sella turcica, optic disc protrusion into the globe, flattening of the posterior globe, prominence of the perioptic nerve CSF spaces, tortuosity of the optic nerve, and cerebro transverse venous sinus stenosis (8,9). Some of these findings, both in isolation and combination, have been described in patients with normal ICP (10). However, an increasing number of these epiphenomena occurring in the same patient seem to be associated with a higher likelihood of raised ICP (11). Indeed, 3 or more of these signs occurring in the same patient is extremely suggestive of increased ICP, although there are occasional exceptions (10).

### OPHTHALMIC METHODS

Since the optic nerve sheath is a dural extension, and the perioptic nerve CSF is generally in communication with the cerebral CSF, it is little surprise that the eye is one of the approaches to the noninvasive assessment of CSF pressure.

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CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalography; Hb, hemoglobin; ICP, intracranial pressure; IOP, intraocular pressure; MRI, magnetic resonance imaging; OCT, optical coherence tomography; oVEMPs, ocular vestibular evoked myogenic potentials; RPE, retinal pigment epithelium; SLT, scanning laser tomography; SVPs, spontaneous venous pulsations; TM, tympanic membrane; VEP, visual evoked potential.

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the primary windows available for ICP evaluation. The ophthalmic techniques that evaluate ICP do so through both anatomic and physiologic assessments.

**Spontaneous Venous Pulsations**

Spontaneous venous pulsations (SVPs) are a subtle, rhythmic variation of central retinal vein caliber seen on the optic disc. They occur due to the variation in the pressure gradient caused by differences in the intraocular and CSF pulse pressure as the retinal vein traverses the lamina cribosa (12), and SVPs recently were demonstrated to be in phase with the ICP (13). SVPs are not observed in about 10% of normal patients; so their absence is generally not interpretable (14), but several studies have suggested that SVPs are only present when the ICP is normal (12,14).

A recent prospective study found that the sensitivity of the presence of SVPs for normal ICP was 94% (15), suggesting that SVPs are not 100% sensitive for normal ICP. Interpretation is further complicated because many conditions, such as idiopathic intracranial hypertension (IIH), have fluctuations in the ICP that could allow SVPs to be observed during a period when the ICP is normal (12). Furthermore, SVPs are often evaluated in the sitting position, which leads to a lower and potentially normal ICP compared with the lateral decubitus position in which ICP is typically measured (14).

Absence of SVPs occurs in normal individuals and in many cases of optic disc edema not related to increased ICP (12). In contrast, the presence of SVPs indicates that the intraocular pressure (IOP) is close to the central retinal venous pressure (16). Since central retinal venous pressure correlates closely to ICP, SVPs are a very sensitive sign for normal ICP, but like any diagnostic test, their presence should be interpreted in the context of the overall clinical setting.

**Intraocular Pressure**

IOP is one measure for which the issue of mean vs individual prediction discussed previously is particularly relevant. For example, a highly significant positive association between ICP and the mean IOP has been demonstrated \((P < 0.001)\), but ICP alone only accounts for 10% of the variation on average for a given individual's IOP \((R^2 = 0.109)\) leading to poor accuracy (17). This means that although IOP does generally increase as ICP increases, it is not useful for predicting a given patient’s ICP.

**Venous Ophthalmodynamometry**

Venous ophthalmodynamometry uses the influence of IOP on SVPs, which when present, indicates that the IOP is close to the central retinal venous pressure, by applying pressure to the globe to increase the IOP until the central retinal vein collapses. This external pressure is then added to the baseline IOP, providing the venous outflow pressure that has been shown to closely correlate with the ICP (16,18). A study of 102 patients with extraventricular catheters showed that increased central retinal vein pressure (>30 mm Hg or 40.8 cm H₂O) had an 84% of sensitivity and 93% of specificity for increased ICP (>15 mm Hg or 20.4 cm H₂O); however, this is probably inadequate sensitivity to avoid invasive ICP measurement in most clinical settings.

**Optic Nerve Sheath Diameter**

Several studies of emergency department and neurocritical care patients have demonstrated in controlled conditions that the optic nerve sheath expands linearly in most persons after a pressure threshold is achieved; however, this initial threshold varies between individuals, ranging between 15 and 30 mm Hg (20.4–40.8 cm H₂O) (19). The expansion has been shown to be reversible, at least in the acute setting (19). Ultrasound is the most commonly employed technique to assess the optic nerve sheath diameter, although both MRI and CT have also been used (20,21). Several studies have demonstrated that enlargement of the optic nerve sheath is strongly associated with increased ICP (19,20,22,23). Similarly, the optic nerve sheath has been shown to be enlarged in patients with IIH compared with controls (24).

Although most studies have used an optic nerve sheath cutoff of ≥5 mm, cutoffs from 4.5 to 5.8 mm have been used, and studies have also defined increased ICP by different thresholds, anywhere between 14.7 and 30 mm Hg (20–40.8 cm H₂O) (19,20,22–25). Limitations of ultrasound to assess the optic nerve sheath include other hypoechoic artifacts that can be confused with the optic nerve–optic nerve sheath complex, interexamination variability based on sonographer experience, and the small size of the structure relative to the tiny differences differentiating normal vs abnormal optic nerve sheath diameters (22). These limitations combined with the variety of optic nerve sheath cutoffs proposed, different ICP thresholds evaluated, heterogeneity of populations studied, and variation in methods used make it difficult to determine whether this technique has sufficient sensitivity and specificity for the noninvasive evaluation and monitoring of patients with possible or known disorders of ICP.

**Optical Coherence Tomography**

Although optical coherence tomography (OCT) can be used for quantitative measurement and monitoring the retinal nerve fiber layer (RNFL) in papilledema, there are significant limitations to its use in clinical practice. For example, automated algorithms fail when disc edema is severe and reductions in the RNFL thickness do not necessarily represent improvements in edema, but can instead represent optic nerve atrophy.

Recently, a deflection of the periapillary retinal pigment epithelium (RPE) and Bruch membrane into the eye has been noted in 67% of patients with papilledema; this OCT finding is not typically seen in normal controls or in patients with other causes of disc edema, suggesting its
potential use to differentiate papilledema from other causes of disc edema or pseudo-disc edema (26). Interestingly, the deflections normalized when disc edema resolved, and they correlated with changes in clinical condition. Although this finding requires further validation, it appears likely that evaluation of the peripapillary RPE/Bruch membrane angle by OCT will be another useful technique for qualitatively evaluating and monitoring papilledema. However, whether these findings quantitatively correlate with changes in ICP remains to be shown.

Scanning Laser Tomography
Scanning laser tomography (SLT) represents an alternative method to OCT by which the RNFL can be evaluated. Kupersmith et al (26) have found that SLT shows decreased retardance in regions of early axonal injury. SLT, unlike OCT, may be able to differentiate edema from atrophy in papilledema. Although one study has shown a significant relationship between optic nerve head volume and height with ICP, its predictive ability at the individual level is not sufficient to reliably estimate the ICP (27).

Pupillometry
Quantitative pupillometers can measure subtle changes in the pupillary light response. Taylor et al (28) studied a commercially available handheld pupillometer (ForSite; Neuro-Optics Inc, Irvine, CA) and found that in normal individuals, the pupil size decreases on average by 34% in response to a standardized light stimulus. After head trauma, the response decreased to 20%, and a 10% change was associated with an ICP over 20 mm Hg (27.2 cm H2O) in these patients, suggesting that changes in pupil size measured with a pupillometer may reflect variations in the ICP. However, pupil reactivity is subject to several factors that limit its utility, including certain medical, ocular, and non-ICP related neurological conditions, various medications, the emotional state of the individual, and the time of day (29).

OTIC APPROACHES
Like the eye, the ear has direct communication with the CSF and provides another window for the noninvasive evaluation of CSF pressure. Techniques to estimate ICP related to the ear leverage the direct connection between the perilymph of the cochlea and the CSF in the posterior cranial fossa through the cochlear aqueduct.

Ocular Vestibular Evoked Myogenic Potentials
Ocular vestibular evoked myogenic potentials (oVEMP)s are short-latency electromyographic activity of the extraocular muscles evoked by vestibular stimulation. They can be recorded with surface electrodes beneath the eye contralateral to the stimulated ear. A recent study of 20 healthy volunteers found a decreasing amplitude of oVEMP with increasing head down position, and the authors suggested that oVEMP may be suited for noninvasive ICP monitoring (30).

Tympnic Membrane Displacement
Displacement of the tympanic membrane (TM) can be measured during the acoustic middle-ear reflex. Displacement of the TM is altered when increased ICP translates into increased perilymphatic pressure through the cochlear aqueduct that alters the position of the stapes in the oval window (30).

Although the technique seems to have relatively good test–retest reliability in the same test session, there is substantial intersubject variability. Furthermore, the test is subject to additional limitations: 1) a substantial proportion of the population does not have a patent cochlear aqueduct and 2) pathology along the acoustic middle-ear reflex arc can interfere with measurement (31).

The usefulness of TM displacement for evaluation of increased ICP seems to be limited by its intersubject variability, but its good reliability makes it a candidate for monitoring changes in the status of patients in whom the ICP has already been established by other means (32).

Otoacoustic Emissions
An alternative to TM displacement measurements is otoacoustic emissions (OAEs), a sound generated by the inner ear, which can be evoked by several techniques. In particular, distortion product otoacoustic emissions (DPOAEs) have been shown to change with ICP (33–35). Changes in DPOAEs require a patent cochlear aqueduct but are not subject to the additional components of the middle-ear reflex arc, such as the brainstem, required by TM displacement measurements. Like TM displacement, OAEs are subject to significant intersubject variability with good intrasubject reliability. Therefore, they may also be valuable for monitoring patients when the ICP has already been established by another method.

ELECTROPHYSIOLOGIC METHODS

Visual Evoked Potentials
Two studies by York et al (36,37) in the early 1980s found a relatively strong relationship (R2 = 0.7) between ICP and the N2 latency of the visual evoked potential (VEP) (36,37). No ophthalmic examination seems to have been performed to rule out ophthalmic disease that could affect the VEP, but the strong intrapatient correlations with ICP were quite remarkable (36). More recent studies, however, have suggested that high variability in normal subjects limits the ability of VEP to predict ICP (38).

Electroencephalography
A study of 62 patients showed a relatively strong correlation between a pressure index derived from electroencephalography
(EEG) power spectrum analysis and the invasively determined ICP (39). Further validation of EEG power spectrum analysis will be needed to determine its clinical utility.

**FLUID DYNAMIC APPROACHES**

Ultrasound, MRI, and infrared spectroscopy have been applied to directly study the dynamic changes in ICP, cerebral blood flow, and cerebral compliance.

**Two-Depth Transcranial Doppler**

Two-depth transcranial Doppler assessment of ICP relies on the same principle as blood pressure measurement with a sphygmomanometer. The ophthalmic artery is affected by the ICP intracranially, whereas the extracranial segment can be affected by externally applied pressure to the orbit. The pressure cuff is used to gradually compress the orbital tissues, whereas Doppler ultrasound is used to determine the point at which blood flow in the intra- and extracranial segments of the ophthalmic artery equalizes. At this point, the externally applied pressure is equal to the ICP (40).

Ragauskas et al (40) showed excellent agreement between the absolute ICP determinations using 2-depth transcranial Doppler and those simultaneously measured by LP in a group of patients undergoing neurological evaluation with ICP ranging from 4.4 to 24.3 mm H2O (6–33 mm H2O). Indeed, 98% of patients’ measurements were within ±4 mm Hg (5.4 cm H2O) of the LP determined ICP, a margin of error typical of some invasive monitoring methods, although ±3 mm Hg (4.1 cm H2O) is considered ideal (41). Although this technique seems very promising, a more recent study by the same group reported rather low sensitivity (68%) for differentiating high and low ICP based on a cutoff of 20 mm Hg (27.2 cm H2O) (42).

**Magnetic Resonance Imaging-Based Elastance Index**

MRI using velocity-encoded cine phase-contrast pulse sequences can be used to measure the transcranial blood and CSF volumetric flow rates, which allow a derivation of the ICP through an elastance index (43). ICP predicted by this dynamic MRI method has been shown to have an excellent correlation (R2 = 0.965, P < 0.005) with invasively measured ICP. Likewise, normal values have been shown to be a strong predictor of resolution of symptoms of high ICP in patients with hydrocephalus without surgical intervention (44) and to correlate with the shunt valve opening pressure in children with hydrocephalus (45). Nevertheless, this technique requires further study in a larger cohort of patients to fully evaluate its diagnostic capabilities.

**Ultrasound Time of Flight**

Several techniques for noninvasive ICP evaluation have been developed based on the measurement of acoustic properties of the intracranial structures by the propagation speed and attenuation of ultrasound (46,47). Using advanced signal processing, the dynamic monitoring of the ICP waves can be translated into a noninvasive ICP measurement. In a group of 40 patients with a wide range of ICPs from approximately 0 to 70 mm Hg (0–95 cm H2O), there was a very strong correlation (R2 = 0.99) (47). Like the MRI-based techniques discussed above, further study is needed.

**Near-Infrared Spectroscopy**

Near-infrared spectroscopy is a method by which regional changes in cerebral blood oxygenation, and thereby regional blood flow, can be monitored (48). A study of near-infrared spectroscopy during CSF infusion studies and among patients with traumatic brain injury show that changes in oxygenation correlate with vasogenic ICP slow waves (49). The applicability of these findings to other settings is unclear.

**CONCLUSIONS**

Numerous techniques have been brought to bear on the problem of noninvasive ICP assessment and monitoring, but so far, no individual technique clearly represents a complete solution. It may be possible to improve upon the capabilities of a single method by combining it with other complementary techniques. This approach has already met with some success (50,51).

However, because the diagnostic criteria for many conditions, such as IIH, rely not only upon the ICP itself, but on the CSF contents, even if an accurate noninvasive method of assessing ICP was available, one could not yet fully escape the need for invasive ICP measurements, at least for diagnosis. Possibly as technology advances we will even be able to noninvasively estimate the contents of the CSF. In fact, such a method currently exists for CSF lactic acid (52).

As emphasized by Horton in a recent editorial on the results of the Idiopathic Intracranial Hypertension Treatment Trial, “performing LPs in a patient with IIH is often difficult and erroneous readings of CSF pressure are not uncommon. Even if the opening pressure is recorded accurately, it represents only a single value for a parameter that varies substantially during the course of a normal day. There is an urgent need for a reliable, noninvasive technique to measure human ICP” (53). Although several promising methods have been suggested for the noninvasive assessment of ICP, none is currently reliable for predicting a given patient’s ICP.

**REFERENCES**

State-of-the-Art Review


A 16-Year-Old Boy With a Suprasellar Mass

Madhura A. Tamhankar, MD, Michele E. Paessler, DO, Julia N. Kharlip, MD, Karuna V. Shekdar, MD, Jon M. Burnham, MD, MSCE, Kristina A. Cole, MD, PhD

Dr. Tamhankar:

A 16-year-old man had headaches and nausea for 6 months. He denied visual symptoms, fevers, chills, abdominal pain, weight loss, or loss of appetite; however, he had been experiencing increased thirst and urination for 2 years. Magnetic resonance imaging (MRI) was performed.

Dr. Shekdar:

Initial MRI of the brain reveals a suprasellar mass that is 1.1 x 1.1 x 0.7 cm in dimension, extending along the infundibulum into the suprasellar cistern and abutting the optic chiasm (Fig. 1A, B). This mass appears to extend into the hypothalamus. It is isointense on T1-weighted images and enhances diffusely with gadolinium. The pituitary gland is flattened and displaced, and there is mild displacement of the chiasm. The rest of the brain MRI is normal.

The radiologic differential of this mass causing pituitary stalk thickening and diabetes insipidus includes conditions such as Langerhans cell histiocytosis, sarcoidosis, Wegener granulomatosis, lymphocytic hypophysitis, tuberculosis, and neoplastic lesions such as lymphoma, leukemia, germ cell tumor, craniopharyngioma, and hypothalamic/chiasmal glioma (1, 2).

Drs. Tamhankar and Kharlip:

The patient subsequently underwent an endocrinologic evaluation that revealed hypopituitarism characterized by central hypothyroidism, hypogonadism, growth hormone deficiency, and diabetes insipidus. He was placed on desmopressin acetate and levotyroxine as well as testosterone. Growth hormone replacement was withheld until the nature of the pituitary lesion could be ascertained. He was referred for a neuro-ophthalmologic examination.

The patient’s visual acuity was 20/20 bilaterally with normal color vision and normal pupillary reactions to light stimulation; there was no relative afferent pupillary defect. Automated perimetry (Humphrey 24-2) showed an incomplete bitemporal hemianopia (Fig. 2A). There was bilateral optic disc pallor.

The patient underwent a lumbar puncture with cytology, a bone scan, and a whole-body positron emission tomography/computed tomography (PET/CT), all of which gave normal results. Serum and cerebrospinal fluid (CSF) tumor markers a-fetoprotein (αFP) and β-human chorionic gonadotropin levels were normal. Shortly afterward, the patient underwent a transphenoidal biopsy of the mass.

Dr. Paessler:

The specimen obtained at biopsy demonstrates a dense lymphoplasmacytic infiltrate with scattered plasma cells and few histiocytes with residual pituitary acini in the background and rare germinal centers. The lymphocytes are predominantly small, although there are occasional large transformed lymphocytes (Fig. 3A). No neoplasm is seen. The findings were thought to be most consistent with lymphocytic hypophysitis.

Dr. Tamhankar:

After the diagnosis of lymphocytic hypophysitis, the patient was started on 60 mg of oral prednisone per day for 2 weeks followed by a 4-week taper. His visual fields initially improved (Fig. 2B). Two weeks later, visual acuity in the left eye declined to 20/70, whereas acuity in the right eye remained 20/20. Worsening of visual fields occurred after discontinuation of steroids (Fig. 2C), and another MRI of the brain was obtained.

Dr. Shekdar:

MRI reveals persistence of the mass, which is essentially unchanged compared with the initial scan, except for a new area of enhancement and thickening of the left side of the optic chiasm (Fig. 4).

Dr. Tamhankar:

It was thought that the chiasmal changes represented spread of contiguous inflammation from an inflamed pituitary gland. Given the rapidity of visual loss, the decision was made to treat the patient with intravenous methylprednisolone 250 mg every 4 hours for 3 days. On this regimen, visual acuity in the...
left eye improved to 20/40 along with improvement in visual fields (Fig. 2D). Accordingly, a slower taper of prednisone was instituted over the next 3 weeks from 80 to 60 mg. Follow-up MRI showed reduction in the size of the sellar mass; however, there was persistent, unchanged enhancement, and thickening of the left side of the optic chiasm. Due to the unusual clinical course necessitating prolonged steroid therapy, a review of the original pathology was requested.

**Dr. Paessler:**

The original histology slides were reviewed and additional immunohistochemical stains were performed. These demonstrated that the diffuse infiltrate was composed predominantly of CD20+, CD79a+ B cells (Fig. 3B) and admixture of small CD3- and CD5-positive T cells. Kappa and lambda immunoglobulin light chain stains did not reveal a monoclonal population. CD1a stain was negative, and CD3 and CD5 stains highlighted reactive T cells. Ki67 was positive in a cluster of cells consistent with germinal center B cells. Stains for CD10, BCL1, and BCL6 were non-diagnostic. Given the diffuse B-lymphocytic infiltrate, a small B-cell lymphoma was considered in the differential diagnosis. Attempts were made to test for IgH clonality with molecular methods; however, the tiny focus containing atypical lymphocytes was not present in additional sections, and the test could not be performed.

**Dr. Tamhankar:**

Although lymphoma could not be excluded based on the morphology and immunophenotype of the infiltrate, the findings in this clinical context, coupled with the location of lesion, relative stability of the lesion on MRI over a 5-month period, age of the patient, long duration of previous symptoms, and negative whole-body PET scan were still thought to be compatible with a marked inflammatory response, as seen in lymphocytic hypophysitis.

**Drs. Burnham and Tamhankar:**

Because this was thought to be an aggressive form of lymphocytic hypophysitis, the patient was maintained on 60 mg/d of prednisone for 3 weeks, and then a slow taper of 5 mg of prednisone per week was instituted. He began to experience side effects from chronic steroid use, and it was decided to switch him to a steroid-sparing agent. He was first given mycophenolate mofetil. As further attempts to wean him from prednisone led to visual decline, he underwent plasmapheresis and then given 2 cycles of cyclophosphamide. In addition, because the majority of lymphocytes were CD20 positive, rituximab was added, and prednisone was tapered gradually.
During the next 8 weeks, the patient’s visual fields fluctuated. Vision remained 20/20, right eye, but decreased to 20/50, left eye. On repeat MRI, there was a slight decrease in chiasmal thickening and enhancement (Fig. 5). On tapering the prednisone to 30 mg/d, the patient experienced an acute drop in visual acuity in the left eye to 20/100, associated with worsening of his visual fields (Fig. 2E). Once again, the original biopsy specimen was reviewed.

**FIG. 3.** Transsphenoidal biopsy specimen. **A.** The tissue demonstrates a predominance of lymphocytes (hematoxylin and eosin, ×40). **B.** Immunostaining shows that the majority of lymphocytes are C20 positive (×40). **C.** Atypical cells are present (arrows) (hematoxylin and eosin, ×20). **D.** The large atypical cells show positive staining for CD117 confirming the diagnosis of germinoma (×20). **E.** Characteristic 2-cell pattern of large polygonal germinoma cells (arrows) adjacent to lymphocytes (hematoxylin and eosin, ×63).

**FIG. 4.** Magnetic resonance imaging 5 months after initial presentation. Postcontrast sagittal (A) and coronal (B) T1 images reveal that the sellar mass is unchanged but there is thickening and enhancement of the left side of the optic chiasm (arrow).
We now noted a focal area of large atypical cells amidst the diffuse lymphocytic infiltrate on one of the fragments of tissue. This raised concern for a neoplasm (Fig. 3C). The specimen was sent to the National Cancer Institute, where the original hematoxylin and eosin slides were destained and then restained with CD117. There was positive staining in the large atypical cells (Fig. 3D), consistent with the diagnosis of a germinoma (Fig. 3E).

