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Advanced Imaging of Anterior Visual Pathway Ischemia: State of the Art and Future Directions

Edward P. Quigley III, MD, PhD, Anne Osborn, MD

It is truly an exciting time to be neuroophthalmologists and neuroradiologists. Our two subspecialties are accelerating together. As magnetic resonance imaging (MRI) improves, we neuroradiologists can provide confirmation and evaluation of pathologies previously identified only clinically. Two articles appearing in this issue of the *Journal of Neuro-Ophthalmology* (1,2) demonstrate this coalescence of clinical acumen and improvements in neuroimaging. In particular, recent advances in MRI of acute ischemia facilitate the brave new world of visual pathway imaging. Higher field magnets, improved coil arrays, and new MR sequences are all contributing factors. In particular, diffusion-weighted imaging (DWI) has been improved upon with diffusion tensor imaging (DTI). In this editorial, we will discuss the imaging advances in the context of the two reports appearing in the Journal. Next, we would like to introduce current and some future imaging advances on the near horizon. In addition, we will discuss the hurdles and limitations of imaging on the cutting edge of ischemic optic pathology.

“MRI restricted diffusion in optic nerve infarction after autologous fat transplantation,” by Lee et al (1) is an elegant display of imaging complementing the clinical evaluation. In the patient described with acute post procedural deficits from autologous fat transplantation, ischemia in the middle cerebral artery distribution did not explain the clinical deficit. Careful analysis of routinely acquired MR imaging demonstrated additional pathology along the optic nerve. As in brain parenchyma, if diffusion hyperintensity is present, then one should evaluate the corresponding apparent diffusion coefficient (ADC) map values. In this case, ADC values were both qualitatively and quantitatively decreased. This excludes T2 shine through phenomenon. The ADC values obtained are comparable to brain parenchymal ischemic values. This paper demonstrates the critical role of considering external carotid to internal carotid arterial anastamoses. Retrograde injury to the optic nerve has demonstrated via embolization to the internal carotid and ophthalmic arteries (3).

“Chiasmal stroke following open heart surgery,” by Fabian et al (2) provides a superb example of DWI detection of small regions of ischemia. While the optic chiasm is vascularly rich, it is still susceptible to ischemic or compressive injury. Pathology of the sella can compress or remodel the chiasm and embolic phenomenon can cause acute ischemia. While subtle increased diffusion restriction is seen in the chiasm in the case reported by Fabian and colleagues, the decrease in ADC value is compelling. Like routine parenchymal ischemia, DWI is the first MR sequence to become positive for ischemia, then FLAIR, followed by T2. This paper demonstrates the evolution of ischemic chiasmatic T2 hyperintensity four days post ischemia with thin section orbital MRI.

These papers introduce some of key concepts in the modern imaging of the visual pathways (4) and we would like to make some additional recommendations. Routine DWI may depict larger lesions of the optic nerve chiasm or optic radiations. DTI uses multiple diffusion directions of analysis rather than three direction conventional DWI. If possible, both DWI and DTI should be performed at 3 mm intervals rather than routine whole brain 5 mm intervals. Even comparing thin section DWI to DTI, diffusion tensor imaging may better detect small lesions due to higher signal to noise ratio. Imaging limitations are always time and motion degradation. If the patient cannot maintain position for 5-6 minutes for DTI acquisition, routine DWI may be the only imaging choice available.
Ocular motion can significantly degrade both DWI and DTI of the retrobulbar optic nerve. However, DTI is superb for detection of small ischemic lesions. For example, infarcts of the small structures such as the fornices, septum pellucidum, chiasm, hippocampus, and medial longitudinal fasciculus can be seen on DTI (5–7).

Consequently, if ischemic optic neuropathy is suspected clinically, then obtain DWI, DTI, thin section coronal STIR and T2 fat-saturated imaging. Coronal STIR and T2 demonstrate optic nerve and chiasm in cross section. ADC values can be quantitatively measured on vendor specific software or open source imaging software (8). Due to the small size of the optic nerve, volume averaging of adjacent fat, muscle or bone may significantly affect measurements (9,10). Point ADC values can be extracted or qualitative maps can be generated (Fig. 1).