Dr. Paessler:

The patient underwent a repeat metastatic workup, including CSF cytology and MRI of the spine. No evidence of metastases was found, and serum and CSF germ cell markers remained negative. MRI revealed interval enlargement of the chiasmal mass with extension into the left optic nerve and hypothalamus. Given the imaging findings and a decline in the patient’s visual acuity to 20/100, left eye, he underwent proton beam radiation therapy (total dose: 4,500 cGy). This resulted in significant reduction in the size and enhancement of the sellar and chiasmal lesion and stabilization of his vision (Fig. 6).

Drs. Tamhankar and Cole:

The present case emphasizes the challenges sometimes encountered in establishing a correct etiology for suprasellar and sellar masses when they share similar clinical, imaging, and pathologic features. Lymphocytic hypophysitis and germinoma share similarities not just in their clinical and imaging presentations, but also in pathology, rendering the diagnosis difficult in some patients.

Lymphocytic hypophysitis is a rare autoimmune condition that can involve the anterior pituitary, posterior pituitary, or the entire gland. It accounts for 0.38%–1.1% of sellar masses excised during transsphenoidal surgery (3). Although it is most often seen in young women in the antepartum or postpartum period (4), a variant of lymphocytic hypophysitis involving the infundibulum and neurohypophysis causing diabetes insipidus has been reported in men and children (5,6).

Intracranial germinomas comprise 0.1%–3.4% of all intracranial neoplasms, occurring most commonly in the second decade of life in boys (average age: 12 years). They typically arise from the pineal region and less commonly in suprasellar and ventricular locations (7,8). The incidence of intracranial germinoma is higher in Japan than in America (3.4% vs <1%) (9,10).

Lymphocytic hypophysitis and germinoma can present with similar neurological symptoms and signs including headache, visual loss, hypopituitarism, and diabetes insipidus (4,11,12).

The mechanism of visual loss in lymphocytic hypophysitis is usually mechanical compression of the visual pathways (13–15) or an inflammatory optic neuropathy (5,16,17), as was presumed to be the case in our patient. Inflammatory thickening of the optic nerves can be seen on MRI in patients with optic neuropathy. However, the degree of chiasmal enlargement and enhancement in our patient was unusual for lymphocytic hypophysitis (5,16).

Involvement of the visual pathways by germinoma is rare and generally occurs from suprasellar extension (18–21) or,
rarely, from primary tumor infiltration leading to massive enlargement of the optic nerves or chiasm (22–27). On neuroimaging, both lymphocytic hypophysitis and germinoma can demonstrate thickening of the infundibulum. This finding also can be seen in other entities such as Langerhans cell histiocytosis, sarcoidosis, and other neoplastic lesions (1,2). Germinomas in this region typically arise in the suprasellar space and secondarily involve the pituitary stalk. They are isointense or slightly hyperintense to adjacent brain and diffusely enhance with gadolinium. Cystic areas along with variable enhancement can be seen in germinomas (28). In most patients presenting with an isolated sellar mass, endoscopic biopsy is generally required to make the correct diagnosis (29).

Histologically, lymphocytic hypophysitis is composed of a dense lymphoplasmacytic infiltrate in a background of normal hypophysial tissue with a variable number of B and T lymphocytes, neutrophils, eosinophils, and histiocytes (30). In contrast, in 75% of cases, pathologic examination of germinomas reveals infiltrating lymphocytes adjacent to nests of neoplastic cells in a 2-cell pattern (Fig. 3E). The germinoma cells are large polygonal cells with pale eosinophilic cytoplasm with vacuolation, round nuclei, and prominent nucleoli (31). In 25% of cases, lymphocytes largely outnumber the few isolated neoplastic cells. In such cases, the diagnosis can be extremely challenging, as was the case in our patient (32,33). Germinomas are highly immunogenic tumors and can exhibit the highest degree of tumor-infiltrating lymphocytes among human neoplasia (34). Because germinoma cells were not seen on initial examination, germinoma-specific stains were not obtained.

There are fewer than a dozen case reports of an occult germinoma being diagnosed initially as lymphocytic hypophysitis (4,34–41). In some, there was initial clinical suspicion for lymphocytic hypophysitis, but failure to improve with steroids led to a diagnosis of germinoma that was confirmed by biopsy (36,37). In other cases, special stains such as a CD117 and OCT4 led to the diagnosis of germinoma after failure of the sellar mass to regress with steroids (34,38,39), whereas in others, the initial biopsy was interpreted as lymphocytic hypophysitis and later disproved on repeat biopsy performed due to clinical (40,41) or imaging progression (4). Another diagnostic clue was that the mass either did not respond to steroids, or the response was transient and increase in size of the tumor occurred despite steroid treatment.

Our patient was unusual in that there was regression of the sellar mass with prolonged steroid treatment. It is likely that the intense lymphocytic infiltration was steroid responsive, and thus contributed to tumor shrinkage and led us to believe that the mass was inflammatory. Although there are reports of spontaneous (42,43) or steroid-induced regression (44,45) of intracranial germinomas, this is rare (44). The persistent steroid-refractory chiasmal thickening and enhancement in our patient may represent seeding of germinoma cells within the chiasm (18,19,46).

In summary, it is important to remember that germinomas can be accompanied by an intense lymphocytic infiltration that can make the neoplastic cells difficult to identify on histopathological examination (41). It is important to maintain a high index of suspicion for a germ cell tumor in a young male presenting with a suprasellar mass, diabetes mellitus, and hypopituitarism, particularly as delayed diagnosis and treatment may adversely affect overall survival because of tumor dissemination (47,48).

REFERENCES
Clinical-Pathological Case Study

Do Patients With Neurologically Isolated Ocular Motor Cranial Nerve Palsies Require Prompt Neuroimaging?

Nicholas J. Volpe, MD, Andrew G. Lee, MD

Neurologically isolated ocular motor (third, fourth, and sixth) nerve palsies present frequently to neuro-ophthalmologists. In older patients, microvascular ischemia is a common cause, and most patients recover spontaneously within several months. However, some patients have a more serious cause, including life- and vision-threatening conditions, such as expanding aneurysm, pituitary tumor and apoplexy, and brainstem stroke. The issue of whether to obtain neuroimaging in these patients (subjecting them to added time, expense, and risk of intravenous contrast) or following them over time without scanning (with the risk of missing a potentially treatable disease) is a dilemma faced by every physician, compounded by the increased attention paid to resource allocation and rising health care costs. Two experts weigh in on this topic in this Point Counter Point, using the available evidence to support their point of view.

Pro: Neurologically Isolated, Presumed Vasculopathic Ocular Motor Cranial Nerve Palsies Require Prompt Neuroimaging: Nicholas J. Volpe, MD

The necessity, yield, and effect on ultimate outcome of an acutely performed magnetic resonance imaging (MRI) study in a patient with an isolated ocular motor cranial nerve (CN) palsy is a matter of continued debate. This controversy is fueled by attempts to prospectively determine disease or lesion frequency and, frankly, one that no amount of data, can ever resolve. The reader should consider that there is little debate that the “yield” of such studies is around 5% (1). There is a 1 in 20 chance (much higher if you include third nerve palsies) that such a study could lead to a diagnosis of aneurysm, stroke, or tumor. I ask the reader to simply ask: “What would you really want done if you were the vasculopathic patient with a sixth nerve palsy?” Although we live in an era of increasingly constrained resources and we all must participate in the control of costs by reducing unnecessary care and testing, I would suggest that this clinical scenario is not one in which I would recommend our subspecialty try to control health care costs.

The decision to image or not is at least partially based on a long standing and historical practice pattern that is rooted, in my opinion, in a different era of neuroimaging. Recall the days when an astute neuro-ophthalmologist could save the patient an invasive low-yield procedure, such as an arteriogram or pneumoencephalogram, by diagnosing isolated ocular motor CN palsy on a presumed vasculopathic basis. Fast forward and now imagine a time in which neuroimaging, at least in the United States, is readily available and is ordered and used as a screening tool for symptoms and signs with a much lower frequency of identified pathology. We are in an era in which new treatments for strokes and brain tumors have been developed, and there have been a plethora of case reports of isolated CN palsies from life threatening and highly treatable diseases. Finally, added to that debate, prospective studies (1–3), identifying a significant prevalence of important and identifiable lesions, leads me to recommend that most or all of these patients, particularly those with third and sixth nerve palsies, warrant neuroimaging studies.

There are several considerations that support this decision and, at the outset, we must acknowledge that this is a decision that must be made on an individual basis by clinicians assessing patients with a specific set of symptoms. It is clear that the prevalence of identifiable and, more importantly, treatable pathology where there is evidence that treatment is cost effective and definitely matters (i.e., malignancy) is low. However, the argument that the decision to order an MRI here is not cost-effective or not reducing risk falls short. There is uniform agreement that both complete and partial third nerve palsies should be imaged because of the significant frequency of life-threatening aneurysms. For the fourth and the sixth nerve palsy, the majority of which are due to an ischemic or demyelinating process have an excellent prognosis for spontaneous recovery over 3 months. In these patients, MRI is unlikely to yield...
meaningful results that affect patient management. However, I do not agree that reduced testing in neuro-ophthalmic practice is our moment to be fiscally responsible. The words of Johnston and Hauser (4) urging restraint in contributing to rising health care costs are compelling and factual. Although not specifically studying this group of patients, another study found that neuro-ophthalmologists’ decision to order imaging studies is cost effective in patients with CN palsies (all comers, not just older patients) (5). The advantages of identifying these disorders sooner rather than later are myriad and include improved clinical outcome, patients’ psychosocial benefit, and avoiding the perception that appropriate diagnosis was delayed by a clinician’s ignorance. In addition, other common neuro-ophthalmic scenarios in which MRIs are commonly ordered have a similarly low yield. For instance, unexplained facial or eye pain or unexplained, nonprogressive, unilateral optic atrophy are conditions shown to have a similar lower yield on neuroimaging studies even when ordered by an expert (6,7). Although I am aware of the societal fiscal issues related to responsibly caring for our population, that should never interfere with an individual physician’s decision to order testing for an individual patient. There is a long list of tests that we order on our patients, also with low yield although often with high stakes, that have never been proven to be cost effective. Similarly, we have adopted many “expensive” behaviors (e.g., serial optical coherence tomography in various optic neuropathies) that have not been proven to impact patient outcomes, but still remain an important part of our tool box and assist the clinician trying to make the best possible decision for an individual patient.

The studies performed by Chou et al (2), Murchison et al (3) (single center), and Tamhankar et al (1) (multicenter) have attempted to guide clinical decision making. Each study has its potential flaws and biases and, in fact, the reader could likely use any of the studies to support the decision to image or not to image. In each of these studies between 1% and 16% of patients (depending on which study and which subset of patients analyzed), all evaluated by neuro-ophthalmologists and presumed to have vasculopathic ocular motor cranial neuropathies were found to have various conditions ranging from stroke, cerebral hemorrhage, pituitary apoplexy, aneurysm, and benign and malignant brain tumors. These important conditions were detected in patients who would have otherwise been thought to have vasculopathic CN palsy.

Furthering the case for imaging, creating restricted guidelines might lead to a false sense of security and reassurance in the hands of a non-neuro-ophthalmologist who is not as experienced in recognizing the subtleties of cases that demand further attention. We can assume that the experienced neuro-ophthalmologist can recognize patterns of human disease and variances that will inform his or her decision to image (the tempo at which symptoms develop or some subtle-associated symptom or examination finding). However, a blanket statement about isolated CN palsies in vasculopathic patients not needing neuroimaging studies, unless they fail to recover, is likely to provide nonexperts with a false sense of assurance in clinical situations that are really not straightforward. Given the relatively low access to neuro-ophthalmologists, it seems prudent to recommend imaging studies in the setting of all patients with isolated ocular motor CN palsy.

It is not appropriate for us to conclude, through generalization, that treating some of these patients for their identified condition “would not have mattered” or has not been proven to improve outcomes. I think that the reader would certainly want to know whether they had a brainstem stroke causing a sixth nerve palsy vs a normal MRI and presumed vasculopathic palsy. Similarly, the presence of pituitary apoplexy or a small structural lesion such as an aneurysm is high-stakes diagnoses that require prompt attention. As modern imaging studies evolve, and our ability to image CNs in a more detailed fashion increases, the argument that we might gain a better understanding of the mechanism of these palsies, or discover previously unknown abnormalities, may also prove to be important.

In some cases, a false sense of security, both for the doctor and for the patient, can come from a clinical course of spontaneous resolution. Spontaneous resolution by no means excludes important pathologies. Certainly, for most brainstem strokes, the clinical symptom of an isolated cranial nerve palsy will spontaneously resolve. Spontaneous resolution of ocular motor CN palsies has been described in the setting of structural skull-based lesions (8). These lesions may not require immediate or urgent treatment or might declare themselves at a later date, but ultimately in this era of available treatments and patients perception of “sooner would have been better,” most would argue for prompt diagnosis and subsequent decision making in the setting of skull-based neoplasms.

Ultimately, we agree that each clinician must decide what age, what risk factors, what clinical scenario (pretest likelihood), and what access and availability issues affect his or her decision to image patients. My work and that of others on this topic is meant to guide this decision, and I agree that there is insufficient data to force or mandate a practice pattern. However, one must acknowledge, based on the reported studies, that there is a small but significant yield from these diagnostic tests and that clinically patients with structural lesions are not easily distinguished from their counterparts with the more innocent vasculopathic palsy. Clinicians must decide, based on the case in front of them, whether the information obtained from an MRI could matter to this particular patient. If one considers the various circumstances in neuro-ophthalmic practice where MRIs are ordered, isolated ocular motor CN palsies should be added to the list of where neuroimaging could prove helpful. I believe that the yield is high enough to allow for this to be “cost effective” for an individual patient.
Con: Patients With Neurologically Isolated, Presumed Vasculopathic Ocular Motor Cranial Nerve Palsies Do Not Require Initial Neuroimaging: Andrew G. Lee, MD

I do not disagree with my colleague that neuroimaging has an important role in the evaluation of many ocular motor cranial neuropathies; instead it is my contention that the value of such imaging in neurologically isolated, non-third nerve-related, and presumed vasculopathic ocular motor CN palsies is limited and ultimately not cost effective. My arguments against neuroimaging in this setting include: 1) high cost, 2) low yield in this clinical setting, and 3) the lack of significant impact on the treatment plan or prognosis for the majority of patients.

High Cost

Cranial MRI is expensive, and a complete head and orbit study with fat suppression and intravenous contrast adds a significant additional cost. In an editorial on the cost of stroke imaging in Annals of Neurology, Johnson and Hauser (4) wrote that “Neurologists can no longer ignore the headlines about rising healthcare costs. Setting aside the politics and the biases, it is undeniable that the costs of healthcare in the United States continue to rise at an alarming rate that will either bankrupt us or force us to ration. We have all seen the numbers. US healthcare costs accounted for 16% of total gross domestic product (GDP) in 2008, well above all other large countries, with France a distant second at 11% of GDP. Worse yet, healthcare costs are rising faster than GDP and, if unchecked (an impossibility), are predicted to bring down the US government and the competitiveness of our businesses.” Likewise, we as neuro-ophthalmologists also must face the reality of cost containment and the utilization and yield of neuroimaging. We as specialty leaders also need to stand firm in our conviction that our clinical judgment and pretest likelihood of disease (e.g., vasculopathic etiology) still counts for more than any test including neuroimaging.

Murchison et al (3) prospectively studied 93 patients (older than 50 years) with acute isolated ocular motor cranial mononeuropathies. Although 4 of these 93 patients (4%) had lesions on MRI, only 1 (1%) had a lesion related directly to the cranial mononeuropathy. The total modeled cost of imaging spent for these 93 patients was $131,688 to determine an underlying cause in only 1 patient and in whom there was no ultimate change in treatment. These authors concluded that “it may not be medically necessary to perform MRI scanning on every patient with an isolated CN III, IV, or VI palsy.” In my opinion, it is very difficult to justify the high cost of negative neuroimaging for the majority of patients with an acute and neurologically isolated mononeuropathy secondary to ischemia to find the 1 treatable lesion.

Low Yield

Tamhankar et al (1) performed a prospective study to estimate the proportion of patients presenting with isolated third, fourth, or sixth nerve palsies of presumed microvascular origin vs other more concerning intraocular causes. These authors evaluated 109 patients, aged 50 years or older, with acute isolated CN palsies all of whom had an MRI of the brain. Among these 109 patients, there were 22 who had palsies of the third nerve, 25 of the fourth nerve, and 62 of the sixth nerve. A cause other than presumed microvascular ischemia was identified in 18 patients (16.5%; 95% confidence interval, 10.7–24.6). As expected, the presence of vasculopathic risk factors (e.g., diabetes, hypertension, hypercholesterolemia, coronary artery disease, myocardial infarction, stroke, and smoking) was significantly associated with a presumed microvascular cause (P = 0.003, Fisher exact test) but these vasculopathic risk factors were also present in 11/18 patients (61%) with other causes. In the group of patients who had vasculopathic risk factors only with no other significant medical condition, 8/80 (10%) were found to have other causes. These alternative etiologies included midbrain infarction, neoplasm, inflammation, pituitary apoplexy, and giant cell arteritis (GCA). If the patients with third nerve palsies and GCA were excluded, then the prevalence of other causes of fourth and sixth nerve palsies was 3/64 (4.6%). The authors concluded that for “acute isolated ocular motor nerve palsies, a substantial proportion of patients had other causes, including neoplasm, GCA, and brain stem infarction” and that “brain MRI and laboratory workup have a role in the initial evaluation of older patients with isolated acute ocular motor nerve palsies regardless of whether vascular risk factors are present.”

I believe that a strong case can be made using the same data from this report to conclude the opposite: those patients with neurologically isolated ocular motor cranial neuropathy should not undergo neuroimaging because the yield is low overall (i.e., 16.5%) for finding an alternative etiology. If third nerve palsy and GCA are removed from the cohort, the yield drops to 4.6%. I would argue that obtaining a brain MRI in these patients actually might harm the patient because a CT angiogram (CTA) or magnetic resonance angiography (MRA) study are typically the first line studies for third nerve palsy and MRI of brain in GCA would be expected to be normal.
Thus, ordering an MRI in these settings might delay diagnosis, provide a false sense of security for etiology, and add the cost neuroimaging.

There is already considerable clinical evidence to support the concept that a third nerve palsy does not carry the same clinical significance for harboring a serious underlying intracranial problem as an isolated fourth or sixth nerve palsy, and that combining all 3 ocular motor cranial nerve palsies is not a valid method of imaging yield for all cranial mononeuropathies.

In my clinical practice and in the literature, the most common etiologies for fourth nerve palsy are congenital, traumatic, and ischemic, and the yield for neuroimaging in this setting is extremely low. Third nerve palsy, in contrast, especially incomplete palsies (e.g., divisional palsies) or pupil-involving palsies, are especially dangerous, and the presence of vasculopathic risk factors would not dissuade me from imaging for aneurysm (e.g., CTA or MRA) even when neurologically isolated. Likewise, a sixth nerve palsy, even in isolation, is potentially more dangerous than a fourth nerve palsy and may be due to a clival or cavernous sinus lesion. In addition, sixth nerve palsy is also of concern because of the possibility of a nonlocalizing sign of increased intracranial pressure.

Lack of Impact on Treatment Plan or Prognosis

Another prospective study (9) evaluated the use of MRI in 43 consecutive patients with acquired sixth palsies, and causative lesions were identified in 27 of 43 patients (62.8%). However, the median age of these patients with lesions on initial imaging was 43 years compared with 56 years in the patients with normal MRI results, and individual case details were lacking to determine whether a “reasonable and prudent” neuro-ophthalmologist would have judged the sixth nerve palsy to be isolated or presumed vasculopathic. Another prospective study (2) evaluated ocular motor cranial mononeuropathies and included only patients older than 50 years. Nine of 66 patients (13.6%) had a cause other than a microvascular etiology but unfortunately included 9 patients with pupil-involving third nerve palsies and 10 patients with partial third nerve palsies (who I would have imagined [e.g., CTA and MRI/MRA]). In fact, 2 of these patients were found to have aneurysms. Thus, the actual diagnostic yield for neuroimaging was 7 of 66 patients (10.6%). The most frequent finding in this study was meningioma (3/7 patients), and it is unlikely that these cranial neuropathies would have resolved spontaneously. A delay in diagnosis during an observation period likely would have had no impact on the final treatment or prognosis for meningioma. Excluding these patients, the diagnostic yield would be mere 4/66 patients (6.1%).

Based on 1) the high cost of neuroimaging, 2) the low yield of imaging in the appropriate clinical setting, and 3) the lack of change based on such imaging on the treatment plan or the prognosis for the majority of patients, I do not believe that neuroimaging is warranted for every vasculopathic patient with an acute, neurologically isolated, ocular motor cranial neuropathy. Ultimately, patients and doctors should be free to make an informed choice based on pretest likelihood of disease and an individual risk-to-benefit decision analysis and I do not believe that neuro-ophthalmologists should be forced into any single evaluation paradigm that mandates expensive and potentially unnecessary testing. Such unnecessary testing, mandated by a published paradigm, risks bankrupting our country’s health care finances.

Volpe Rebuttal

A palsy is not always just a palsy, and I believe part of the problem is that we are analyzing third, fourth, and sixth nerve palsies together. I share my colleague’s concern about the high cost, low yield, and a lack of change in management as highly intuitive and largely evidence based. This argument could guide decisions about large populations and the allocation of limited health care resources as a model of health care delivery. Isolated ocular motor CN palsy is not a clinical setting in which an MRI will uniformly lead to a high-yield diagnosis or one that would usually impact a patient’s management with a specific result. That being said, I would urge the reader to think again about what they would want done if it were themselves and whether in their minds there is a value to a 5% identification rate of conditions such as brainstem stroke, pituitary apoplexy, or a skull-based neoplasm or vascular lesion.