In contrast to normal brain parenchyma, the visual pathways are a highly organized group of fibers. Similar to analysis of DWI and DTI in the spinal cord, one can further divide optic nerve diffusion parameters into longitudinal and axial components (11,12). There are differential decreases in diffusion parameters in optic neuritis (13,14).

However, for ischemic optic neuropathy, these differences have not yet been fully evaluated. Factors that limit quantitative analysis are small size of structures, limited signal-to-noise ratio, susceptibility from orbital fat and aerated sinuses, and “wrap-around” artifact from small field of view (15). Jeong et al have developed IMIV DTI, interleaved multiple inner volume diffusion tensor imaging, to address this last issue (16,17). We have applied this method to optic neuritis and hope to apply to acute optic pathway ischemia (Fig. 1). To address the low signal from optic nerves, Parker and Hadley have developed an optic nerve surface coil for 3T imaging (18).

Future imaging advances in visual pathway imaging will include diffusion spectrum imaging and diffusion kurtosis imaging. Diffusion spectrum imaging can resolve crossing fiber pathways like the chiasm (19). Diffusion kurtosis addresses linear assumptions in conventional DTI (20). These methods have the potential to analyze the chiasmatic decussation. Clinical applications of higher magnetic field strength MR and improved tractography techniques will continue to elucidate anatomy and pathology (21–23).

In conclusion, neuroradiology is applying new techniques to better image the visual pathway from the fundus to the calcarine cortex. We now can provide imaging evidence to support astute neuro-ophthalmologic examination. MRI, particularly DTI, can now demonstrate the acute onset and subsequent evolution of visual pathway ischemia. Ongoing advances in MR sequences, more powerful magnets, and new coil arrays provide complementary imaging which will continue to improve in months and years to come.

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MRI and Positron Emission Tomography Findings in Heidenhain Variant Creutzfeldt-Jakob Disease

Sashank Prasad, MD, Edward B. Lee, MD, PhD, John H. Woo, MD, Abass Alavi, MD, Steven L. Galetta, MD

Abstract: The typical presentation of Heidenhain variant Creutzfeldt-Jakob disease (CJD) is a rapidly progressive visual loss in the setting of a relatively normal ophthalmologic examination. At presentation, patients with this uniformly fatal illness frequently demonstrate only minor cortical abnormalities on MRI. Here, we document the clinical presentation and imaging results of a patient with...
A 66-year-old woman noticed slowly progressive blurred vision in the left inferior visual field. There were no headaches or other accompanying symptoms. An ophthalmologic examination revealed a homonymous left inferior field cut and no other abnormalities. Brain MRI was normal.

Over several weeks, visual loss gradually extended into the right inferior visual field (Fig. 1). She was referred for neuro-ophthalmic consultation. The patient described visual hallucinations in the form of shimmering orange lights in her peripheral vision along with palinopsia. Knitting had become difficult because of impaired depth perception. She had developed mild gait unsteadiness. There were no deficits of memory, language, or behavior, nor was there weakness or numbness.

On examination, she was alert and fully oriented. She named 28 of 30 items on the Boston naming task and comprehended complex verbal commands. She was fluent, and she could repeat normally. On memory testing the patient recalled 10 of 10 elements in a story after a 5-minute delay. Visuospatial testing revealed difficulty copying a cube, although she drew a clock face correctly. On testing of executive functions, she named 18 words beginning with the letter F in 1 minute. She completed oral trials successfully, performed simple calculations, and demonstrated normal praxis.

Corrected visual acuity was 20/25 in each eye. The patient correctly named colors but reported desaturation of blue and yellow. She identified the control Ishihara color plate but none of the test plates and made numerous errors arranging the desaturated L’Anthony D-15 color panel. She was unable to perceive a stereoscopic image with the Titmus stereotest (3,000 arcsec retinal disparity). Confrontation visual fields demonstrated a dense left inferior quadrant scotoma and a partial right inferior quadrant scotoma. Within the blind field, however, she correctly discriminated motion cues (the Riddoch phenomenon). The patient reported persistence of visual images a few moments after shifting gaze but correctly described all elements of both the “cookie-thief” picture and a Navon figure. Pupillary responses, ocular motility, and fundus examinations were normal.