In addition, I wonder if we are only disagreeing about fourth nerve palsies. My colleague specifically writes about his own clinical practice and informs the reader that third nerve palsies are almost always imaged with MRI and MRA or CTA. He goes on to state that sixth nerve palsies in isolation are potentially more dangerous because of clival or cavernous sinus lesions and the possibility of sixth nerve palsy being nonlocalizing due to elevated intracranial pressure. Are we willing to concede that third and sixth nerve palsies warrant imaging? I would add to the sixth nerve palsy argument that the yield has certainly shown to be high enough in people younger than 50 years (seemingly an arbitrary cutoff). Perhaps 55, 60, or 70 years is the new 50 for this diagnosis? In the end, I do not recommend doing yet another multicenter prospective trial to determine the yield of imaging studies on elderly patients with isolated fourth nerve palsies. For these patients, I am willing to concede!

Lee Rebuttal

Dr Volpe asks the reader to consider “What would you really want done if you were the vasculopathic patient with a sixth nerve palsy?” I would argue that the answer is “it depends.” Neuroimaging is not always benign, and these studies can uncover incidental and unrelated pathology (e.g., frontal or falk meningioma) that can increase rather than decrease patient anxiety and may lead to further unwarranted studies. In addition, gadolinium contrast in MRI has some risks especially in patients with renal failure (e.g., nephrogenic systemic dermopathy) that might
preclude appropriate use of contrast or produce unwanted side effects. Finally, if the question really is “What would the readers of our journal really want to do if they developed a vasculopathic sixth nerve palsy?” then I would imagine that they would answer: “I would like to make my own decision after appropriate informed consent and an individualized analysis of risk, benefit and cost.” The clinician’s role is to provide sufficient information to the patient to make a decision and not to make the decision per se unless specifically asked to do so.

CONCLUSIONS

Every patient presenting with an isolated ocular motor CN palsy potentially harbors a serious underlying cause, and the diagnosis of a treatable condition can be vision or life-saving. Before ordering neuroimaging, we all perform a formal or informal risk stratification assessment, based on a variety of factors, such as age, vasculopathic risk factors, associated clinical findings, the pretest probability of identifying a causative lesion, and the time and cost of the scan. It is also worth acknowledging that although our neuroimaging capacities are constantly improving, the ever-increasing sensitivity is not necessarily accompanied by increasing specificity, so an MRI might not show a causative lesion, but uncover unrelated findings, or “incidentalomas” that require further testing. Although we tend to lump third, fourth, and sixth nerve palsies together, our experts argue convincingly that not all CNs are created equally, and we can use our knowledge about anatomy and pathophysiology to identify the patients at the highest risk for serious underlying pathology, with the highest yield for neuroimaging.

REFERENCES


Importance: Acetazolamide is commonly used to treat idiopathic intracranial hypertension (IIH), but there is insufficient information to establish an evidence base for its use.

Objective: To determine whether acetazolamide is beneficial in improving vision when added to a low-sodium weight-reduction diet in patients with IIH and mild visual loss.

Design, Setting, and Participants: A multicenter, randomized, double-masked, placebo-controlled study of acetazolamide in 165 participants with IIH and mild visual loss who received a low-sodium weight-reduction diet. Participants were enrolled at 38 academic and private practice sites in North America from March 2010 to November 2012 and followed up for 6 months (last visit in June 2013). All participants met the modified Dandy criteria for IIH and had a perimetric mean deviation (PMD) between −2 and −7 dB. The mean age was 29 years, and all but 4 participants were women.

Interventions: Low-sodium weight-reduction diet plus the maximally tolerated dosage of acetazolamide (up to 4 g/d) or matching placebo for 6 months.

Main Outcomes and Measures: The planned primary outcome variable was the change in PMD from baseline to Month 6 in the most affected eye, as measured using a Humphrey field analyzer. PMD is a measure of global visual field loss (mean deviation from age-corrected normal values), with a range of 2 to −32 dB; larger negative values indicate greater vision loss. Secondary outcome variables included changes in papilledema grade, quality of life (Visual Function Questionnaire 25 [VFQ-25] and 36-item Short Form Health Survey), headache disability, and weight at Month 6.

Results: The mean improvement in PMD was greater with acetazolamide (1.43 dB, from −3.53 at baseline to −2.10 dB at Month 6; n = 86) than with placebo (0.71 dB, from −3.53 to −2.82 dB; n = 79); the difference was 0.71 dB (95% confidence interval [CI]: 0–1.43 dB; P = 0.050). Mean improvements in papilledema grade (acetazolamide: −1.31, from 2.76 to 1.45; placebo: −0.61, from 2.76 to 2.15; treatment effect: −0.70; 95% CI: −0.99 to −0.41; P < 0.001) and vision-related quality of life as measured by the National Eye Institute VFQ-25 (acetazolamide: 8.33, from 82.97 to 91.30; placebo: 1.98, from 82.97 to 84.95; treatment effect: 6.35; 95% CI: 2.22–10.47; P = 0.003) and its 10-item neuro-ophthalmic supplement (acetazolamide: 9.82, from 75.45 to 85.27; placebo: 1.59, from 75.45 to 77.04; treatment effect: 8.23; 95% CI: 3.89–12.56; P < 0.001) were also observed with acetazolamide. Participants assigned to acetazolamide also experienced a reduction in weight (acetazolamide: −7.50 kg, from 107.72 to 100.22 kg; placebo: −3.45 kg, from 107.72 to 104.27 kg; treatment effect: −4.05 kg; 95% CI: −6.27 to −1.83 kg; P < 0.001).

Conclusions and Relevance: In patients with IIH and mild visual loss, the use of acetazolamide with a low-sodium weight-reduction diet compared with a diet alone resulted in modest improvement in visual field function. The clinical importance of this improvement remains to be determined.

Acetazolamide has been the “standard of care” for treatment of mild visual loss in patients with idiopathic intracranial hypertension (IIH) for years. However, we now have evidence from this multicenter, double-masked, randomized, controlled clinical trial that acetazolamide provides modest improvement in visual function as measured by perimetric mean deviation. There was also an improvement in the grade of papilledema and quality of life measures.

There are numerous limitations to this study, some nicely outlined in the accompanying editorial by Horton (1). First, those enrolled most often had only mild visual loss, limiting the ability to show benefit. This was necessary because those with more severe visual loss who are more likely to benefit would not be eligible for a placebo arm of the study. Indeed, those with more severe papilledema had more benefit than those with milder papilledema. Additionally, a weight-loss program was included, and those on acetazolamide lost more weight than those on placebo.

The NORDIC IIHTT is likely the most important multicenter clinical trial in neuro-ophthalmology since the ONTT, helping to move our field forward from one of the describing phenomenology on individual experiences to an evidence-based subspecialty. Although it helps put us “on the map,” we need more studies to overcome headlines like this from the May 9, 2014 issue of ASCRS EyeWorld Weekly Update as it reported on the IIHTT:

“Glaucome drug improves vision in women with IIH.”

Someday we hope to see “Neuro-Ophthalmology drug improves vision in patients with glaucoma.”

—Mark L. Moster, MD

Six subjects on acetazolamide were hospitalized for kidney stones, elevated liver function, pancreatitis, and diverticulitis. There was 1 subject with an allergic reaction and 1 with hypokalemia. We are not told what dose of acetazolamide they were taking.
were on. The treatment paradigm for the IIHTT called for increasing the Diamox as tolerated up to 4 g/d. I do not know that I can fully recommend that strategy. However, in this study, the mean maximal dose was 2.5 g/d, and the IIHTT suggests that this dose is relatively safe, so there may be a significant “wiggle room” to move up from the standard 1 g/d that many folks use. I have seen less than 1% of my patients develop kidney stones on an average of 1 g/d and none have developed pancreatitis or elevated liver function tests. This may be a dose-related issue.

—Michael S. Lee, MD

REFERENCE


Purpose: To compare the risk of developing compressive optic neuropathy in patients with active thyroid eye disease (TED) treated with corticosteroids with or without orbital radiotherapy.

Design: A retrospective single-center case–control study.

Methods: The clinical charts of 351 patients with active TED who received corticosteroids with or without orbital radiotherapy between 1999 and 2010 were reviewed. Patients with compressive optic neuropathy at the time of presentation were excluded. Group 1 received corticosteroids only and Group 2 received corticosteroids and orbital radiotherapy. The primary outcome measure was the development of compressive optic neuropathy. Secondary outcome measures were changes in other parameters indicating the activity or severity of TED including soft tissue inflammation, diplopia, ocular motility restriction, and appearance.

Results: There were 144 cases in Group 1 and 105 in Group 2. Both groups were matched for age, gender, and stability of thyroid function. The 2 groups differed only in the modality of treatment for active TED. The main indication for treatment in both groups was soft tissue inflammation. Corticosteroids were initiated at an average of 2.6 months in Group 1 and 2.5 months in Group 2 after symptom onset. Group 2 received orbital radiotherapy on an average of 4.2 months after the initiation of corticosteroid therapy, and 8% of the cases were intolerant to corticosteroids. At an average of 3.2-year follow-up, compressive optic neuropathy had developed in 17% (n = 25) of Group 1 and 0% of Group 2 (P < 0.0001), on average 5.5 months after the initiation of corticosteroid therapy. Although both groups experienced a significant reduction in periocular inflammation, the radiotherapy-treated group demonstrated a significantly greater improvement in ocular motility.

Conclusions: The rate of compressive optic neuropathy was significantly lower and improvement in ocular motility greater in patients receiving orbital radiotherapy in addition to corticosteroids. Patients with active TED seem to have an effective and sustained response to orbital radiotherapy combined with corticosteroids, which is protective against disease progression and the development of compressive optic neuropathy.

In this retrospective study, patients with active thyroid eye disease (TED), defined as a score of >4 on the VISA classification, were offered 50 mg of oral prednisone. If the response was positive, then the patient was given 250–500 mg IV Solu-Medrol weekly and tapered slowly. Investigators offered fractionated, orbital external beam radiation therapy (XRT) to patients with any of the following characteristics: 1) double vision, 2) ophthalmoplegia, or 3) poorly responsive to, intolerant of, or dependent on corticosteroids. Both groups began steroids approximately 2.5 months after presentation, and the XRT group received radiation at an average of 6.7 months after presentation. Interestingly, compressive optic neuropathy did not develop in the XRT group but occurred in 17% of the steroid-only group at an average of 8.1 months after presentation.

This study continues to add to the debate on the efficacy of orbital XRT in active TED. There were reasonable number of patients in each group, and both groups had similar doses of corticosteroids making XRT the main difference in treatment. The biggest limitation here is the selection bias—not all patients were given the option of orbital XRT. However, I like that patients received orbital XRT relatively early into the course of their disease. Overall, I have not been a big fan of orbital XRT for TED. I use it, but not that often. This article raises my interest level in considering it.

—Michael S. Lee, MD

Michael, I agree that the main limitation may be the selection bias you have noted. Another confounding issue is that 48% of those with compressive optic neuropathy were on disease-modulating agents besides corticosteroids. The patients who received these agents were those with aggressive disease who for various reasons were not given XRT, including systemic vascular disease. It is possible that they are at a higher risk of developing compressive optic neuropathy.

XRT did show benefit on subjective diplopia and objective ocular motility measurements in these patients. With the above limitations noted, it is likely that XRT also may protect some from developing compressive optic neuropathy.

—Mark L. Moster, MD

Objective: To study the prognostic importance of Horner syndrome (HS) in patients with internal carotid artery dissection (ICAD) or vertebral artery dissection (VAD).

Methods: In this observational study, characteristics and outcome of patients with ICAD or VAD from the CADISP (Cervical Artery Dissection and Ischemic Stroke Patients) database were analyzed. The presence of HS was systematically assessed using a standardized questionnaire. Patients with HS (HS+) were compared with HS− patients. Crude odds ratios (ORs) with 95% confidence intervals and ORs adjusted for age, sex, center, arterial occlusion, bilateral dissection, stroke severity, and type of antithrombotic treatment were calculated.

Results: We analyzed 765 patients (n = 496 with ICAD, n = 269 with VAD, n = 303 prospective, n = 462 retrospective). HS was present in 191 (38.5%) of the patients with ICAD and 36 (13.4%) of the patients with VAD (P < 0.001). HS+ ICAD patients presented less often with stroke or TIA (P < 0.001), less often had bilateral (P = 0.019) or occlusive (P = 0.001) dissections, and had fewer severe strokes (P = 0.041) than HS− ICAD patients. HS+ ICAD patients had a better functional 3-month outcome than those without HS (ORcrude = 4.0 [2.4–6.7]) and also after adjustment for outcome-relevant covariates (ORadjusted = 2.0 [1.1–4.0]). HS+ ICAD patients were less likely to have new strokes than HS− ICAD patients (P = 0.039). HS+ VAD patients more often had vessel occlusion (P = 0.014) than HS− patients but did not differ in any of the other aforementioned variables.

Conclusions: In patients with ICAD, HS is an easily assessable marker that might indicate a more benign clinical course. HS had no prognostic meaning in patients with VAD.

In clinical practice, we often see isolated Horner syndrome (HS) as the presentation of an internal carotid artery dissection (ICAD). In the past, almost all of these patients were treated with anticoagulation, but there has been a move toward antiplatelet agents in the stroke community even in acute cases and, with either treatment, patients have done relatively well. This study looked at the prognosis of the presence or absence of HS (not necessarily isolated), and the main finding was that there were fewer strokes and less severe strokes if HS was present. The authors postulate that an HS presentation may represent a more benign tear in the outer wall of the internal carotid artery, compared with those that are closer to the inner wall that spare the sympathetic fibers. The findings are consistent with prior reports of a less-frequent stroke risk with HS than other presentations. Nonetheless, the stroke risk is still high, and it is hard to predict who is at risk and we still have to figure out the optimal treatment.

Not surprisingly, in vertebral artery dissection, the presence of a HS made little difference because in those cases the Horner syndrome is a manifestation of the brain stem infarct, rather than related to any fibers in the vertebral artery.

—Mark L. Moster, MD

About 85% of the ICAD without HS and 37% of the ICAD with HS had a stroke or transient ischemic attack (TIA) at baseline. We know that patients with stroke or TIA are more likely to experience another stroke. In this study, after adjusting for age, gender, medical facility, vessel occlusion, bilateral ICAD, and anticoagulation, HS− patients were more likely to have a stroke in the following 3 months. However, they did not adjust for stroke/TIA at baseline. I wonder if they had performed this, whether it would have changed the “protective effect” of HS. Did the greater likelihood of stroke among those who did not have HS occur because they had more strokes at baseline rather than the HS itself?

—Michael S. Lee, MD


Purpose: To examine the influence of experimentally reduced cerebrospinal fluid pressure on retinal nerve fiber layer (RNFL) thickness and neuroretinal rim area of the optic nerve head.

Methods: The experimental study included 9 monkeys that underwent an implantation of a lumbar–peritoneal cerebrospinal fluid (CSF) shunt. In the study group (n = 4 monkeys), the shunt was opened to achieve a CSF of approximately 40 mm H2O, whereas the shunt remained closed in the control group (n = 5 monkeys). At baseline and in monthly intervals thereafter, optical coherence tomographic and photographic images of the optic nerve head and RNFL were taken of all monkeys.

Results: Two of the 4 monkeys of the study group showed bilaterally a progressive reduction in RNFL thickness between 12% and 30%, reduction in neuroretinal rim area and volume, and an increase in cup/disc area ratios. A third monkey developed a splinter-like disc hemorrhage in 1 eye. The fourth monkey of the study group did not develop morphologic changes during follow-up, nor did any monkey of the control group.

Conclusions: Experimental and chronic reduction in CSF in monkeys was associated with the development of an optic neuropathy in some monkeys.

In this experimental animal study, the investigators implanted a programmable lumbar-peritoneal shunt into 9 rhesus monkeys. The valve was not opened in 5 control monkeys, and the valve was set to achieve a cerebrospinal fluid pressure (CSFP) of 4 cm H2O in 4 monkeys. The CSFP, measured intraoperatively and postoperatively, declined in the study animals from 7.4 mm Hg (10 cm H2O) at baseline to less than 2 mm Hg (2.7 cm H2O) for the study. The CSFP did not change significantly in the control animals. The following parameters were assessed at baseline and monthly for 1 year: retinal nerve fiber layer (RNFL) thickness, optic nerve head area, neuroretinal rim area, and cup-to-disc ratio. At 1-year follow-up, 2 monkeys showed progressive thinning of the mean RNFL of 20–30 μm.
The area of the neuroretinal rim significantly decreased and the cup-to-disc ratio significantly increased. The other 2 study animals and the control animals had no appreciable changes in the study parameters, but 1 low-pressure monkey had a disc hemorrhage. The intraocular pressure did not change over the study period in either group, and no morphologic changes of the lamina cribrosa were observed.

This has implications for patients with glaucoma or with low CSFP. Ren et al (1) found a significantly lower CSFP among patients with low-tension glaucoma compared with controls. There have been 2 reports of optic neuropathy associated with spontaneous intracranial hypotension (2,3). I have observed patients with idiopathic intracranial hypertension progressively lose vision after receiving a shunt. I have thought of the visual loss occurring despite maximally lowering the CSFP, but perhaps a component may be because the CSFP was maximally lowered.

—Michael S. Lee, MD

There is a small growing literature supporting the importance of trans-lamina cribrosa pressure (intraocular pressure – intracranial pressure [ICP]) in the pathogenesis and prognosis of glaucoma. However, the studies in humans are limited by the measurement of ICP at 1 point in time, during a lumbar puncture. Animal studies like this one will help clarify the true importance of translaminar pressure differences in patients with both glaucoma and papilledema.

—Mark L. Moster, MD

REFERENCES


Objective: To monitor the changes in optic nerve sheath diameter (ONSD) induced by acute exposure to hypobaric hypoxia and to investigate the factors associated with these changes, including the development of acute mountain sickness (AMS).

Methods: In this cohort study, neurologic signs and symptoms, cardiovascular parameters, and ultrasonography of ONSD were prospectively assessed in 19 healthy lowlanders at baseline and after ascent to 3,830 m (3 hr, 9 hr, 24 hr, 48 hr, 72 hr, and 8 d) by blinded investigators. Potential confounding factors (e.g., altitude variations and physical effort) were minimized. A multivariate analysis of factors associated with ONSD was performed by means of generalized estimating equations.

Results: ONSD increased with exposure to altitude in all participants (P < 0.001). The increase between 9 and 24 hours was larger in patients who developed AMS (P = 0.001). There was no influence of sex, oxygen saturation, or acclimatization on ONSD.

Conclusions: Both physiologic and pathologic responses to hypobaric hypoxia were independently associated with changes in ONSD. Studies on a larger cohort, at a range of altitudes, and with baseline neuroimaging techniques are necessary to further understand the clinical significance of increased ONSD during exposure to hypobaric hypoxia.

This small study demonstrated an increase in optic nerve sheath diameter (ONSD) within 3 hours of reaching 3,830-m altitude by helicopter with further increase at 24 hours and a parabolic pattern, decreasing a little at 72 hours and then stable until 8 days. The 3 patients who developed acute mountain sickness (AMS) had a greater increase in ONSD between 9 and 24 hours than those without AMS. If these findings hold up in larger studies, then orbital ultrasound may be used clinically to predict AMS presymptomatically with possible earlier intervention.

This article is another example where examination of the eye provides insights into neurologic disease.

—Mark L. Moster, MD

Obviously, the change in ONSD is the greatest concern here, but the differences in technique and results of the ultrasound are worth noting. In this study, the authors describe placing the probe on the temporal part of the closed upper eyelid. The mean baseline ONSD was 5.45 mm when measured 3 mm behind the globe. Others have reported that the upper limit of normal is 3 mm and that patients with papilledema are more apt to have ONSD greater than 3.3 mm (1). This likely has to do with probe placement and angle of imaging.

—Michael S. Lee, MD

REFERENCE


Importance: Retrospective studies have demonstrated disparate outcomes after acute optic neuritis in individuals of African descent compared with individuals of white race/ethnicity. However, published analyses of the prospectively
collected Optic Neuritis Treatment Trial (ONTT) data identified no association between worse visual outcomes and black race/ethnicity.

**Objectives:** To investigate the associations of age, sex, and race/ethnicity with visual outcomes after acute optic neuritis through application of longitudinal data analysis techniques to the ONTT data set.

**Design:** Secondary analysis of the ONTT (a prospective randomized controlled trial) data set. Our models included effects of treatment (placebo, oral prednisone, or intravenous methylprednisolone), time, and treatment × time interaction, as well as demographic covariates of age, sex, and race/ethnicity.

**Setting and Participants:** The ONTT data were collected at multiple centers in the United States. Patients of black (n = 58) and white (n = 388) race/ethnicity with acute optic neuritis who enrolled in the ONTT within 8 days of symptom onset were included in the analyses.

**Main Outcomes and Measures:** The contrast sensitivity (CS) and visual acuity (logMAR) in the affected eye were modeled using 2-stage mixed-effects regression techniques. All available follow-up data from baseline to 15 to 18 years were included.

**Results:** The data identified no relationship of age, sex, or treatment with CS or visual acuity outcomes. Race/ethnicity was significantly related to CS (P < 0.001) and visual acuity (P < 0.001) for a 15-year period after acute optic neuritis, with black race/ethnicity being associated with worse scores for both.

**Conclusions and Relevance:** Race/ethnicity seems to be associated with CS and visual acuity outcomes in affected eyes after acute optic neuritis. To our knowledge, this is the largest cohort of black race/ethnicity with acute optic neuritis to be studied and represents the first evidence from a prospectively collected data set to support a hypothesis of race/ethnicity-dependent visual outcomes of acute optic neuritis.

The authors downloaded the publically available data set from the Optic Neuritis Treatment Trial (ONTT) to assess visual outcomes based on race. The original ONTT publications compared cross-sectional visual outcomes at each follow-up visit and found no racial differences in outcomes. Moss et al used longitudinal data analyses, which better model changes in individual outcomes and differences between groups. These analyses also are less affected by missing data points. The authors found that black race/ethnicity was significantly associated with poorer visual acuity and contrast sensitivity (CS) at baseline and all time points for the 15-year follow-up. These data comport with other studies that have shown worse outcomes for patients of black race/ethnicity. The reasons for these findings are unclear and may be biologic, socioeconomic, or due to other factors.

I find it fascinating that newer statistical models can uncover significantly different observations from original publications, and it makes me wonder what other large studies could have different findings based on reanalysis of the data. It is great that these data are publically available. I went to the following Web site and downloaded the ONTT data for myself: http://lons.jaeb.org. It comes as a zip file with multiple data tables. I have not taken a look at the data yet, but who knows what one might find?

—Michael S. Lee, MD

This reevaluation of ONTT data found poorer visual acuity (VA) and CS at all times in the black patients. The authors claim “the magnitude of the effect is within the range of significant changes based on the variability of the Pelli-Robson test and is clinically significant because of correlations between CS and vision-associated quality of life.” However, if one looks at the graphs of the recovery in blacks and whites, the visual outcome is very similar for both, and the logMAR VA is very close to 0.0 even in the black population.

An additional concern that was raised by the authors is that the ONTT data were analyzed before our current neuro-myelitis optica (NMO) diagnostic criteria. Indeed, NMO, with its much poorer recovery in even a few patients could shift the recovery curve to the degree reported in this study.

The authors quote 2 other studies, showing poorer outcome in patients of African descent. These were also before our current understanding of NMO and one of the studies (1) is clearly describing a different population of patients. This retrospective study of 10 patients in South Africa included 8 of the 10 cases with bilateral involvement, 8 of the 10 with optic disc edema (mild to severe), and none (of 6 patients who had a cerebrospinal fluid examination) with oligoclonal bands. These features contrast with the ONTT population and really represent atypical optic neuritis.

—Mark L. Moster, MD

**REFERENCE**

Dr. Airy’s “Morbid Affection of the Eyesight”: Lessons From Teichopsia Circa 1870

Frederick E. Lepore, MD

Abstract: Hubert Airy’s iconic drawing of his own migraine visual aura for which he coined the term, “teichopsia,” conveys important lessons for the contemporary clinician. His observations of the expansion (“build-up”), minification/magnification, and color/achromatopsia of migrainous teichopsia are consistent with (and possibly anticipatory of) the later discoveries of cortical spreading depression, cortical magnification of primary visual cortex (V1), and specialized cortical centers for color vision.

When results of detailed physical examination or post-mortem findings were unavailable, the 18th century physician relied exclusively on his powers of observation. Such was the case in 1870, when Hubert Airy (1) created the iconic image of his own visual aura (Fig. 1) recognizable to migraineurs over 140 years later.

Although Airy’s contribution to the fields of neurology and ophthalmology immeasurably helped to define classic migraine, he never used the term “migraine.” As implied by the title, “On a distinct form of Transient Hemiopsia,” Airy sought to describe (and illustrate) his episodic “half-blindness.” The accuracy of his meticulous observations of movement/expansion, regional miniaturization/magnification, and color of his visual aura anticipated present-day concepts of visual neuroanatomy and neurophysiology and provide illuminating lessons for the present-day clinician.

Hubert Airy was a 31-year-old Cambridge-matriculated MA, MD, when his account of visual symptoms was read before the Royal Society. Over the preceding 16 years, he had experienced “transient hemiopsia” “much oftener” than a 100 times. His salient observations included:

1. Gradual enlargement over 20 to 25 minutes of a horseshoe-shaped arch with an advancing “zigzag” margin followed by scotoma identically in both eyes.
2. The serrated margin “varied with changing gleams of red and blue and yellow and green, and orange.”
3. The size of the “teeth” of the serrated margin were of variable size: “small and fine” near his central point of visual fixation and “larger and larger” with increasing distance from fixation.
4. Near the end of the visual aura, his “headache comes on gradually.” (In 1865, his migraineur father, Sir George Airy (2), the Astronomer Royal, described similar obscurations of vision without headache).

Airy recognized the “inaccuracy and insufficiency” of the term “hemioepia” and proposed teichopsia (from the Greek “town-wall” and “vision”) in its stead. A birds-eye view of the zigzag layout of walls enclosing a medieval fortified town (3) was evocative of “the bastioned form of transient Hemiopsia” that Airy pictured in his report.

LESSON 1: BUILD-UP

In Airy’s account, his teichopsia was a dynamic process, which would enlarge slowly at first and then more rapidly as it progressed to “gradual occupation of one (lateral) half of the field of view.” This build-up of the fortification spectrum is a hallmark of classic migraine (4) and over 70 years later, led Lashley (5) to speculate on the pathogenesis of the visual aura as he timed the progression of his own “scintillating scotomas.” Airy lacked an accurate map of primary visual cortex, and this deficiency was not to be remedied until 13 years after his death by the retinotopic schema of visual cortex derived from Gordon Holmes’ (6) study of head wounds during the Great War. Lashley proposed that a “wave of strong excitation” traversed 67 mm of visual cortex from occipital pole to rostral calcarine cortex during the 20 minutes’ migration of his visual aura, and he calculated the rate of propagation of this disturbance at 3 mm/min or less. But what was this “wave”?

Although the underlying pathophysiology of teichopsia is still unknown, a potential neural mechanism came to light in 1944, when Leao’s (7) stimulating bipolar electrodes elicited a wave of depolarization progressing across rabbit cortex at 3–5 mm/min followed by depression of spontaneous neuronal electrical activity, the phenomenon of cortical spreading depression (CSD). The similar rates of
progression of Lashley’s aura and Leao’s CSD led Milner (8) to posit in 1958 that migraine scotomas are the conscious experience of CSD. In 2001, Hadjikhani et al (9) found that using magnetic resonance imaging (MRI), the average velocity of blood oxygenation level-dependent (BOLD) signal migration on extrastriate cortex during classic migraine (without teichopsia) to be $3.5 \pm 1.1$ mm/min. Tempering the assertion that BOLD signal change is a surrogate for CSD is the absence of any recording of electroencephalographic changes of CSD in migraine patients (10), and the uncertainty whether BOLD signal strength is due to excitatory or inhibitory neurophysiological mechanisms (11).

LESSON 2: MINIFICATION/MAGNIFICATION

Airy observed that the formed elements (teeth) of his teichopsia were small and fine near the point of visual fixation ("sight-point") and "large-toothed towards the periphery of the field." A plausible explanation for minification in the center of the visual field would await Holmes’ (6) wartime evidence of "cortical magnification" of the central visual field. In 1991, Horton and Hoyt (12) found that "55% of the surface area of primary visual cortex is devoted to the representation of the central 10° of vision." Such cortical magnification would presuppose that in the case of 2 identically sized patches of visual cortex undergoing teichopsia-producing migrainous "discharges," the size of the visual elements would seem smaller when generated by the patch of cortex at the occipital pole and larger when generated by the patch subserving peripheral field in anterior calcarine cortex. This was borne out by Brindley and Lewin (13) who demonstrated variability of phosphenes produced by electrical stimulation with $0.8 \times 0.9$ mm platinum electrodes applied to cortex of a blind glaucoma patient. A phosphene produced within 10° of fixation seemed as a "very small spot of white light" and phosphenes elicited more than 20° from fixation were larger ("clouds"). Other scientist migraineurs including Lashley (5), Grusser (14), and Airy (2) also documented that the visual elements of migraine aura seem larger with increasing distance from the fixation point of vision.

In addition, the perceived velocity of teichopsia is not uniform as observed by Airy (1), but rather seems to migrate more slowly because the wave of CSD, which is propagated at a constant rate, traverses the region of cortical magnification subserving central vision, and seems to move more quickly in the peripheral field of vision as CSD passes across regions of cortical minification (15).

LESSON 3: COLOR IS DISSOCIABLE FROM TEICHOPSIA

Although Airy’s fully developed teichopsia was “splendid with large gleams of blue and red and green,” color was not an invariable accompaniment, and Airy devotes nearly a page to the “total absence of color” during the teichopsia experienced by Sir Charles Wheatstone, a famed British scientist and inventor. In an effort to explore the variable relationship of color to teichopsia, I asked my patients with classic or acephalgic migraine if their visual aura seemed in migrainous patches of visual cortex undergoing teichopsia-producing migrainous "discharges," the size of the visual elements would seem smaller when generated by the patch of cortex at the occipital pole and larger when generated by the patch subserving peripheral field in anterior calcarine cortex. This was borne out by Brindley and Lewin (13) who demonstrated variability of phosphenes produced by electrical stimulation with $0.8 \times 0.9$ mm platinum electrodes applied to cortex of a blind glaucoma patient. A phosphene produced within 10° of fixation seemed as a "very small spot of white light" and phosphenes elicited more than 20° from fixation were larger ("clouds"). Other scientist migraineurs including Lashley (5), Grusser (14), and Airy (2) also documented that the visual elements of migraine aura seem larger with increasing distance from the fixation point of vision.

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Where in the visual pathway could this dissociation of color from form take place? Although wavelength (as distinguished from color) perception could be selectively disrupted at the level of retinal cones (16) or parvocellular layers (17) of the lateral geniculate nucleus (LGN), the center-surround receptive fields of retinal ganglion and LGN neurons would be unlikely sources for the complex geometry of teichopsis. Within the primary visual cortex (V1), dysfunction of wavelength detecting blob cells and unimpaired function of the orientation-selective interblob cells could account for perception of achromatopsic complex forms. Possibly, the distinctive function and metabolism of blob cells using cytochrome oxidase and the presence of double-opponent receptive fields could be subjected to selective metabolic vulnerability during migraine aura (17).

The cortical region that “is critical for color vision,” is V4 complex located in the fusiform gyrus (18). V4 receives input from blob cells through the “thin stripes” of V2 and transcends “simple” wavelength detection with its capacity for color constancy when viewing objects illuminated with light of varying wavelengths. Zeki (18) contends that color constancy relies on the brain’s ability to take a ratio of light of any waveband reflected from a surface and its surrounds. Although Zeki notes that it is “impossible to detach color completely from form,” patients with lesions of the fusiform gyri (and V4) can accurately see forms and shapes, but they lack color. Could migraine-induced selective stimulation of V1 without involvement of V4 account for colorless visual auras? Possibly it could, if CSD travels, as posited by Hansen et al (15) “in a nonconcentric manner across different cortical regions” with variable effects on some portions of visual cortex while sparing others.

Alternatively, could the association of the teichopsis of Airy with color be due to an anatomic (or physiologic) pairing of the fusiform gyrus and the site(s) of origin of teichopsis? Several supporting lines of anatomical evidence include the abnormally thickened occipital lobe (V3A) cortex and subjacent white matter in migraineurs (19) and the internally generated percept of color in grapemone-color synesthesia, which occurs in the setting of increased anatomical connectivity of the fusiform gyrus (20). Blob and interblob cells notwithstanding the dichotomy between orientation-selective and wavelength-sensitive neurons in V1 is not absolute. There are neurons in primate V1 (and V2) that respond to both form and color (21), and these could conceivably underlie migraineous colored teichopsis.

WHEN TEOICHIOPSIS?

Hubert Airy pursued a career in British public health as a Medical Inspector with the Local Government Board and published articles on topics in natural history such as bird flight (22), but he never again wrote on the topics of neurology or ophthalmology. In his long and enduring contribution to clinical neuroscience (1), Airy (23) conceded that “it is impossible at present to do more than guess at the locus morbi,” but he nevertheless speculated “that the seat of the affection must lie at some point behind the chiasma.” Airy’s assignment of the “visual derangement” to the brain and not to the eyes was of fundamental importance. The persistence of the descriptive but inaccurate diagnosis of “optical migraine” reminds the contemporary clinician of Airy’s revolutionary conceptualization of migraine as a brain disorder.

The quest to localize teichopsis has continued to the present. The distinctive geometric configuration led Richards (24) to posit ocular dominance columns, and Shams and Plant (25) to propose the orientation-specific cells in V1 “interblobs” as neural substrates for teichopsis. However, the hypothesis of V1 as a starting point for visual aura should be questioned after Hadjikhani et al (9) reported initial BOLD signal changes on MRI in V3A in a migraineur with aura of white “TV snow.”

With his exacting characterization of teichopsis as a “Photograph of a morbid process going on in the brain,” Airy ushered an archetypal visual hallucination into the realm of brain biology. This was no mean feat! Seven hundred years earlier migraine auras were apprehended as “the Fall of the Angels” by Hildegard of Bingen (26). Airy surveyed a world of internally generated visual perceptions which, at times, resembled Alice’s Adventures in Wonderland published 5 years earlier by Lewis Carroll, a migraineur, who had been introduced to Airy’s account of teichopsis by Latham’s pamphlet “On Nervous or Sick-Headache” (27). In “normal” visual perception, we know that “no matter how hard you try, you can’t see the world in black and white; nor can you see only the left (or right) half of your field of view” (28). These normative rules of perception were broken by Airy’s description of teichopsis consisting exclusively of internally generated percepts (29).

What had begun as an attempt “to collect and record facts” (Airy’s italics) about “a morbid affection of the eye-sight” was, in retrospect, a groundbreaking exploration of a little known region of conscious visual experience. Brought forth in the 33rd year of Queen Victoria’s reign, Airy’s magisterial delineation of teichopsis continues to inform, instruct, and challenge clinicians.

REFERENCES

Pediatric Optic Nerve Sheath Meningioma

We read with great interest the report by Nabavizadeh et al (1) regarding the rare occurrence and aggressive behavior of optic nerve sheath meningioma in the pediatric population (2,3). We had the opportunity to evaluate a 10-year-old girl with a 2-month history of progressive left proptosis. Brain magnetic resonance image (MRI) demonstrated a left intraorbital mass with thickening of the orbital portion of the optic nerve with intense and heterogeneous contrast enhancement. The provisional diagnosis was optic nerve glioma. Two months later, MRI showed enlargement of the mass with extension to the orbital apex but without evidence of intracranial invasion (Fig. 1). Because of rapid tumor growth, the patient underwent frontotemporal craniotomy for tumor excision. Histopathology of the specimen showed fragments of optic nerve surrounded and infiltrated by round aggregates of cells with eosinophilic cytoplasm, round-to-oval uniform nuclei with some pseudoinclusions. No necrosis and mitotic figures were found. Immunohistochemical staining revealed diffuse cytoplasmic epithelial membrane antigen expression, confirming a meningothelial origin (Fig. 2). Progesterone receptor, glial fibrillary acidic protein, leukocyte common antigen, and S-100 were negative. Ki-67 labeling index was 6%–7%, and Bcl-2 labeling index was 15%–20%. The final diagnosis was meningothelial meningioma, WHO Grade I, with recommendation of careful follow-up because of the Ki-67 index. No recurrence of disease was documented on MRI 3 months later.

Clinical behavior of primary optic nerve sheath meningioma seems more aggressive in pediatric patients than in adults, with rapid visual decline and greater likelihood of intracranial extension and recurrence. Although established

**FIG. 1.** Magnetic resonance imaging of left optic nerve sheath meningioma in the axial plane. (A) T2, (B) precontrast T1, (C) postcontrast T1.

**FIG. 2.** Histopathology of neoplasm. A. The optic nerve is infiltrated with aggregates of cells containing cytoplasm and uniform nuclei. Necrosis and mitotic figures are absent (hematoxylin and eosin, ×100). B. Immunohistochemical staining shows tumor cells are positive for epithelial membrane antigen (×200).
guidelines are lacking, reports in the literature of optic nerve sheath meningioma in children support surgical excision (2–5). In our patient, rapid progression documented with MRI and the immunohistochemical pattern of a Grade I meningioma with negative progesteron receptor combined with a strongly positive Bcl-2 immunoreaction and Ki-67 proliferative index >3% indicated aggressive behavior of the neoplasm (6).

Distinguishing optic nerve sheath meningioma from optic nerve glioma with MRI early in the clinical course may be difficult with neuroimaging (2,3). Gliomas usually are characterized by fusiform enlargement with kinking and tortuosity, with no calcification and variable contrast enhancement. Optic nerve sheath meningiomas often lead to tubular enlargement with homogeneous texture and smooth or slightly lobulated peripheral margins, presence of calcifications, and homogeneous contrast enhancement (7,8). Our case confirms that pediatric optic nerve sheath meningioma is uncommon, but may grow rapidly, exhibiting more aggressive clinical behavior than its adult counterpart.

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The authors report no conflicts of interest.

REFERENCES

Optic Neuritis in the Setting of NMDA Receptor Encephalitis

We read with great interest the report by Sawanura et al (1) on anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. We evaluated a patient who experienced optic neuritis (ON) with optic disc swelling in the setting of anti-NMDAR encephalitis relapse. No evidence of tumor was detected.

A 29-year-old otherwise healthy man experienced acute generalized tonic–clonic seizures preceded by severe daily headaches, acute left-sided weakness, and dysarthria. Systemic work-up was normal including autoantibodies (anti-nuclear, anti-DNA, anti-Ro, anti-La, lupus-like anticoagulant, anticardiolipin, anti-beta2-glycoprotein, and anti-neutrophil cytoplasmic antibodies) as well as cryoglobulins, complement levels, angiotensin-converting enzyme, rheumatoid factor, ammonia and lactate levels, and Coomb test. Serologies were negative for Borrelia burgdorferi, HIV-1 and 2; hepatitis A, B, and C; venereal disease research laboratory test; chlamydia; and mycoplasma. A cerebrospinal fluid (CSF) study revealed lymphocytic pleocytosis with 512 cells per milliliter, elevated protein of 1.64 g/L, normal glucose, and positive oligoclonal bands. CSF PCR testing for herpes simplex virus, varicella-zoster virus, cytomegalovirus, human herpesvirus 6, and enterovirus were all negative. Brain magnetic resonance imaging (MRI) showed a right frontal cortical hyperintensity on T2 and fluid-attenuated inversion recovery (FLAIR) sequences. There was abnormal slow activity in the delta range, predominantly in the right hemisphere on the electroencephalogram (EEG). A diagnosis of presumed lymphocytic meningitis was established. The patient received intravenous methylprednisolone (1 g/day) for 5 days and phenytoin with a clinical improvement. Three months later, brain MRI was unremarkable and the patient was symptom free.

Three years later, he was readmitted to hospital because of headache and fluctuating motor and sensory deficits on the left side. Visual function was normal, but there was mild weakness in the left arm and touch impairment. Brain MRI revealed right frontotemporal hyperintensity without contrast
Letters to the Editor: Optic Neuritis in the Setting of NMDA Receptor Encephalitis

We read with great interest the report by Sawanura et al (1) on anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. We evaluated a patient who experienced optic neuritis (ON) with optic disc swelling in the setting of anti-NMDAR encephalitis relapse. No evidence of tumor was detected.

A 29-year-old otherwise healthy man experienced acute generalized tonic–clonic seizures preceded by severe daily headaches, acute left-sided weakness, and dysarthria. Systemic work-up was normal including autoantibodies (anti-nuclear, anti-DNA, anti-Ro, anti-La, lupus-like anticoagulant, antipartial 2-glycoprotein, and anti-neutrophil cytoplasmic antibodies) as well as cryoglobulins, complement, antiphospholipid, anti-DNA, anti-Ro, anti-La, lupus-like anticoagulant, antiphospholipid, antithrombin, and antithrombin III antibodies. Serologies were negative for Borrelia burgdorferi, HIV-1 and HIV-2, hepatitis A, B, and C, veneral disease research laboratory test; chlamydia; and mycoplasma. A cerebrospinal fluid (CSF) study revealed lymphocytic pleocytosis with 512 cells per milliliter, elevated protein of 1.64 g/L, normal glucose, and positive oligoclonal bands. CSF PCR testing for herpes simplex virus, varicella-zoster virus, cytomegalovirus, human herpesvirus 6, and enterovirus were all negative. Brain magnetic resonance imaging (MRI) showed a right frontal cortical hyperintensity on T2 and fluid-attenuated inversion recovery (FLAIR) sequences. There was abnormal slow activity in the delta range, predominantly in the right hemisphere on the electroencephalogram (EEG). A diagnosis of presumed lymphocytic meningitis was established. The patient received intravenous methylprednisolone (1 g/day) for 5 days and phenytoin with a clinical improvement. Three months later, brain MRI was unremarkable and the patient was symptom free.

Three years later, he was readmitted to hospital because of headache and fluctuating motor and sensory deficits on the left side. Visual function was normal, but there was mild weakness in the left arm and touch impairment. Brain MRI revealed right frontotemporal hyperintensity without contrast...
enhancement (Fig. 1). EEG did not show epileptic discharges and CSF analysis was normal. Ten days after admission, the patient complained of painless blurred vision. Visual acuity was 20/60 in the right eye and 20/20 in the left eye, with a right relative afferent pupillary defect. On visual field testing, there was a central scotoma in the right eye and peripheral constriction in the left eye. Ophthalmoscopy showed marked right optic disc swelling (Fig. 2).

The patient was treated with intravenous methylprednisolone (1 g/day) for 5 days. When steroids were tapered, he developed altered mental status with disorientation, psychomotor agitation, visual hallucinations, and disorganized behavior. MRI revealed abnormal signal along the entire right optic nerve and similar change along the prechiasmatic portion of the left optic nerve (Fig. 3). Tumor serological markers and extensive panel of paraneoplastic antibodies in serum were negative (anti-Hu, anti-MA1/2, anti-CV2/CRMP-5, anti-amphiphysin). NMDAR antibodies were detected in CSF (2). NMO-IgG/AQP4 antibodies were negative, but antibodies to myelin oligodendrocyte glycoprotein (MOG-Ab) were found both in serum and CSF (3). Additional work-up for malignancy, including thoracic, abdominal, and pelvic computed tomography, as well as a whole-body positron emission tomography and testicular ultrasound failed to reveal evidence of tumor.