Strength was normal. There was no myoclonus, numbness, or dysmetria. She reached for objects accurately, without past-pointing or tremor. Tandem gait was mildly impaired. Reflexes were normal, and symmetric and plantar responses were flexor.

A repeat brain MRI revealed slight abnormalities of the occipital cortical ribbon, including hyperintensity on FLAIR imaging and diffusion-weighted imaging that was more prominent on the right (Fig. 1). In addition, there were nonspecific white matter hyperintensities, consistent with small vessel ischemia. The basal ganglia and thalami were normal. An MRI perfusion study (using the unenhanced arterial spin labeling technique) revealed slightly decreased occipital blood flow. Fluorodexoyglucose-positron emission tomography, in contrast to the MRI studies, revealed striking abnormalities, with severe hypometabolism of the bilateral occipital and parieto-temporal cortices (right greater than left) (Fig. 1).

Cerebrospinal fluid analysis showed no cells, protein 52 mg/dL, glucose 56 mg/dL, and normal cytology. The 14-3-3 immunoassay revealed only weak immunoreactivity and was considered an ambiguous result. CT of the chest and abdomen were normal. Testing for paraneoplastic antibodies was negative. An electroencephalogram (EEG) revealed a normal posterior dominant rhythm, without focal slowing or paroxysmal sharp waves. Visual evoked responses were normal (P100 latency, 103 milliseconds in the right eye, 101 milliseconds in the left eye).

The patient went completely blind over a period of 8 weeks. She died 12 weeks from the onset of symptoms and terminally she had myoclonus and impaired arousal and orientation. At autopsy, there was severe neuronal loss and gliosis with spongiform vacuolization that predominantly affected the occipital lobes (Fig. 1). Western blot analysis demonstrated accumulation of protease-resistant PrPSc (type 1), and genetic sequencing revealed the homozygous methionine polymorphism at codon 129 of the PrP gene. The Heidenhain variant of sporadic Creutzfeldt-Jakob disease (CJD) describes a rare rapidly progressing dementia in which prominent visual changes constitute the initial symptoms. In 1929, Heidenhain first described this entity, reporting 5 cases sharing this striking clinical presentation in whom histopathological analysis revealed severe abnormalities including neuronal loss, gliosis, and vacuolization that were most prominent in the occipital lobes (1). Publication of cases with similar clinical and pathological features led to the proposal that this entity be named the Heidenhain variant (2). After several decades without insight into the pathogenesis of these disorders, Stanley Prusiner (3) advanced the prion hypothesis, which implicates the misfolding of the normal PrP protein into the protease-resistant PrPSc isoform. Almost all cases of Heidenhain variant CJD (including our patient) are homozygous for methionine at codon 129 of the PrP gene, but the significance of this association remains unclear (4).

The clinical diagnostic features of Heidenhain variant CJD have been well characterized (5–15). In comparison to...
patients with ataxia-predominant CJD. Heidenhain patients have a similar age at onset, although they have a more rapid deterioration (mean disease duration, 5.7 vs 7.5 months) (7). Heidenhain patients commonly report a variety of visual symptoms, including blurring, field constriction, metamorphopsia, visual hallucinations, or visual neglect. In our patient, widespread posterior metabolic abnormalities in striate cortex and visual association areas (including color processing area V4 and motion processing area V5) accounted for the patient’s bilateral homonymous visual field defects, impaired color processing, and palinopsia.

It is common for the brain MRI in Heidenhain variant CJD to be normal or show only minimal changes, particularly early in the disease course (8). As our case demonstrates, severe progressive cortical visual loss may occur with only minimal structural changes identified by MRI. On the other hand, several recent reports of Heidenhain variant CJD have demonstrated that nuclear imaging studies may reveal conspicuously abnormal areas of hypometabolism (9–12). Reduced occipital blood flow has also been reported using nuclear imaging techniques, including Xe-133 SPECT (5), 99mTc-SPECT (13), and [15O]H2O PET (11). In many of these cases, however, Heidenhain variant CJD was suspected without pathological confirmation (9–12).