The patient was diagnosed with anti-NMDAR encephalitis and given 5 days of intravenous immunoglobulins (0.4 g/kg), which led to a dramatic improvement of symptoms and neuroimaging findings. Two months later, visual acuity was 20/20 in both eyes, with normal visual fields and mild optic disc pallor in the right eye.

To the best of our knowledge, this is the first case of optic neuritis (ON) occurring in an adult patient with anti-NMDAR encephalitis. Two of the previously reported cases of ON were in Asian children (4,5), who experienced relapsing ON superimposed upon the typical symptoms of

**FIG. 1.** Fluid-attenuated inversion recovery (FLAIR) imaging. **A.** At the onset of relapse, there is cortical hyperintensity (arrows) in the right frontal lobe. **B.** Improvement of the imaging abnormality (arrows) 3 months later.

**FIG. 2.** There is right optic disc edema with peripapillary hemorrhage and tortuosity and dilation of retinal veins. The left fundus is normal.
NMDAR encephalitis. In both cases, no other antibodies were detected, including NMO-IgG/AQP4 antibodies. A third case was a 15-year-old girl who developed most of the symptoms of NMDAR encephalitis and had NMDAR antibodies (6). The patient later experienced recurrent longitudinally extensive transverse myelitis and ON fulfilling the Wingerchuk criteria for NMO (7), despite NMO-IgG/AQP4 seronegativity.

In our patient, there was acute ON with right optic disc swelling and neuroimaging abnormalities of both optic nerves. In keeping with the favorable prognosis of NMDAR encephalitis (8), he was free of visual and neurological symptoms 2 months after beginning the treatment. Our patient did not have an underlying teratoma, which is not surprising given that only 6% of young male patients with anti-NMDAR encephalitis have an associated tumor (8). We detected MOG-Ab in the serum and CSF of our patient. The presence of this antibody may indicate an overlap of autoimmune mechanisms in patients with blend phenotypes. Unlike IgG/AQP4, which appears to be the pathogenic in NMO, the role of MOG-Ab remains to be established and deserves further investigation.

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REFERENCES


James A. Sharpe, MD, FRCP(C) (1941-2013)

James Arthur Sharpe, stalwart neuro-ophthalmologist, researcher, mentor and friend, passed away peacefully at home on November 12, 2013 at age 72 from complications of bladder cancer.

Jim was born and raised in Brantford, Ontario, the only son of John Ernest and Lavina Mae Sharpe. He decided early in life that he wanted to pursue a medical career and obtained his Doctor in Medicine from the University of Western Ontario in 1966, graduating as valedictorian. He spent the next 6 years training between Montreal and Toronto in medicine, ophthalmology, neurology and neuropathology. Then, between 1972 and 1974, Jim completed four separate fellowships, including neuro-ophthalmological stints in San Francisco (with Dr. Hoyt), Miami (with Drs. Daroff and Glaser) and London (with Dr. Sanders).

Fresh from his academic world travels, Dr. Sharpe joined Dr. J.L. Silversides in establishing the first neuro-ophthalmology clinic in Toronto. Jim was a superb clinician, serving as a final word on obscure and unusual problems upon referrals from all over Canada. He ran a busy outpatient and inpatient consultation service for over 30 years, seeing patients almost until the end. Jim expected residents and fellows to present cases accurately and efficiently, and many a trainee experienced a tense moment when historical or examination details were not crisply described. There were also droll moments in clinic, mostly of the “absent-minded professor” variety, when, immersed in a fog of clinical concentration, Dr. Sharpe would walk out of the exam room wearing the patient’s spectacles rather than his own.

During his training, Jim developed a fascination for describing and measuring eye movement disorders. One of his early achievements in Toronto was the development of a state-of-the-art magnetic search coil laboratory. His inquisitive mind and relentless work ethic led him to a sustained and vibrant record of research and clinical publication, which included over 180 papers and book chapters and 6 books. Some of this work reflected carefully planned inquiries into normal human physiology or the disorders imposed by focal brain lesions or degenerative states. Other investigations were of the classical opportunistic type, carefully teasing out the basis of abnormality in a unique patient. Jim’s knowledge of neuroanatomy was legendary; many a fellow was taken to task for a lack of intimacy with the Olszewski-Baxter atlas of brainstem cytoarchitecture. One of Jim’s favorite collaborators was the late David Tomlinson, PhD, whose primateneurophysiology laboratory was next door to the human ocular motility suite. Joint discussions of the latest work in cat, rabbit or monkey eye movements often led to an investigation of normal physiology in *Homo sapiens*, with fellows and lab assistants frequently serving as subjects. Dr. Sharpe contributed to our understanding of normal smooth pursuit, saccadic and vestibular eye movements and to the disorders that arise from focal brain lesions and degenerative conditions like Alzheimer’s and Parkinson’s diseases.

A continuous stream of over 30 fellows was drawn from around the world by Dr. Sharpe’s reputation for clinical and research excellence. They were rewarded with a phenomenal start to an academic career. Of course, this did not necessarily come easily. To fellows and residents, Jim was a man of few wasted words, presenting a stern visage that encouraged maximal effort. One’s first clinic days had a strong “sink-or-swim” quality. One greenhorn, naively expecting a day off after driving 2500 miles across North America after residency, was told that he was expected in clinic promptly at 8:00 AM the following day. Another recalls Dr. Sharpe leading him into a room on his first day, seeing a patient sitting expectantly at the Goldmann perimeter and being told to complete the unfamiliar test without delay.

Jim was without equal as a research mentor. He was particularly generous of his time when it came to reviewing research projects and drafting papers. Many hours were typically spent discussing fellow’s attempts at technical prose, focusing on Jim’s copious written corrections, all of which were scrawled in red ink with an unmistakable left-handed tilt. Rich debates often ensued on the nuances of the English language and new words (or unfamiliar Canadian spellings) frequently entered most trainees’ personal lexicons. Looking back upon our time with him, it appeared that Jim formulated career development plans for us without ever openly discussing them. Fellows were thus assigned to projects of ever-increasing difficulty, unaware that a scheme for success had been put into place. As a tribute, Jim’s fellows organized a well-attended symposium in his honor in September 2009.

Dr. Sharpe rose quickly through the ranks of academia, becoming a Professor of Neurology, Ophthalmology, and Otolaryngology at age 45. As one of the foremost neurologists in Canada, he served as Head of the Division of Neurology at the University of Toronto from 1989-2002.
and as Editor-in-Chief of the Canadian Journal of Neurological Sciences from 1991-1999. He worked as an editor or reviewer for many other journals and as a course director or participant at meetings worldwide. Jim greatly enjoyed sharing his latest results with colleagues at meetings, most of them highly technical eye movement studies that might not have seemed as attractive to those more interested in afferent problems. As a founding member of the humorously-named “Square Wave Jerk Club”, Jim took the resultant good-natured ribbing in stride.

Dr. Sharpe was particularly proud of his role in organized neuro-ophthalmology. He was an early and active member of the Rocky Mountain Neuro-ophthalmology Society and its successor, the North American Neuro-ophthalmology Society (NANOS). He served on the NANOS Board for 12 years, including two years as President (1992-1994), and was given the group’s Distinguished Service Award in 2004. He served as President of the International Neuro-ophthalmology Society from 1998-2000.

In his off time, Jim was a humble and devoted family man who took delight in his children and grandchildren. He was an avid golfer who spent many happy hours on his home course, the Brantford Golf and Country Club. He bought a sailboat and learned to ply the waters of Lake Ontario and the North Channel of Lake Huron. He was also an enthusiastic skier whose optimism was such that he bought a new pair of skis a few months before passing, believing that he would have plenty of opportunity to use them. Jim is survived by his children, Jason, Peter and Katie, his fiancée Adrienne, his former wife Evie and a growing roster of grandchildren. He will be missed by all.

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A Tribute to Dr James Arthur Sharpe

Jim was a world-renowned neurologist and neuro-ophthalmologist who was known for his great and inquisitive mind. His brilliance was evident early in his life, when he was the valedictorian of his graduating medical class at the University of Western Ontario. He became fascinated by how the brain and the eye worked together and decided to pursue a neurology residency at the University of Toronto. After residency, his thirst for knowledge and scientific curiosity led him to complete not 1, 2, or 3, but 4 fellowships in neurophysiology and neuro-ophthalmology—something that could definitely qualify him for the Guinness book of world records. It is no surprise that after his formal training, he became a rising star as an academic physician and leader. He quickly ascended through the ranks to become a full professor of neurology, ophthalmology, and otolaryngology at the University of Toronto, when he was only 45 years old. Three years later, he became the head of neurology at the University of Toronto, a role he served for 13 years until 2002.

Jim was also a prominent scientist and a giant in the field of eye movement research. He had published seminal papers in a wide variety of topics that were truly groundbreaking. He was instrumental in advancing our field and was recognized internationally as a pioneer. He served as the President of the North American Neuro-Ophthalmology Society, as well as the Editor-in-Chief of the Canadian Journal of Neurological Sciences. Of all the awards he was honored to receive, the one that he was most proud of was the Distinguished Service Award, the highest award given by the North American Neuro-Ophthalmology Society.

Jim has mentored numerous neurology and ophthalmology residents, fellows, and students. Many of his trainees have in turn become expert clinicians and scientists, professors, and departmental chairs all over the world. The spontaneous outpouring of emotions in response to his death reveals how much he meant to his trainees and colleagues and how deep we feel the loss of a cherished mentor and a genuine friend.

I have known Jim since I was a first year ophthalmology resident. For those of us who have been a resident in Toronto, I think you too will remember that time in your lives and understand why I was quite intimidated by Jim in the beginning, as we all know he held very high standards. He introduced me to the vertiginous, yet intriguing, world of nystagmus, the dizzying yet fascinating world of vestibular disorders, and the blindingly complex and yet captivating world of neuro-ophthalmology. I became so inspired by him—not only did I become his fellow, I also did a PhD with him to explore the exciting world of critical thinking, scientific discovery, and meticulous research. In fact, Jim was so meticulous that I still fondly remember his “infamous red pen” and the countless number of drafts we went through together with each article we published. I must say though, while he had high expectations and kept raising the bar for me, he was always kind, patient, and thoughtful with a great sense of humor.

We, who worked with Jim, know him to be the consummate detective in solving the most mysterious cases. In fact, he was a “doctor’s doctor.” Many of us would send him the most difficult and complex patients that we could not figure out. He would always come up with the most marvelous diagnosis, complete with an explanation of the relevant brain pathway and a recitation of the pertinent article, the authors, the year it was written, and the name of the journal where it was published!

We also know that Jim had some challenges with his bedside manner. He reminded me of Colombo, a detective TV character who was absolutely brilliant in getting to the truth. Just like Colombo, Jim may have seemed disheveled and a little eccentric at times, but that was because he did not care for appearances.

Jim was so focused on how to help the patient and to pass on his knowledge to us that he would sometimes forget that there was a patient in the room listening to him. They would often have an expression on their face as if to say: “Hey, doctor, I am here. What about me?” As usual, not surprisingly, it was exactly at that moment he would choose to leave the room and leave it to us to explain to the patient what had just happened!

Over the years, Jim continued to be a beloved mentor, a wonderful colleague, and a trusted friend. He has inspired each and every one of us in such a unique and unforgettable way that his former fellows from around the world decided to acknowledge his achievements and contributions to our lives by organizing a symposium in his honor in Toronto 4 years ago. I am really glad that we did. He was able to enjoy fully the academic exchanges, the scientific vigor, and the precious friendships that we shared. It was also wonderful to see him celebrating his achievements with his family: Adrienne, his children (Jason, Peter, and Katie), and his grandchildren, all of whom we know he cared for and loved deeply.

I talked to Jim the day before he died. I mustered the courage to say what I wanted to say and had not. I told him that I loved him. Little did I know that would be the last thing I said to him. I am glad I did.

Jim, you taught me not only to be a good doctor and scientist, you also taught me to be strong and to stand up...
for what I believe. You taught me to persevere despite any setbacks and failures. You taught me to live life fully—like a torch, make it burn as brightly as possible before handing it on to future generations. Your life was truly one that was dedicated to medicine and to nurturing future generations of physicians and researchers. We know that now it is up to us to carry on your torch. We miss you already. Bon voyage.

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The North American Neuro-ophthalmology Society (NANOS) held its 40th annual meeting at the Wyndham Rio Mar Beach Resort, Rio Grande, PR. Besides unrelenting sunshine and ocean surf, we had scintillating discussions about cutting edge research and relevant clinical challenges.

This year, we had a special symposium which began on Saturday March 1. “When Neurosurgery and Neuro-Ophthalmology Collide” organized by Karl Golnik and Neil Miller. The 4 sessions covered issues of comanagement, baseline testing before surgery, complications, and what the neuro-ophthalmologist can do to prevent or assist in neurosurgical adventures.

The Frank Walsh Session was chaired by Prem Subramanian from Johns Hopkins University. The Hopkins team included Ari Blitz, neuroradiologist, and Charles Eberhart, neuropathologist. The expert panel of Sophia Chung, Deborah Friedman, and Steven Newman provided commentary. At the end of the morning and afternoon sessions, key points were reviewed. The best Walsh paper was for “Muscle Bound or Unbound,” by Dane Breker et al (Ann Arbor, MI).

Meeting symposia included: 1) “Journal Club” featuring updates on transient ischemic attacks and stroke prevention, myasthenia gravis, traumatic brain injury, and treatment of nystagmus. 2) “Hot Topics: Zebra taming:” paraneoplastic syndromes, toxic and nutritional optic neuropathies, hereditary optic neuropathies, and IgG 4 disease. The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) group covered the initial baseline findings of the Idiopathic Intracranial Hypertension Treatment Trial. Lively discussions about “Eye Pain in the Quiet Eye” and “Non-organic Neuro-ophthalmology” kept NANOS members in their seats until the meeting closed.


The scientific platform and poster sessions were well attended. There were 245 poster presentations, a record for a NANOS meeting. The newly named James Sharpe Best Abstract Award went to Krista Kinard (University of Utah) for “Chronic migraine is associated with reduced corneal nerve fiber density and length.” The resident awardee was Ajay E. Kariyan, (University of Miami) for “Orbital fibroblasts from thyroid eye disease patients differ in proliferative and adipogenic responses depending on disease sub-type.” The medical student awardee, Matthew Miller (University of Utah) presented “A comparison of clinical features of pseudotumor cerebri secondary to tetracyclines and idiopathic intracranial hypertension.”

The 2014 Thomas and Susan Carlow Young Investigator Award was presented to Patrick Yu-Wai-Man (Newcastle, United Kingdom) for his research on Hereditary Optic Neuropathies and for his presentation: “The molecular and Neuro-ophthalmological features of autosomal recessive spastic ataxia of Charlevoix-Saguenay.”

FIG. 1. Anthony Arnold, MD receives the Distinguished Service Award from North American Neuro-Ophthalmology Society.
Beau Bruce (Emory University) received the NANOS Pilot Grant Award for “Non-mydriatic ocular fundus photography for the acute risk stratification of patients with transient ischemic attack and minor stroke.”

Linus Da-Shih Sun (New York, NY) won the NANOS-Fight for Sight joint award for “Quantitative eye movements to evaluate corollary discharge.”

The 2014 Jacobson Lecture delivered by Len Levin (Montreal, Quebec) was a tour de force multimedia mystery story—“Seeking Sense in Cecocentral Scotomas: three questions and four answers.”

The 2014 Tom Carlow Distinguished Service Award, NANOS’s highest honor, was bestowed on Anthony (Tony) Arnold from University of California, Los Angeles (Fig. 1).

There was a record of 564 registrants for the NANOS meeting representing 34 countries (excluding the United States). There were spectacular social events as well. Tours of Old San Juan, the El Yunque rainforest, and a bioluminescent mangrove channels kayak event were really interesting and well attended.

Janel Fick and her outstanding staff hosted the very well-organized meeting. See you in San Diego, California in 2015!

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Beginning almost 25 years ago, optical coherence tomography (OCT) began its journey into the mainstream of ophthalmology. Initially developed commercially for retinal and vitreo–retinal interface diseases and glaucoma, this revolutionary technology has proved to ultimately have broader applications in neuro-ophthalmology and neurology, 2 specialties in which a better understanding of OCT has led to more widespread investigation and clinical use.

This year at the annual meeting, the North American Neuro-Ophthalmology Society (NANOS) leadership designed a symposium in which several “early adapters” of OCT in neuro-ophthalmology presented data regarding the state-of-the-art of this technology. A series of case studies by this group complemented the 4 presentations and illustrated how real-world use of OCT could help us to solve otherwise difficult clinical diagnoses. In this special edition of the Journal of Neuro-Ophthalmology, readers can learn more from the energy and enthusiasm of that symposium.

For those of us who remember neuro-ophthalmology in the pre-imaging era, the OCT symposium evoked memories of the Frank Walsh meetings in the 1970s and 1980s. It was during this time that the first computed tomographic and magnetic resonance (MRI) images were brought to our specialty. OCT now joins these imaging modalities as a technology that will change neuro-ophthalmology forever. A quantitative and qualitative ophthalmoscope, OCT represents the most significant advance toward in vivo visualization of the optic nerve and retina since Charles Scheppens literally used his head with the indirect ophthalmoscope to augment the power of Helmholtz’s first device.

However, despite the rich history of discovery within neuro-ophthalmology, OCT was not always embraced as a tool that would add to the direct ophthalmoscope, the 90-diopter lens and fundus photography with monochromatic light. Through a series of investigations, first in optic neuritis (ON) and multiple sclerosis (MS) and following in other neuro-ophthalmologic disorders, OCT began to take center stage as a way to correlate structure with visual function. These observations were not only useful to validate clinical visual outcome measures such as low-contrast letter acuity, but established the anterior visual pathway as a model for testing new therapies that involve neuroprotection and repair.

With the advent of capabilities for computerized segmentation of the ganglion cell layer (neurons, “retinal gray matter”) in addition to retinal nerve fiber layer (RNFL; axons), neuro-ophthalmologists can now examine the eye in a manner analogous to how MRI evolved to evaluate the brain in greater detail than ever before. Its ability to identify retinal disease and to document optic disc swelling that eludes even the most astute clinical eye has also brought OCT to the forefront as a clinical tool for neurologists. Although OCT will never replace the neuro-ophthalmologic examination, it does represent a useful, and often revealing, extension of it.

At the NANOS OCT symposium, both the didactic lectures and the case presentations provided a refreshing and positive vibe about OCT in neuro-ophthalmology. As Fiona Costello’s paper comprehensively reviews in this supplement, OCT devices are improving both in terms of hardware and software. We now have images with resolution down to within 5–6 μm; quantitative measurements have coefficients of variability of 2.5%. Although time-domain OCT had a single commercial platform, competition and the free market system have likely advanced the newer spectral-domain OCT technologies even further. For these advances, we must thank the collaborating innovators from the fields of biomedical engineering, clinical ophthalmology, commercial imaging companies, and the United States Food and Drug Administration (FDA) device division. All of these groups have worked together to...
produce a technology that has and will continue to improve
the lives of thousands of patients. OCT enables safer, quick-
er, and more accurate diagnosis and, in the care of patients,
nothing is more rewarding.

In the second article of this supplement, Randy Kardon
comprehensively and elegantly provides the Journal of Neu-or-Ophthalmology readers with a scientific summary of OCT,
using papilledema as the clinical platform for discussion.
His outstanding review should make all of us look at pap-
illedema like we have never done in the past and should
provide models of how we should always do so in the
future.

OCT technologies have also emerged to the forefront of
considerations by the global regulatory community in the
evaluation of visual outcomes in phase 2, 3, and 4 clinical
trials. Laura Balcer’s detailed and all-inclusive commentary
should empower the neuro-ophthalmology community
with the critical thinking required to properly evaluate clin-
cial trials reporting efficacy and safety results in clinical trials
and in peer-reviewed publications. Her team’s work has led
to collaborative efforts in MS culminating in the first-ever
use of acute ON as the model for testing a new remyelinating
agent in a Phase 2 clinical trial. Within that ongoing
study, OCT measures are key outcomes of the visual path-
way axonal and neuronal loss that so invariably occur after
even a single episode of ON. In clinical trials where pre-
venting axonal and neuronal loss are the primary goal, OCT
no doubt has a bright future. For clinical uses in which our
goal is to improve on subjective observations, OCT will be
even more helpful. Although we will always admire the
beautiful anatomic drawings of Cajal, we will also continue
to apply objective measurement techniques such as OCT
for evaluation of the optic nerve and retina.

Even more exciting will be the next dimension of OCT:
MultiColor imaging. As described by Robert Sergott, this
technology involves expertise of biomedical engineers and
imaging physicists, yet will make us better clinicians. This
will be possible by facilitating topographic imaging of the
inner, mid, and deep retinal layers, giving neuro-
ophthalmologists an even greater window on this relatively
unexplored area of the nervous system. The currently
untreatable neuro-degenerative diseases await the applica-
tion of OCT and MultiColor imaging to localize damage
and target new therapies. The fast-growing area of sports-
related concussion and study of athletes exposed contact
sports will also benefit from OCT to corroborate clinical
signs of brain dysfunction in vivo. The next NANOS
symposium on OCT will report on these findings, and
likely offer us techniques molecular imaging, OCT angio-
graphy and total RNFL analysis.

OCT puts into practice one of Fiona Costello’s favor-
"The retina is both the back of the eye and the
front of the brain.” In that spirit of innovation, we also
should recall the words of Steven Jobs as we evaluate any
new technologies, “It is really hard to design products by
focus groups. A lot of times, people do not know what
they want until you show it to them.” These words
should inspire us all to continue to think forward, artic-
ulate new ideas, and thus create the future of neuro-
ophthalmology.
Optical Coherence Tomography Technologies: Which Machine Do You Want to Own?

Fiona E. Costello, MD, FRCP

Abstract: Optical coherence tomography (OCT) has evolved over the past decade to become one of the most important ancillary tests in ophthalmic practice. This noninvasive ocular imaging technique provides high-resolution, cross-sectional images of the retinal nerve fiber layer (RNFL), macular region, ganglion cell layer, and optic nerve head. With OCT, we can learn much about axonal–neuronal integrity in the anterior aspect of the afferent visual pathway and gain insights about mechanisms of brain injury in various central nervous system disorders.

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Spectral of “Fourier” domain optical coherence tomography (OCT) has been commercially available since 2006, and since this time OCT has become a cornerstone in clinical ophthalmic practice. Previous generations of time-domain OCT (TD-OCT) featured an axial resolution of approximately 8–10 μm of tissue (1). In the modern era, spectral domain OCT (SD-OCT) provides scan rates of 20,000–52,000 A-scans per second to achieve a resolution of 5–7 μm (1). This is approximately 50-fold faster than the previous generations of TD-OCT (2).

OPTICAL COHERENCE TOMOGRAPHY: WHAT IS OUT THERE?

Currently, there are several different SD-OCT machines (Table 1). The decision regarding which machine to buy should take into account a variety of factors including: the main purpose of the machine (research vs clinical), the setting (neuro-ophthalmic vs general ophthalmic practice), cost, space, and the ability to build on existing platforms with future software developments. The cautious consumer should also consider hardware, image quality, and software issues.

Hardware

When choosing an SD-OCT machine, there are several hardware specifications to keep in mind, including the light source, speed of the image sensor, and the instrument’s non-OCT imaging capabilities (6). The quality of axial resolution is determined by the light source in the OCT machine, such that broader bandwidth sources produce better results. Recent progress in the field of broadband superluminescent diodes has made high resolution imaging (5–7 μm) with SD-OCT more affordable. As advanced superluminescent diodes and laser technologies become cheaper, commercial ultrahigh resolution (approximating 2–3 μm) machines will emerge as options to consider (6).

In addition to axial resolution, image acquisition speed is another important hardware specification. Some SD-OCT machines enable 3D retinal reconstructions. The fast scanning speeds that facilitate this feature should translate into more efficient patient flow, improved patient comfort, reduced opportunity for disruptive eye movements, and increased opportunities for the machine to control noise (6). That said, enhanced speed may affect image quality, particularly in patients with anterior segment abnormalities. When evaluating the performance of a given OCT machine, it is important to think above and beyond the demonstration images and review the quality of the more rapidly acquired 3D-OCT images, which will better reflect data collected in a clinical setting (6).

Several commercially available OCT instruments allow for “upgrade” options, such as the line-scanning laser ophthalmoscope, fluorescein angiography, indocyanine green, autofluorescence, and microperimetry. These “combo” packages present potential advantages and disadvantages. The upgraded features may allow comparisons between OCT and non-OCT images that may assist diagnostic or management decision making. Yet, combining too many critical functions into a single machine can become
problematic if the device breaks down or if patients requiring only OCT scans are delayed by patients receiving time-consuming angiography and/or microperimetry studies (6). Other important hardware factors to consider include the ergonomics of the device and the service and support of the manufacturer.

**Image Quality**
SD-OCT machines have a “sweet spot” of maximum sensitivity, and by extension, image quality that resides either on the vitreous or the choroid side of the retina (6). For this reason, before capture, the operator using the machine may need to select which tissue to image with higher sensitivity (inner retina or choroid) and then keep the patient’s eye in a position that maximizes this signal. Some SD-OCT machines may be more susceptible than previous TD-OCT devices to disruptions caused by media opacities and corneal disease. In these situations, increased “noise” may obscure subtle features including subretinal fluid and make it difficult to distinguish pathological findings from normal tissue structures. It is important to look for devices that consistently produce a brighter signal in the outer retinal layers as compared with the vitreous. Because grayscale images may hide the “speckles” that signify vitreous opacities and mask noise problems, pseudocolor images should be used to assess the quality of the vitreous signal and to expose potential problems that can be masked with grayscale images (6).

**Software**
The large data sets acquired by SD-OCT instruments allow for several capabilities. Dense 3D-OCT scans produce maps that can be aligned with non-OCT imaging modalities, such as color fundus imaging. Any well-designed SD-OCT instrument should include point-to-point registration capabilities that allow users to identify areas either in the OCT or non-OCT image and see the corresponding point of interest (6). With proper software, the same point in the fundus can be compared between visits improving the reproducibility of longitudinal clinical measurements (6).

For an SD-OCT device to perform effective intervisit alignment or produce good 3D reconstructions, it must account for eye movements that occur during image acquisition. Effective eye-tracking software can help correct this problem. Therefore, when evaluating SD-OCT machines, it is wise to evaluate 3D reconstructions and intervisit comparisons to demonstrate registration problems. This requires ergonomic software that can be easily operated by the clinic staff. Furthermore, it would be optimal for SD-OCT machines to have the capacity to integrate robust network support software, so that large files can be transferred efficiently and rapidly across local networks directly to patient-care areas (6).

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**TABLE 1. Currently available spectral-domain optical coherence tomography machines (3–5, 9–12)**

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<tr>
<th>Machine</th>
<th>Manufacturer</th>
<th>Product Description</th>
<th>Features</th>
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<tr>
<td>CIRRUS HD-OCT 5000 and 500</td>
<td>Carl Zeiss Meditec</td>
<td>Cirrus compares retinal measurements from prior visits to recent visits to generate a thickness map, aided by a retinal tracking system (FastTrac). This feature helps to reduce eye motion artifacts, provide precise macular thickness measurements, and enable advanced RPE analysis. Specialized software (Guided Progression Analysis) makes it possible to determine change for RNFL, ONH, and outer plexiform layer disc measurements centered on the fovea (FoveaFinder). The RNFL, macular thickness, and optic disc measurements have been validated, showing excellent repeatability and accurate segmentation. The ONH algorithm is designed to measure the neuroretinal rim while accounting for tilted discs. disruptions to the 3.4-mm diameter peripapillary RNFL calculation (AutoCenter), which is not operator dependent. The Cirrus HD-OCT technology allows expanded capabilities to share data between instruments and review stations.</td>
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<th>Machine</th>
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<tr>
<td>SPECTRALIS HRA + OCT</td>
<td>Heidelberg Engineering</td>
<td>The platform includes multiple models at various price points. The so-called “workhorse” is the SPECTRALIS OCT, an economical, easy-to-use version with one-touch preset scan patterns. Additional models built on this base platform allow clinicians to tailor a system to the evolving needs of their practice. Using an upgradeable platform approach, SPECTRALIS has enhanced the role of SD-OCT by integrating it with cSLO. Different SPECTRALIS models include: OCT, OCT&lt;sup&gt;Plus&lt;/sup&gt; with Multicolor, HRA, FA + OCT, HRA + OCT, OCT&lt;sup&gt;Plus&lt;/sup&gt; with BluePeak, OCT with BluePeak.</td>
<td>The advantages of cSLO over traditional fundus photography include: improved image quality, small depth of focus, suppression of scattered light, increased patient comfort (less bright light exposure), 3D-imaging capability, video capability, and effective imaging of patients who fail to dilate well. The specialized (TruTrack) eye tracking system reduces eye motion artifact and ensures point-to-point correlations between OCT and fundus images without postprocessing the data. This technology (TruTrack) also minimizes operator variability in follow-up scans (AutoRescan) adding precision to measuring changes in RNFL values over time. The Heidelberg Noise Reduction option provides enhanced image detail. The noninvasive blue laser autofluorescence (BluePeak) imaging takes advantage of the natural fluorescent properties of lipofuscin to capture FAF images, providing structural and metabolic information about the retina. Deeper retinal structures are imaged with the EDI feature, which provides detailed views of choroid and lamina cribrosa. The SPECTRALIS Anterior Segment Module offers image acquisition of the cornea, sclera, and the anterior chamber angle, providing a detailed view of the anterior segment. IR imaging provides a variant of fundus photography that uses infrared light rather than white light for illumination. This provides several advantages including: reduced light exposure and decreased patient sensitivity, improved penetration through unclear media, and enhanced visualization of epiretinal membranes and cystoid macular edema compared with fundus photography and red-free imaging. Foveal-to-Disc Alignment technology (FoDi) tracks and aligns circle scans to improve the accuracy of RNFL scans, by overcoming effects of head tilt and eye rotation. The Region Finder software allows the instrument to quantify and track dark areas on BluePeak images. SPECTRALIS MultiColor imaging delivers high contrast, detailed images even in difficult patients including those with cataracts or nystagmus. SPECTRALIS confocal scanning laser ophthalmoscope (cSLO) with Blue Reflectance imaging uses blue light to illuminate the retina. This wavelength accentuates the visibility of blood vessels and enhances the contrast of certain structures on the surface of the retina, making them easier to see relative to white light illuminated images. The SPECTRALIS cSLO technology enhances FA by increasing the signal-to-noise ratio and blocking out-of-focus and scattered light. SPECTRALIS FA can be combined with ICGA to view retinal and choroidal blood flow. The Widefield imaging feature allows a broader view of the retina beyond the macula. The Noncontact Ultrawidefield Angiography module offers the widest view of the retina with a 1-shot view, making it possible to detect peripheral changes of interest. This feature can be combined with fluorescein and indocyanine green techniques, either individually or together. The machines use the Heidelberg Eye Explorer (HEYEX) software platform and database to store patient information and images. Image acquisition and analysis is controlled by HEYEX plug-in software modules that are specific to each device. Network connections between devices allow access to the common HEYEX database.</td>
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<td>Machine</td>
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<tr>
<td>iVue SD-OCT</td>
<td>Optovue, Inc</td>
<td>The iVue is described as the most compact SD-OCT system</td>
<td>This machine is designed to be very easy and fast and includes a convenient footswitch control and touch screen on the scanner head. Anterior Segment imaging provides visualization and measurement of the angle and the cornea. Corneal thickness is offered as a full 6 x 6-mm pachymetry map with minimum thickness marker, in addition to a user-defined corneal point thickness. Additional features includes: ganglion layer thickness imaging with ganglion cell complex upgrade, and 3D “En Face” analysis upgrade. The iVue SD-OCT is available with a 21.5 inch screen or with the optional laptop configuration for maximum portability. Color-coded retinal thickness mapping enables segmenting of the inner, outer, and full retina with overlayed ETDRS thickness values.</td>
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<tr>
<td>3D OCT 2000</td>
<td>Topcon Medical Systems</td>
<td>This is the first SD-OCT to incorporate a high resolution fundus camera and a color touch screen display in a compact, space saving design</td>
<td>It is possible to obtain dynamic viewing of data, with 3D, 2D, and fundus images simultaneously (FastMap software). Moreover, users can determine the location of the OCT image within the fundus image (Pin-Point Registration). Serial examinations may be viewed and compared. The EyeRoute Image Management System provides access to images.</td>
</tr>
<tr>
<td>OCT/SLO combination imaging system</td>
<td>Optos, Inc</td>
<td>The OCT SLO system combines SD-OCT imaging with a cSLO in 1 instrument</td>
<td>The cSLO provides high resolution images and retinal tracking before, during, and after the OCT scan. The SLO “Lock and Track” function ensures that follow-up scans are obtained from the same location in an operator-independent fashion. The SLO confocal fundus image and the OCT image are generated through the same optics and are pixel-to-pixel correspondent, ensuring precise OCT registration. Furthermore, 3D topographies can be aligned to the SLO image to compensate for rotation and shift. The “AutoCompare” features allows automatic comparison of multiple topographic maps taken over time including retinal thickness. With Optos’ “Viewer Software,” any clinician can view the system database from a remote computer or laptop, including OCT scans, 3D topography scans, RNFL scans, and optic nerve views.</td>
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<tr>
<td>SD-OCT Copernicus</td>
<td>Optopol/Canon, Inc</td>
<td>SOCT Copernicus HR is a SD-OCT with UHR (3 μm)</td>
<td>Ultrahigh scanning speed (52,000 A-scans per second) shortens data collecting and improves the comfort of examination for both patient and operator. The SOCT Copernicus HR Glaucoma Module allows for the detection and management of glaucoma. The tool tracks progression with time. Software features include retina and RNFL volume maps, optic nerve head analysis, 3D visualization, and traction visualization. The DDLS provides a novel way to analyze the optic nerve. Instead of a cup/disc (c/d) ratio, a rim/disc (r/d) ratio and the nerve size is measured. This method is reported to be superior than any other reporting measure because it eliminates the effects of disc size and provides more weightage to the neuroretinal rim damage. The anterior segment module allows cornea and anterior imaging with a resolution of 3 μm. The new advanced 3D module allows visualization of 3D reconstructions. SD-OCT images can be stored in the central area and be accessible from different locations.</td>
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DDLS, Disc Damage Likelihood Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; FAF, fundus autofluorescence; ICGA, indocyanine green angiography; ONH, optic nerve head; cSLO, confocal scanning laser ophthalmoscopy; RNFL, retinal nerve fiber layer; RPE, retinal pigment epithelial analysis.

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CONSIDERING THE BELLS AND WHISTLES

Retinal Sector Analysis
Retinal axons of some retinal sectors are more vulnerable than others in certain disease states. Quantitative analysis of retinal sectors allows for sensitive detection of axonal loss in all regions (7).

Retinal Nerve Fiber Layer Thickness and Effectivity Maps
Using individual circular RNFL scans at the optic nerve to accurately localize focal and peripheral loss of retinal axons is challenging. One possible approach is the development of RNFL thickness maps. An integrative approach combining polarizing sensitive OCT data with RNFL thickness maps may help predict the topography of RNFL loss in neuro-ophthalmic diseases (7).

Retinal Layer Segmentation Algorithms
With the introduction of SD-OCT, RNFL image quality allows for segmentation and quantification of individual layers. New segmentation algorithms for quantitative analyses of individual retinal layers may facilitate better tracking of progression in neuro-ophthalmic diseases (7).

Fluorescence Labeling
As an example, fluorescence labeling of a protein that binds to a key component initiating apoptosis enables real-time in vivo monitoring of retinal ganglion cell apoptosis. Detection of this phenomenon provides a promising surrogate outcome for neuroprotective treatment strategies in glaucoma, dementia, and potentially multiple sclerosis (7).

Optical Coherence Microscopy and Action Potentials
With optical coherence microscopy, the structural assessment of action potentials has become a reality. Functional imaging of the human retina in vivo may allow us to investigate whether axonal dysfunction precedes retinal ganglion cell layer or RNFL loss in different disease states (7).

Choroidal Imaging
Most commercially available SD-OCT systems can be used to evaluate choroidal thickness (1). The method used for choroidal thickness analysis involves manual measurements taken perpendicularly from the outer edge of the retinal pigment epithelial analysis to the inner sclera (choroid-sclera junction) using the software within the system (1).

Color Imaging
Multicolor imaging delivers high contrast, detailed images, even in patients with cataracts or nystagmus. The image clarity and detail is highly improved and can increase sensitivity in the detection of pathology in the posterior pole.

FUTURE DIRECTIONS: EMERGING APPLICATIONS OF OPTICAL COHERENCE TOMOGRAPHY

Ultra-High Resolution Optical Coherence Tomography
Ultra-high resolution OCT uses an ultrabroadband with light sources to provide axial resolutions approximating 2–3 μm, which reveals retinal morphology in high detail. However, because this technology requires femtosecond lasers and expensive light sources, it has not been widely used as a commercially available OCT system for clinical settings (8).

Mobile Spectral Domain Optical Coherence Tomography
The commercialization of mobile SD-OCT systems may expand the application spectrum to allow analysis of subjects manifesting significant motion, including adult and pediatric patient groups. The first commercialized mobile SD-OCT scanner (Biopitgen Inc, Research Triangle Park, NC) provides a light hand-held imaging probe that can be maneuvered independently. This technique may be used in the imaging of small animal eyes in the research setting. Other applications for this technique include evaluating foveal architecture in pediatric ocular albinism, and the extent of retinal pathology accrued from shaken-baby syndrome (8).

Spectral Domain Optical Coherence Tomography for Intraoperative Use in Vitreoretinal Surgery
Vitreoretinal surgeons have long relied on the optical stereo microscope to visualize the surgical field. Even with recent design improvements, there are limitations to intraoperative visualization and accurate localization with this approach (8). Current imaging modalities do not provide real-time cross-sectional images of the change in location of a surgical instrument relative to tissue or of tissue deformation during surgery. This feedback may be important in judging whether to continue a specific maneuver. A SD-OCT surgical microscope could potentially provide a base for significant advances in ocular surgery and other branches of microsurgical intervention. Moreover, this imaging modality may also be useful for subretinal drug-delivery applications (8).

Functional/Targeted Spectral Domain Optical Coherence Tomography Imaging
Unlike many other medical imaging modalities with functional adjuncts, such as CT and magnetic resonance imaging, SD-OCT with functional targeting offers unique advantages in ocular surgery. This technology could allow for real-time visualization of retinal and choroidal blood flow during surgery, providing surgeons with an unprecedented level of intraoperative feedback. This could lead to improved surgical outcomes and reduced complications. The future of SD-OCT imaging in ocular surgery is promising, with ongoing research likely to further refine and extend its clinical applications.
imaging (MRI), ophthalmic use of SD-OCT has been restricted to structural imaging (8). Two new functional SD-OCT imaging modalities are emerging with a wide spectrum of potential diagnostic applications:

- Doppler SD-OCT for blood-flow imaging: Doppler OCT technology was first developed using TD-OCT systems and was later used for retinal flow analysis (8). However, the slow data acquisition coupled with patient head motion restricted the reliability of the data. In SD-OCT systems, Doppler flow velocities are acquired much more quickly, and recent extensions to Doppler SD-OCT are enabling complete 3D mapping of the retinal vasculature for the first time, with potential applications in monitoring diabetic retinopathy and other blinding diseases with a vascular component (8). In multiple sclerosis, perivasculitis is believed to lead to extravascular hyaline deposits in a process referred to as “vascular sheathing.” These changes may lead to increased rigidity of retinal vasculature and, by extension, rapid pulse propagation from the posterior (chorioid) to the anterior (retinal vasculature) circulation (7). This hypothesis could potentially be investigated by combination of SD-OCT with Doppler velocity measures. This technique is non-invasive and allows for accurate topographic localization of retinal blood vessels (7).

- Polarization-Sensitive OCT: Polarization-sensitive SD-OCT (PS SD-OCT) yields depth-resolved information about any light polarization changing properties of the sample related to tissue birefringence (7,8). The birefringence of the RNFL is related to the structure of neurofilaments and microtubules. Studies have shown that the birefringence of the RNFL is not constant, but varies by a factor of 3 around the nasal and temporal quadrants. This property distinguishes the RNFL from other retinal structures, which are either polarization preserving (e.g., photoreceptor layer) or polarization scrambling/depolarizing (e.g., retinal pigmented epithelium) (8). Because changes to the axonal cytoskeleton such as neurofilament compactness, phosphorylation, and stoichiometry can precede axonal loss, there might be an opportunity to detect early stages of axonal pathology in diseases like multiple sclerosis with PS-OCT (7).

**Longer Wavelength and Swept Source Technology**

For adequate analysis of choroidal thickness and volume in healthy and diseased states, the clarity of the choroid–sclera interface is important. This can be achieved by increasing the depth of tissue penetration using a longer wavelength of incident light centered near 1050 nm, so that attenuation from scattering can be reduced (1). The acquisition of scans is much faster in swept source OCT (SS-OCT), when compared with the SD-OCT systems. The SS-OCT systems have axial scan rates of up to 100,000–236,000 A-scans per second, which is 5–10 times that of the SD-OCT systems (1). Data can be acquired much faster, and volumetric assessment of the choroid is also feasible (1). As longer-wavelength OCT systems including SS-OCT become available, the visualization of choroid–sclera interface is expected to improve (1). Volumetric analysis of the choroid and that of the various pathological features such as choroidal neovascularization and subretinal/intraretinal fluid, may be possible (1). Such volumetric analysis is expected to help with monitoring the progression of diseases such as diabetic retinopathy, as well as assessment of the response to treatments.

**Enface Imaging**

Enface imaging allows the clinician to visualize 3D data in a fundus projection. Using this technique, particular retinal and/or choroidal layers at a given depth are projected onto an enface view. Although cross-sectional images (B-scans) have helped in delineating pathological features in retinal diseases, the microstructural changes and morphology of the retinal and choroidal vasculature are difficult to evaluate using B-scans (1).

This is expected to improve because enface imaging provides more detail about the subtle pathological features in the retina and choroid in diseased states (1). In addition, the involvement of the specific vascular layers of the choroid in different diseases, such as diabetic retinopathy, and inherited retinal dystrophies is expected to be unveiled in additional details using this technique (1).

**REFERENCES**


Optical Coherence Tomography in Papilledema: What Am I Missing?

Randy Kardon, MD, PhD

Background: Grading of papilledema severity is subjective and based on monocular fundus features of the optic nerve. Interobserver agreement on grading the severity of papilledema is poor among expert observers, even using well-defined criteria such as the Frisen scale, which is a non-continuous ordinal scale of grading. Furthermore, non-expert clinicians often find it difficult to properly view and interpret features of the optic nerve using ophthalmoscopy, which can lead to failure to diagnose papilledema in non-ophthalmologic care settings. This may delay treatment, which can result in vision loss. Distinguishing papilledema from pseudopapilledema can also be difficult when surface drusen are not easily identified. Once papilledema is diagnosed, it is often difficult to determine whether a reduction in optic nerve edema is due solely to improvement in the status of the nerve or whether this represents concomitant loss of axons and viable retinal ganglion cells, leading to a poor visual outcome. Timely advancement of treatment would occur if loss of neurons could be diagnosed at an earlier stage of evaluation while optic disc edema is still present. This review will critically assess the role of optical coherence tomography (OCT) in solving these problems by providing an advanced imaging approach for diagnosis of papilledema and evaluating its severity on a continuous scale and evaluating the causes of visual loss in the setting of a swollen nerve.

Methods Acquisition: The published literature (PubMed) was reviewed from 2000 to 2014 on the use of OCT for diagnosing papilledema, differentiating it from pseudopapilledema, providing a continuous scale of its severity and in evaluating causes of visual loss.

Results: Recent evidence shows that OCT analysis of the retinal nerve fiber layer and retinal ganglion cell layer in papilledema can be associated with misleading artifacts due to layer segmentation failures. Newer 3D algorithms using neighboring locations help to overcome these problems. Disc volume appears to be a promising continuous measure of papilledema that is robust and has less associated artifacts. Buried optic disc drusen can be identified using enhanced depth OCT imaging, but recent studies have shown poor ability to differentiate papilledema from pseudopapilledema using OCT when the degree of disc evaluation is similar. Analysis of the retinal ganglion cell layer shows promise of early detection of vision loss due to neuronal injury. Subretinal fluid is easily identified with OCT and can help to identify a potentially reversible component of vision loss. Newer OCT imaging methods will allow the definition of capillaries and flow within them in and around the optic nerve head.

Conclusions: Currently, the most useful OCT derived features relevant to papilledema are disc volume, subretinal fluid, buried disc drusen, and thickness of the retinal ganglion cell layer.

doi: 10.1097/WNO.0000000000000162
Distinguishing papilledema from pseudopapilledema

J Neuro-Ophthalmol 2014

Reproducibility for 3 different observers, who staged the same fundus photographs for disc swelling on 2 separate occasions. Each dot represents 1 photograph. The diagonals represent identity of stage numbers on test and retest. The first graph is for medical students, the second graph is for ophthalmology residents, and the third graph is for expert specialist neuro-ophthalmologists (1).

- Distinguishing papilledema from pseudopapilledema is difficult when obvious surface drusen are not present. Buried drusen, when not calcified, may not be readily apparent using funduscopy, ultrasound, OCT, or computed tomographic (CT) scans.
- It is often difficult to determine whether a reduction in optic disc edema is due solely to improvement in the status of the nerve, or whether this represents concomitant loss of axons and viable retinal ganglion cells, leading to a poor visual outcome. More timely advancement of treatment would occur if loss of neurons could be diagnosed at an earlier stage of evaluation while optic disc edema is still present.

An important (and reachable) long-term goal is to provide a portable, low cost retinal imaging device with embedded software that would not require expertise for acquiring and making a diagnosis of papilledema or other optic nerve pathology. Ultimately, generation of an automated report providing diagnostic probability at the point of care and at the time of image acquisition is needed, which would bypass the need for a telemedicine reading center. Use of such a device would be adopted in clinical settings lacking easy access to ophthalmologists and neuro-ophthalmologists, such as in emergency rooms, family practice offices, neurology and neurosurgery clinics and inpatient units. This report will outline and define the critical need for new imaging modalities such as OCT and image analysis aimed at providing tools for improved diagnosis of papilledema, differentiating papilledema from pseudopapilledema and other causes of optic nerve edema, and for identifying early signs of retinal nerve loss to optimize treatment and prevent vision loss.

**DIAGNOSIS AND GRADING OF SEVERITY OF PAPILLEDEMA BASED ON FUNDUS FEATURES: ARE WE GOOD ENOUGH?**

Many clinicians are confident in their ability to accurately diagnose and grade the severity of papilledema, and most use the accepted standard of the Frisen grading scale (1). However, even in the original report by Frisen, there was intraobserver variability in grading of photographs on repeat testing, whether the grading was done by a medical student, resident, or expert (Fig. 1). Significant variability among experts in grading papilledema from digital fundus photographs has also been demonstrated by Scott et al (2) (Fig. 2) and Sinclair et al (3) (Fig. 3).

These studies give us pause in relying on humans (including experts) to accurately and reliably diagnose and grade papilledema. Efforts to refine and provide more specific criteria for each Frisen scale may help to improve reliability between observers. Since the Frisen scale consists of 6 grades (0–5) that are non-continuous, a further improvement would be to devise a continuous grading scale, based on structural features that could be objectively quantified by computerized image analysis of fundus images. Echegaray et al (4) have shown that quantitative analysis of digital fundus images is a promising approach and features that incorporate sharpness of the disc border, texture of the retinal nerve fiber layer (RNFL), and discontinuity of blood vessels can be used by a machine classifier to assign a Frisen grade to a disc photograph. The next step would be to map features from digital fundus photography to a continuous scale based on OCT measurements of papilledema such as disc volume or thickness of the peripapillary retina (5,6). This would associate fundus photo features with OCT-based features, so that the quantification of papilledema on a continuous scale could be made (superseding the non-continuous Frisen scale) using either of these 2 imaging modalities. The imaging modality to be used could be flexible and selected for a given patient based on availability and cost in a telemedicine setting where the patient enters the medical system.

**TOWARD A CONTINUOUS SCALE QUANTIFICATION OF PAPILLEDEMA SEVERITY (RETINAL NERVE FIBER LAYER, TOTAL RETINAL THICKNESS, AND DISC VOLUME)**

With the availability of time-domain OCT early in the 21st century, there had already been attempts at quantifying...
papilledema using confocal microscopy with Heidelberg Retinal Tomography (HRT) and scanning laser polarimetry (SLP). HRT appeared promising (7) but was limited by the difficulty in defining an appropriate “reference plane” in the peripapillary retina for quantifying elevation of the nerve head above that plane, especially in higher grades of papilledema. Even in glaucomatous optic neuropathy, there was disagreement as to what portion of the retina was best suited for a reference plane that was not affected by the pathology being evaluated. Also, the availability of HRT was not widespread; only some academic institutions had the resources and interest to acquire the instrumentation for evaluating the optic nerve and retina using confocal laser microscopy. SLP, which also predated OCT, was gaining use for glaucoma evaluation and was based on changes in the retardation of reflected polarized light from the RNFL that contained regularly oriented microtubules and microfilaments, which could modify polarized light passing through it. Reports of its use showing thickening of the RNFL in papilledema were initially negative or only showed mild thickening (8,9); there was very little change in retardation of polarized light by axoplasmic flow stasis, since in most cases, the organization of the microfilament substructure was unaffected. However, SLP did reveal axon loss, similar to its use in glaucoma (8–10).

Unlike HRT, OCT provided information on retinal thickening, and in particular, peripapillary thickening of the RNFL in papilledema without the need for a reference plane (11–21). Since OCT was based on actual thickness of the retinal layers, it complimented SLP, which primarily demonstrated loss of microtubule and microfilament organization within the axon bundles. However, it was soon noticed that in the presence of moderate-to-severe papilledema (Frisen Grade 3 or above), substantial thickening of the peripapillary RNFL would often cause the software algorithm that was used for determining the RNFL borders to fail in over one-third of the cases (2), causing inaccurate reporting of RNFL thickness. A significant improvement in the quantification of papilledema was achieved by segmenting the total retinal thickness (TRT) in the same peripapillary scan, since the inner and outer borders of the retina can be more readily defined by automated software in the presence of moderate to severe papilledema. The TRT was found to highly correlate with the RNFL thickness in eyes where the algorithm did not fail.

Automated software segmentation of the retinal layers using a 3D graph-based approach has significantly improved the accuracy of defining the thickness of the retinal layers in...
papilledema (6), resulting in much fewer algorithm failures. With this approach, the entire surface of each retinal layer is determined within the scan volume using all of the surrounding 3D features in the OCT scan and not just the features in each individual B scan. Wang et al (6) used this approach to segment the volume of the optic disc, which highly correlates with the RNFL, TRT, and Frisen grade of papilledema in patients with raised intracranial pressure (Fig. 4).

**ADVANCED FEATURE ANALYSIS OF THE DISC USING DIGITAL FUNDUS PHOTOGRAPHY AND OCT**

The ability to accurately derive an OCT-based, continuous measurement of papilledema (e.g., total disc volume, as explained in the previous section) provides an objective means of quantifying the severity of papilledema. The next step forward is to map other OCT and fundus based features to a continuous scale of disc volume, such as shape of the disc volume, deformation of Bruch’s membrane at the neural canal and texture, along with fundus based features to further enhance the ability to differentiate papilledema from other forms of optic disc edema and pseudopapilledema. This will also allow quantification of features of digital fundus photographs as shown in Figure 5 (e.g., obscuration of the disc margin, discontinuity of disc vessels, and texture of the peripapillary nerve fiber layer) to be mapped to OCT disc volume, and will provide the possibility of a continuous scale software measure of papilledema that can be derived and embedded in teleretinal imaging devices at the site of image capture for immediate diagnosis (4,6,22).

Another OCT-based feature, which provides information about the direction of force vectors at the optic disc in papilledema, is the deformation of Bruch’s membrane surrounding the neural canal due to a pressure differential between the retrobulbar optic nerve and vitreous cavity (Fig. 6). The shape characteristics of Bruch’s membrane in this area, in terms of the degree of angling toward the vitreous, can help in monitoring of the force differential over time as the intracranial pressure changes and may also help to differentiate papilledema from other causes of optic disc edema or pseudopapilledema (23,24). This angle can vary to some degree within normal eyes without papilledema. The angle may be slightly positive angling toward the vitreous, neutral and horizontal, or negative, angling toward the retrobulbar compartment. A very positive angle

**FIG. 4.** A. Examples of how disc volume, derived from OCT, increases with increasing Frisen grade of papilledema (lower left section of figure). B scan sagittal sections are shown in the upper row and corresponding 3D disc volumes are shown in lower row. There is a highly linear correlation between Frisen grade and the disc volume (B) and disc volume and the retinal nerve fiber layer (RNFL) and total retinal thickness (C) (6).

**FIG. 5.** Computerized image analysis features of fundus photos that are specific for papilledema and its degree of severity include, from left to right, texture (“entropy”) of the peripapillary retina (with insert), degree of definition of the disc border, vessel discontinuity index due to obscuration of retinal vessels by edematous overlying retinal nerve fiber layer, 3D disc volume derived from stereo pairs of disc photographs (4).
in an eye suspected of having papilledema may be very helpful, but slightly positive or neutral angle does not rule out papilledema. A change in the angle from positive to less positive after treatment or after lumbar puncture would also enforce a suspicion of papilledema and would verify a treatment effect (Pat Sibony, MD, personal communication, February 2014). Newer generation OCT instruments with enhanced depth penetration and longer wavelength light (exceeding 1 μm) provide even greater resolution of deeper structures, such as Bruch’s membrane, even in the presence of optic disc edema.

**DIFFERENTIATING PAPILLEDEMA FROM PSEUDOPAPILLEDEMA USING OCT**

The ability to differentiate papilledema due to raised intracranial pressure from other forms of optic disc edema or from pseudopapilledema can be challenging, particularly when the degree of edema is not severe (i.e., Frisen Grade 1 or 2). When calcified optic disc drusen are located superficially, the diagnosis is relatively easy and can be made with careful ophthalmoscopic observation. When calcified drusen are deep and buried under the surface, clinical observation may be equivocal, and the use of autofluorescence, ultrasound, or observation of CT scans of the optic nerve have been useful. OCT has been used to differentiate papilledema from pseudopapilledema (25–33) (Fig. 7). Sometimes calcified drusen and their shadows, visualized on OCT, are not easy to distinguish from large, superficial blood vessels. Non-calcified drusen are not usually visualized, as they are presumed not to exhibit a significant difference in reflectivity from surrounding disc tissue. Often a patient with pseudopapilledema (with or without calcified drusen) may show visual field loss. In these eyes, the RNFL may appear thickened in some areas, presumably due to axoplasmic flow stasis, and thin in other areas, corresponding to locations of visual field loss. Another OCT approach to differentiating papilledema from pseudopapilledema is based on defining topographical shape characteristics of the elevated nerve head. In this approach, a machine classifier is used to define shape characteristics that are more likely to be associated with true papilledema and those characteristics that are more likely to be associated with pseudopapilledema. As outlined in the previous section, shape characteristics of Bruch’s membrane may also help in differentiating papilledema from pseudopapilledema and other forms of optic disc edema not due to raised intracranial pressure.

**WHY IS MY PATIENT WITH PAPILLEDEMA LOSING VISION? DIFFERENTIATION OF VISUAL LOSS DUE TO OPTIC NEUROPATHY VS MACULOPATHY (FLUID AND SURFACE WRINKLING)**

When a patient with papilledema has best corrected vision of 20/25 or worse, then there is a concern for whether this may be caused by optic neuropathy, requiring more aggressive treatment, or whether it may be due to a macular abnormality such as subfoveal fluid or choroidal folds. The more benign retinal causes are relatively easy to diagnose with OCT and can help to resolve the uncertainty rather quickly. The most obvious sign that can be discerned with OCT is a neurosensory retinal detachment from peripapillary fluid between the retinal pigment epithelium and...
photoreceptors that tracks into the fovea (34,35). On OCT B scans, the fluid appears dark with low reflectivity. The macular thickness is greater than surrounding areas without fluid on the color OCT thickness plot, and the probability plot shows the area with fluid to be significantly thicker than age matched normative data (Fig. 8). Decrease in vision due to fluid under the fovea is largely reversible and should not be considered a cause of vision loss requiring urgent management. However, rarely, with chronic papilledema, a subretinal neovascular membrane in the peripapillary retina may form and cause fluid that will not resolve unless treated more definitively with either intravitreal anti-vascular endothelial growth factor agents or laser treatment to the peripapillary area in the location of the membrane. Another retinal cause of decreased visual acuity is choroidal folds caused by distortion of the posterior globe by abnormal amounts of fluid under pressure in the subarachnoid space surrounding the optic nerve as it exits the globe. Choroidal folds can be recognized in OCT B scans, in the infrared fundus image, or on digital photography and fundus examination. The folds may contribute to metamorphopsia and are often reversible, but not always, with successful resolution of papilledema. Progressive optic neuropathy due to papilledema requires more aggressive, urgent treatment to attempt to minimize the degree functional and structural deficit and restore any reversible component of vision.

A decline of visual acuity in the absence of macular fluid or folds is usually the most obvious sign of progressive optic neuropathy in this setting. Since RNFL is thickened in papilledema, a reduction in its thickness, assessed by OCT, may be difficult to interpret and could represent either a reduction in disc edema due to improvement or due to axon loss (36–38). Kupersmith et al (10) have reported that axon loss in the presence of papilledema can be revealed by using SLP. Since SLP is sensitive to disorganization of axon microtubules and microfilaments, which may be one of the earliest signs of axon disruption. However, this technology has become somewhat obsolete and was superseded by OCT for glaucoma diagnosis and monitoring. One next generation prototype OCT was developed with the capability of polarization assessment, but is not presently commercially available. As an alternative, assessment of ganglion cell loss by OCT in the setting of papilledema may be suitable for early detection of neuron loss in order to identify patients in need of more aggressive treatment. Since optic disc edema and axon swelling does not appear to directly affect the retinal ganglion cell layer thickness, allowing it to be an effective tool for the early diagnosis of progressive optic neuropathy. However, commercial algorithms for segmenting the ganglion cell-inner plexiform layer (GCL-IPL) complex were designed for normal and glaucoma eyes and often fail in the presence of optic disc edema. OCT algorithms that take advantage of 3D information instead of just 2D information from single B scans are better suited to overcome this problem (6). The working assumption is that thinning of the GCL-IPL will reveal early signs of progressive optic neuropathy in the presence of papilledema. This will undoubtedly be the focus of studies in the near future to understand the usefulness of GCL-IPL thickness in the evaluation and monitoring of papilledema.

**FIG. 7.** A very large, coalescing druse imaged in several SD-OCT modalities. A. Fundus photo with 2 vertical markers placed on either side of the druse (obtained with 3D disc scan on Topcon 3D OCT 2000). B. Low-resolution SD-OCT image, obtained on same 3D disc scan. C. High-resolution image, obtained with 7-line Raster on Topcon 3D OCT 2000. D. High-resolution (5-line Raster) image, obtained with Zeiss Cirrus HD-OCT (30). SD-OCT, spectral domain optical coherence tomography.
Another recent development in OCT, which has possible relevance to understanding the pathogenesis of visual loss in papilledema due to ischemia relates to the visualization of optic nerve capillaries and capillary blood flow. Using phase contrast OCT, it is now possible to visualize capillaries and quantify flow within a capillary bed without the use of contrast agents (39). An example of OCT derived capillary flow in the normal and glaucomatous optic nerve head is shown in Figure 9.

FIG. 8. Papilledema associated with a neurosensory retinal detachment between the left optic nerve and the fovea. A. The macula total retinal thickness plot shows the elevation in the area of the fluid (arrows). B. B scan through the detachment area reveals the fluid (dark reflective layer) between the pigment epithelium and the photoreceptors (arrow). C. 3D macula thickness plot demonstrates the elevation in the area of the detachment with fluid (arrow).

FIG. 9. Disc photographs (A and C) and en face OCT angiograms (B and D) of the optic nerve head in representative normal (A and B) and PPG subjects (C and D). Both examples are from left eyes. In (B) and (D), the solid circles indicate the whole discs, and the dash circles indicate the temporal ellipses. A dense microvascular network was visible on the OCT angiography of the normal disc (B). This network was greatly attenuated in the glaucomatous disc (D) (39). OCT, optical coherence tomography; PPG, preperimetric glaucoma.


Clinical Trials to Clinical Use: Using Vision as a Model for Multiple Sclerosis and Beyond

Laura J. Balcer, MD, MSCE

Abstract: Optical coherence tomography (OCT) has made possible the structure–function correlations that uniquely characterize the afferent visual pathway as a model for understanding multiple sclerosis (MS) and for developing new treatments. During the past decade, OCT measures of retinal nerve fiber layer (RNFL) and ganglion cell/inner plexiform layer (GCL + IPL) thickness have evolved from being a means to validate visual function tests, such as low-contrast letter acuity, to provide a window on the axonal and neuronal loss that are now widely recognized as contributors to permanent visual dysfunction in MS. Although acute optic neuritis (ON) leads to thinning of the RNFL by 20%–40% within 3 months after a single episode, thinning of the RNFL and GCL + IPL occur over time in MS eyes even in the absence of an acute ON history. As such, OCT and its functional and patient-reported correlates of low-contrast acuity and vision-specific quality of life (QOL) have now been incorporated into MS clinical trials. Results of an ongoing, phase 2 trial of a remyelinating agent that uses acute ON as a model for assessing therapeutic efficacy will define even further the important role for OCT in documenting structural changes as we move forward from clinical trials to clinical use.

Just over a decade ago, clinical trials for multiple sclerosis (MS) did not include visual outcomes. Experts recognized the need for more sensitive measures of visual function, and low-contrast letter acuity emerged as a leading candidate to measure visual impairment. Although low-contrast acuity was quickly shown to correlate well with MRI lesion burden, visual-evoked potentials (VEPs), and quality of life (QOL) in MS, it was the introduction of optical coherence tomography (OCT) to the field of MS that allowed for the direct assessment of structure–function correlations in the anterior visual pathways. This unique capacity to link axonal and neuronal loss with specific impairment (vision) in MS makes the anterior visual system an ideal model for testing novel agents for neuroprotection and repair. The latest OCT investigations involve high-resolution spectral-domain OCT (SD-OCT) with segmentation (measurement) of specific retinal layers using computerized algorithms. These methods allow quantitation of both retinal nerve fiber layer (RNFL, axonal) and ganglion cell layer (GCL, neuronal) loss in vivo. New therapies that reduce axonal and neuronal loss by neuroprotective or myelin-repair mechanisms can now be assessed noninvasively by OCT and coupled with visual function data. Most MS clinical trials now include both OCT and visual function testing, and new clinical trials that use acute optic neuritis (ON) as a model will examine the capacity for OCT measures in particular to demonstrate structural evidence for neuroprotection in patients with MS and other neurologic disorders.

This review examines the data from observational studies and ongoing trials, presenting representative group data for visual function, OCT measures, and QOL scales in patients with MS, ON, and disease-free controls. These data, as well as those from meta-analyses within the past 5 years, may be used to provide reference values for the development of clinical trial protocols.

BACKGROUND

In 1974, Frisen and Hoyt (1) first described thinning of the RNFL in patients with MS. Postmortem studies later confirmed the suspicion that atrophy occurred in the RNFL in nearly 71% of the patients studied (2). The invention of OCT has allowed for objective measurement of the layers of the retina in vivo (3–5). Although acute demyelination as
a result of ON is an important contributor to visual loss, axonal and neuronal degeneration in the anterior visual pathways are likely important contributors to visual dysfunction in MS, even in patients without an acute ON history (3,6–10).

Because thinning of the RNFL and GCL + IPL by OCT are associated with reductions in visual function and QOL, OCT measures of axonal and neuronal loss have a unique ability to capture structure–function correlations in MS. Table 1 shows a mean difference in RNFL thickness of 11.8 m between disease-free control and all MS eyes (with and without a history of ON). The ability of OCT to detect these differences supports its potential role as a structural marker in MS clinical trials. OCT provides a noninvasive, objective measure of visual pathway integrity, and, therefore, could be used to determine effectiveness of neuroprotective and other MS therapies. Furthermore, OCT can be used in conjunction with visual function testing to follow disease progression of patients with MS.

FEATURES AND ADVANTAGES OF OCT IMAGING

Within the retina, retinal ganglion cell axons are una
dilated until they pass through the lamia cribosa. Therefore, RNFL imaging has the unique advantage of measuring the thickness of axonal and other retinal structures that can ultimately be used in assessing neurodegeneration and potentially neurorepair. OCT is similar to B-mode ultrasound, but uses light instead of sound to form images. An optical beam is scanned along the retina and the machine measures echo-time delays to synthesize a picture of retinal structure (11–14). Advances in OCT, including the development of spectral-(Fourier) domain technology, provide increased sensitivity and capacity for careful analysis of pathologic changes in the retina in vivo.

Representative group data for OCT in patients with MS and disease-free controls are presented in Table 1. Time-domain OCT (TD-OCT) (first generation widely studied in MS) shows substantial differences in RNFL thickness between eyes of patients with MS and disease-free controls (95.5 ± 14.5 μm vs 104.5 ± 10.7 μm). MS eyes with a history of ON have even greater degrees of thinning on average (85.7 ± 19.0 μm). For SD-OCT techniques, there are differences in scaling from TD-OCT, leading to smaller absolute differences in RNFL thickness (92.9 ± 10.0 μm for controls vs 87.6 ± 11.1 μm in MS eyes without a history of ON). Larger studies will further refine the precision of these representative average values. Statistically combined data for studies of TD-OCT as of 2009 are presented in a meta-analysis by Petzold et al (13) with analyzable data from 36 OCT studies in patients with MS.

An advantage of OCT is that it demonstrates high degrees of both interrater and test–retest reliability for TD and SD techniques (15). In fact, recent studies of SD-OCT show that this newer technology produces measurements that are more reproducible than TD-OCT (16). A study of 58 patients and 38 controls found that intraclass correlation coefficients (ICCs) ranged from 0.92 to 0.97 for intervisit, 0.83 to 0.99 for intrarater, and 0.94 to 0.99 for interrater reproducibility (15). Given its high degrees of reliability, sensitivity, and ease of use (pupillary dilation not usually needed), OCT is an ideal method for assessing pathologic changes in the visual pathway of patients with MS.

OCT INVESTIGATIONS IN MS AND OPTIC NEURITIS

During the course of their disease, between 30% and 70% of patients with MS will have acute ON (17,18). Because patients with acute demyelinating ON typically have symptoms of pain on eye movement, visual acuity loss, color desaturation, and visual field abnormalities, followed by substantial RNFL axonal loss by OCT (20–40 μm on average), ON is an ideal model for studying neuroprotective and neurorepair agents in MS.

In 1999, OCT was first used in a study by Parisi et al (19) to investigate a group of patients who had a history of ON with complete recovery of visual acuity. When compared with control eyes, RNFL thickness was reduced by 46% in the eyes affected by acute ON. The affected eyes were also found to have RNFL thickness decreased by 28% when compared with the unaffected eyes of the same patient (P < 0.01). A subsequent investigation by Tripp et al (20) substantiated these findings among eyes of patients with a history of ON and incomplete recovery. In this cohort of 25 patients with a history of unilateral ON, the ON eyes had a 33% reduction in RNFL thickness of patient eyes compared with disease-free control eyes (P < 0.001) (20). These authors also reported reductions in total macular volume in ON eyes compared with controls (P < 0.001) and also showed differences between affected and unaffected eyes of patients in the study (P < 0.001).

A more recent study by Costello et al (21) demonstrated that close to 75% of patients with MS with ON will have RNFL losses between 10 and 40 μm in their affected eyes within 3–6 months after the acute event. Considering that the average RNFL thickness by TD-OCT in disease-free controls is 105 μm (92 μm in MS eyes) and that healthy control eyes lose only 0.017% of total RNFL thickness annually, the RNFL thinning associated with acute ON is substantial and provides a target for reduction of axonal loss in future clinical trial of ON (16). Costello et al (21) also established a threshold value of 75 μm by TD-OCT, below which there was a corresponding decline in visual function as measured by mean deviation with automated perimetry (21). Among eyes in a collaborative heterogeneous cohort of patients with MS, eyes with a history of ON seem to have
<table>
<thead>
<tr>
<th></th>
<th>Disease-Free Controls</th>
<th>All MS</th>
<th>MS, No History of ON</th>
<th>MS, History of ON</th>
<th>References</th>
</tr>
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<tr>
<td><strong>High-contrast VA,</strong></td>
<td>64 ± 5 (n = 61 eyes)</td>
<td>59 ± 8 (n = 239 eyes)</td>
<td>60 ± 6 (n = 150 eyes)</td>
<td>58 ± 9 (n = 87 eyes)</td>
<td>22,24,25,32,39*,43</td>
</tr>
<tr>
<td><strong>ETDRS,</strong> number of</td>
<td>Binocular testing</td>
<td>66 ± 5 (n = 324 pts)</td>
<td>62 ± 8 (n = 1,007 pts)</td>
<td>63 ± 7 (n = 544 pts)</td>
<td>41,42,43*</td>
</tr>
<tr>
<td><strong>letters correct</strong></td>
<td><strong>Low-contrast letter</strong></td>
<td>34 ± 8 (n = 61 eyes)</td>
<td>26 ± 11 (n = 239 eyes)</td>
<td>28 ± 9 (n = 150 eyes)</td>
<td>24,25,39*,43</td>
</tr>
<tr>
<td><strong>acuity (2.5%), number</strong></td>
<td>Binocular testing</td>
<td>43 ± 6 (n = 324 pts)</td>
<td>36 ± 10 (n = 1,007 pts)</td>
<td>38 ± 9 (n = 544 pts)</td>
<td>41,42,43*</td>
</tr>
<tr>
<td><strong>of letters correct</strong></td>
<td><strong>Low-contrast letter</strong></td>
<td>25 ± 7 (n = 61 eyes)</td>
<td>16 ± 10 (n = 239 eyes)</td>
<td>18 ± 10 (n = 150 eyes)</td>
<td>22,24,25,39*43</td>
</tr>
<tr>
<td><strong>acuity (1.25%), number</strong></td>
<td>Binocular testing</td>
<td>34 ± 8 (n = 324 pts)</td>
<td>24 ± 11 (n = 1,007 pts)</td>
<td>26 ± 11 (n = 544 pts)</td>
<td>41,42*,43</td>
</tr>
<tr>
<td><strong>of letters correct</strong></td>
<td><strong>NEI-VFQ-25</strong></td>
<td>96 ± 4 (n = 31 pts)</td>
<td>88 ± 13 (n = 122 pts)</td>
<td>90 ± 12 (n = 111 pts)</td>
<td>39*,43</td>
</tr>
<tr>
<td><strong>composite score,</strong></td>
<td>Binocular testing</td>
<td>97 ± 3 (n = 31 pts)</td>
<td>87 ± 13 (n = 122 pts)</td>
<td>88 ± 12 (n = 111 pts)</td>
<td>39*,43</td>
</tr>
<tr>
<td><strong>best score = 100</strong></td>
<td><strong>10-item Neuro-</strong></td>
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<td><strong>ophthalmic</strong></td>
<td><strong>supplement to the</strong></td>
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<tr>
<td><strong>NEI-VFQ-25, best</strong></td>
<td><strong>score = 100</strong></td>
<td></td>
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<tr>
<td><strong>TD-OCT</strong></td>
<td><strong>Peripapillary RNFL</strong></td>
<td>104.5 ± 10.7 (n = 219 eyes)</td>
<td>92.5 ± 16.7 (n = 1,058 eyes)</td>
<td>95.6 ± 14.5 (n = 730 eyes)</td>
<td>85.7 ± 19.0 (n = 328 eyes)</td>
</tr>
<tr>
<td><strong>thickness, μm</strong></td>
<td>Total macular volume, mm³</td>
<td>6.84 ± 0.36 (n = 219 eyes)</td>
<td>6.54 ± 0.51 (n = 1,058 eyes)</td>
<td>6.63 ± 0.48 (n = 730 eyes)</td>
<td>6.36 ± 0.53 (n = 328 eyes)</td>
</tr>
<tr>
<td><strong>SD-OCT</strong></td>
<td><strong>Peripapillary RNFL</strong></td>
<td>92.9 ± 10.0 (n = 61 eyes)</td>
<td>84.3 ± 12.8 (n = 239 eyes)</td>
<td>87.6 ± 11.1 (n = 150 eyes)</td>
<td>78.4 ± 13.6 (n = 87 eyes)</td>
</tr>
<tr>
<td><strong>thickness, μm</strong></td>
<td><strong>GCL + IPL, μm</strong></td>
<td>88.9 ± 6.9 (n = 61 eyes)</td>
<td>84.1 ± 8.4 (n = 239 eyes)</td>
<td>87.0 ± 6.6 (n = 150 eyes)</td>
<td>79.7 ± 9.2 (n = 87 eyes)</td>
</tr>
<tr>
<td><strong>Macular RNFL, μm</strong></td>
<td></td>
<td>29.6 ± 6.0 (n = 61 eyes)</td>
<td>23.5 ± 8.2 (n = 239 eyes)</td>
<td>25.5 ± 7.1 (n = 150 eyes)</td>
<td>20.0 ± 9.0 (n = 87 eyes)</td>
</tr>
</tbody>
</table>

ETDRS, Early Treatment Diabetic Retinopathy Study; NEI-VFQ-25, 25-Item National Eye Institute Visual Functioning Questionnaire; SD, spectral-domain (Cirrus platform); TD, time-domain (OCT-3 platform); QOL, quality of life; OCT, optical coherence tomography; MS, multiple sclerosis; ON, optic neuritis; pts, patients; RNFL, retinal nerve fiber layer; GCL-IPL, ganglion cell layer-inner plexiform layer.

*Reference with asterisk is source of data presented in table and rest of the references contain data.
a threshold of approximately 80 μm by TD-OCT, below which they show sustained abnormalities by low-contrast letter acuity.

Trials of neuroprotective or repair agents for ON will likely establish a "therapeutic window" or time frame within which the agent should ideally be given to maximize the effect of preventing axonal/neuronal loss. A recent study used several tests, including high- and low-contrast visual acuity, Farnsworth-Munsell 100 Hue color testing, automated visual fields, pattern VEP, and RNFL thickness by TD-OCT to investigate when changes occurred in the course of ON (22). This study determined that after a mean of 4.75 months of follow-up, 99% of the total amount of RNFL axonal loss had occurred. After 1.65 months (95% confidence interval, 0.96–2.32; P < 0.05), RNFL thinning could be observed when compared with the unaffected fellow eye. Worse recovery was associated with more significant RNFL decline over 3 months of observation (P = 0.002). Significant macular volume loss between initial assessment and follow-up also was established (22,23).

ON is a predictable cause of axonal and neuronal degeneration in the eyes of patients with MS. Interestingly, recent reports have shown that regardless of a history of ON, RNFL thinning can be seen in heterogeneous MS cohorts. Low-contrast letter acuity loss also is associated with RNFL thinning in MS eyes without a history of ON (24). In a cross-sectional study of 90 patients and 36 disease-free controls, RNFL thickness was reduced in the eyes of patients without a history of ON (105 μm; P = 0.03). This study also showed that both MS eyes with a history of ON and MS eyes without a history of ON had significant damage as compared with disease-free controls (24). There was a loss of 4 μm of RNFL thickness for every line of low-contrast letter acuity loss among eyes of MS patients. RNFL thickness was associated with overall degrees of neurologic impairment, worse Expanded Disability Scale Scores (EDSS) and longer disease duration.

Studies have shown that RNFL thickness becomes reduced over time in MS regardless of the history of ON (25). Patients with MS and controls at 3 academic centers underwent OCT imaging and visual testing. In patients without a history of ON, an average RNFL thickness of MS eyes were reduced by 2.9 μm after 2–3 years and by 6.1 μm after 3–4.5 years (P < 0.001). These data would indicate a significant need for monitoring the structural changes even in eyes without a history of ON.

**RESEARCH ON OCT IN MS**

Using scanning laser polarimetry with a GDx-VCC, Zaveri et al (26) demonstrated that RNFL thinning is related to visual loss. Although OCT RNFL thickness is reflective of structural changes in the ganglion cell axons, measurement of the RNFL by scanning laser polarimetry can demonstrate underlying microtubule integrity based on the property of birefringence. This technique is particularly valuable in the setting of MS because it is able to quantify integrity of the RNFL in the setting of optic disc edema.

With the development of SD-OCT, segmentation of the layers of the retina is now possible. This is an important advance because neuronal loss is regarded as a correlate of MS disability (27–31). Studies using TD-OCT had shown decreased total macular volume in patients with MS, and this measure could estimate ganglion cell neuronal loss (32). SD-OCT has provided the first opportunity to more directly estimate thinning of the GCL + IPL through manual segmentation. In a pilot study, Davies et al (33) showed that the eyes of patients with MS (n = 16) had significantly lower GCL volume as compared with controls (P < 0.001). There was not a significant association between GCL and high-contrast visual acuity loss, and low-contrast acuity correlated with GCL volume scores (P = 0.003).

Given the amount of time required to segment retinal layers manually (approximately 2 hours), there is a need for computerized algorithms that allow for measurement of the retinal layers on a large scale. Studies of patients with glaucoma have successfully used computerized segmentation algorithms to quantify the layers of the retina, and these methods have now been applied to SD-OCT images of eyes of patients with MS (34,35).

OCT measurements of RNFL thickness and other parameters can also differ among MS subtypes. Patients with secondary progressive MS (SPMS) have greater reductions in RNFL thickness (83.4 μm by TD-OCT) compared with patients with clinically isolated syndrome (CIS) (101.2 μm, P = 0.0009) and relapsing remitting MS (RRMS) (103.7 μm, P = 0.001) (36). In eyes with a history of ON, patients with SPMS had greater thinning (39.5 μm at follow-up) than in CIS (58.1 μm, P = 0.03) or RRMS (48.2 μm).

Benign MS is another area in which definitions and diagnostic criteria may unintentionally minimize the apparent role of visual pathway disease. Patients with benign MS most typically have an EDSS ≤3 and ≥15 years disease duration, and are therefore thought to follow a milder course when compared with those with typical RRMS. Galetta et al (37) conducted a longitudinal analysis of EDSS scores, visual function, OCT measurements, and QOL assessments in a subset of patients with benign MS. RNFL thickness was measured using TD-OCT and QOL scales, including the NEI-VFQ-25 and SF-36. Using the most common definition of benign MS, 13 patients (26 eyes) met inclusion criteria. Despite the relatively low EDSS score, patients with benign MS had similar if not greater degrees of RNFL thinning from baseline during an average follow-up of 1.6 years (benign MS eyes, 3.6 μm, P = 0.0008 vs baseline, paired t test; typical MS eyes, −3.3 μm, P < 0.0001). Vision-specific QOL scores were likewise worse among patients with benign MS who had similar if not greater degrees of RNFL thinning from


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baseline during an average follow-up of 1.6 years (benign MS eyes, 3.6 μm, \( P = 0.0008 \) vs baseline, paired \( t \) test; typical MS eyes, \(-3.3 \mu m, P < 0.0001\)). Vision-specific QOL scores were likewise worse among patients with benign MS compared with those with typical RRMS (NEI-VFQ-25 composite scores, \( 75 \pm 21 \) vs \( 88 \pm 11, P = 0.005 \), accounting for age) and history ON (\( P = 0.002 \)). These data provide further evidence that the EDSS does not adequately capture visual pathway axonal loss and visual impairment, both of which are likely contributors to disability in patients with benign MS.

Patients with the macular thinning predominant phenotype of MS are of interest to our understanding of gray matter/neuronal loss as manifested in the retina. Saidha et al (38) examined a cohort of patients with normal peripapillary RNFL thickness but thinning of the macular region to the fifth percentile or less using SD-OCT. Although this group had thinning of the outer retinal layers (\(<0.001 \) for inner and outer nuclear layers), there was minimal thinning of the GCL layer, suggesting a unique pattern of retinal neuronal cell loss in patients with this phenotype. Pathologic studies of postmortem eyes of patients with MS (n = 82) have shown GCL loss in 79% (10). Using algorithms originally designed for investigation of GCL + IPL thinning in glaucoma and developed at the University of Pittsburgh, Walter et al (39) investigated in vivo measurement of the GCL + IPL and other retinal layers in MS. In 122 patients (239 eyes) and 31 controls (61 eyes), macular RNFL (\( P < 0.001 \)) and GCL + IPL (\( P = 0.001 \)) were significantly thinner in MS eyes (accounting for age and within-patient, intereye correlations). Macular RNFL thickness and GCL + IPL also were found to be significantly thinner in MS eyes with a history of ON (\( P = 0.006 \)) were the retinal layers that were most strongly associated with reduced vision-specific QOL scores (NEI-VFQ-25 and 10-item supplement composite). Ganglion cell layer neuronal loss in MS is likely to be an important indicator visual pathway disease in MS.

**OCT IN CLINICAL TRIALS: ROLE FOR READING CENTERS**

The incorporation of OCT and visual outcome measures into MS clinical trials has benefited from the presence of OCT reading centers. The University of California Davis Reading Center recently published the results of Stratus (TD) OCT quality control in 2 multicenter MS clinical trials (40). The authors evaluated 19,961 OCT from 981 patients with the goal of determining the influence of OCT quality control procedures on error rate. In trial 1 (design and therapeutic agent not specified in publication), there was no ophthalmic technician certification and data were obtained by the Reading Center retrospectively. However, in trial 2, technicians were certified and submitted data prospectively according to the study protocol. OCT in trial 2 had higher signal strengths, fewer errors, and more usable data compared with trial 1 scans. This study showed that certified technicians and prompt transmission of data for ongoing quality control monitoring provide higher data quality; these factors and the use of Reading Centers should be considered in the design of clinical trials for MS and other neuro-ophthalmologic disorders.

**CONCLUSIONS**

Visual dysfunction is not only an important contributor to impairment and disability in MS, but also represents a unique opportunity for studying disease mechanisms and for testing new therapies that involve neuroprotection and repair. OCT has allowed investigators to examine in vivo the morphologic changes that accompany visual loss. Sensitive visual function tests, including low-contrast letter acuity, have been shown to correlate with OCT measures of axonal and neuronal loss as well as with patient-reported assessments of QOL. These observations have been instrumental in the establishment of a structure–function paradigm for using the anterior visual pathway as a model in MS and other neurologic disorders that affect the anterior visual pathway. Emerging data from ongoing clinical trials will yield important findings for therapeutics in MS, ON, and other neuro-ophthalmologic causes of visual loss (41,42).

**REFERENCES**


Retinal Segmentation Using Multicolor Laser Imaging

Robert C. Sergott, MD

Abstract: Spectral-domain optical coherence tomography (SD-OCT) changed 3 worlds: clinical care, clinical research, and the regulatory environment of phases 2, 3, and 4 pharmaceutical and surgical trials. OCT is now undergoing another transformation with multicolor technology, which acquires images using data from 3 simultaneous lasers: red, green, and blue, taking advantage of the different wavelengths of each of these colors to most precisely image 3 different zones of the retina. Rather than seeing only the surface of the retina and optic disc and any large lesions in the deeper retina, this technology provides a topographic map of the outer (red), mid (green), and inner (blue) retina somewhat similar to what is observed with fundus autofluorescence of deep retina, retinal pigment epithelium, and choroid. Multicolor imaging will supplement and help to define what is observed with traditional fundus photography and SD-OCT. In addition, it may demonstrate abnormalities when routine photography is normal and when SD-OCT findings are equivocal. This review will illustrate the basic principles of multicolor imaging and will show clinical examples of how this technique can further define retinal and optic nerve pathology.

METHODS

A 5-step approach to the interpretation of multicolor images is recommended (Fig. 3):

1. Examine the color-balanced, composite multicolor image to detect areas of pathologic change.
2. Examine the individual images from each colored laser ("source images"), correlating these findings with the color-balanced image. When evaluating these images, the clinician must always ask whether the images may contain artifacts.
3. Assess carefully for evidence of imaging artifacts (see Artifacts section).
4. Correlate the findings of the color-balanced image and the individual laser images and with spectral-domain OCT (SD-OCT) images in the pathological regions.
5. Compare the findings from each eye, correlating with the patient’s history and examination findings.

ARTIFACTS

Artifacts with multicolor laser occur predominantly in the center of the image. Because the lens surfaces are curved, light reflected from the peripheral retina during scanning is scattered out of the beam path and is not captured in the fundus image.

The appearance and brightness of the artifact depends on the ratio of the light intensity reflected from the retina, and the intensity of the light reflected on the lens surfaces. No artifact is visible if the pupil is dilated and/or if the media of the patient are clear.

However, if a patient has a significant cataract and/or if the camera is improperly aligned an artifact appears. In these cases, the sensitivity of the detector will be increased to obtain a clearly illuminated retinal image, and the light reflected on the lens surface is visible. Patients with corneal opacities, optically significant cataracts, poor pupillary dilation, and high myopia are prone to demonstrate artifacts with multicolor imaging (Fig. 4).

Clinical examples are shown below:
- Macular Hole (Fig. 5).
- Papilledema (Fig. 6).
- Nonarteritic anterior ischemic optic neuropathy (Fig. 7).
CONCLUSIONS

Multicolor laser imaging represents the next generation of retinal imaging that will further define and localize pathological processes within the retina that are involved in neuro-ophthalmic diseases.

Multicolor imaging shares the patient friendly nature of OCT with its noninvasive, noncontact, painless techniques. Proper interpretation of the imaging results depends on correlation with “source images” from the infrared, green, and blue lasers as well as correlation with SD-OCT and the patient’s clinical findings.
FIG. 6. Papilledema. **A** and **B**, Spectral-domain optical coherence tomography (SD-OCT) demonstrates optic disc elevation and migration of fluid into the subretinal space (white arrows). Secondary thickening of the inner and mid-retinal layers also is present and disruption of the ellipsoid zone of the photoreceptors in the papillomacular bundle. Multicolor laser image (C) confirms diffuse disc edema and the bright signal in the fovea of the infrared image (D), corresponds to the ellipsoid changes found on SD-OCT. Interestingly, the green and blue laser images (E and F) demonstrate hyperreflectivity (arrows) in a perivenular location.
FIG. 7. Nonarteritic anterior ischemic optic neuropathy (NAION). A, Spectral-domain optical coherence tomography (OCT) demonstrates retinal nerve fiber layer edema in the right eye. The patient has had a prior episode of NAION in the left eye with nerve fiber layer thinning. B, MultiColor image of acute NAION in the right eye (upper left) also demonstrates increased signal in the infrared images of the deep retina inferiorly (upper right) and increased signal in the mid (lower left) and superficial (lower right) retina. C, The left eye with prior NAION has increased signal in the outer retina but dark areas in the superior retina and papillomacular bundle (lower left, lower right) corresponding to the region of retinal nerve fiber layer atrophy seen on the OCT.