The case illustrated here demonstrates pathologically confirmed Heidenhain variant CJD with prominent focal hypometabolism observed on brain PET scan. In contrast, other ancillary tests (including standard MRI sequences, magnetic resonance perfusion, CSF 14-3-3, and EEG) demonstrated only mild abnormalities during the disease course and provided only limited clinical-anatomical correlation with our patient’s visual complaints. Nuclear imaging is a particularly sensitive indicator of the extent of neural dysfunction early in the course of Heidenhain variant CJD, demonstrating severe posterior hypometabolism in cortical regions that correlate with the visually predominant clinical deficits in these patients.

REFERENCES

Chiasmal Stroke Following Open-Heart Surgery

Ido Didi Fabian, MD, Gahl Greenberg, MD, Ruth Huna-Baron, MD

Abstract: A 62-year-old man awoke from aortic valve replacement surgery with a total loss of vision in his right eye and a temporal visual field defect in his left eye. Automated visual field examination confirmed a right-sided anterior junction syndrome, and a right-sided chiasmal infarct was demonstrated by MRI. Although rare, chiasmal stroke is a potential complication of open-heart surgery.

CASE REPORT

A 62-year-old man with diabetes mellitus, hypertension, and aortic stenosis but no ocular history was admitted to the thoracic surgical department at our institution for an AVR procedure. The surgery was uneventful, with no hypotension (lowest perfusion pressure: 55 mm Hg), arrhythmia, or severe blood loss (lowest hemoglobin: 8.1 gm/dL). The patient was kept in the supine position for 2.5 hours throughout the procedure and was on a cardiopulmonary bypass membrane oxygenator machine (D905 Avant oxygenator; Sorin Biomedica, Mirandola, Italy) for a total of 1.5 hours.

The patient awoke from surgery complaining of total loss of vision in his right eye and a visual field defect in his left eye. Bedside ophthalmologic examination revealed no light perception in the right eye and J16 near visual acuity in the left eye. The right pupil was amaurotic. Confrontation visual field testing detected a temporal defect in the left eye. Anterior segments were unremarkable, and neither retinopathy nor emboli were noted on dilated funduscopic examination. The rest of the neurological evaluation was normal.

Brain CT showed chronic ischemic changes in the left occipital pole. A chiasmatic lesion was suspected, and 48 hour after AVR, the patient underwent MRI of the brain and orbits. Diffusion-weighted imaging (DWI) showed an abnormality involving the distal aspect of the right optic nerve and the right side of the optic chiasm (Fig. 1), which was also present on T2 images (Fig. 2). MRI also showed an acute cortical infarct in the left occipital pole and 2 other small ischemic foci in the left parietal lobe and the left cerebellar hemisphere. The patient was diagnosed as having multiple brain infarctions.

On the fifth day postoperatively, visual acuity was light perception in the right eye and 20/100 in the left eye. Automated visual field testing revealed a temporal defect in the left eye (Fig. 3A). The patient underwent transthoracic echocardiography and carotid Doppler examination, both of which failed to demonstrate a possible source of emboli.

At 7-week follow-up, MRI showed evolution of the chiasmal infarct (Fig. 4), which was unchanged 2 months later. Five months following surgery, vision had improved to hand motions in the right eye and 20/20 in the left eye. There was minimal improvement in visual field testing (Fig. 3B).

DISCUSSION

Perioperative visual loss among patients undergoing non-ocular surgery occurs in less than 0.001% of cases (3,4), whereas the prevalence of visual loss after cardiac surgery is estimated to be 100 times greater (5–7). The most commonly affected site is the optic nerve with the mechanism being ischemic in origin. If the optic chiasm is involved, it may be the result of an expanding sellar or parasellar mass, such as pituitary apoplexy or a rapidly expanding adenoma (8).
An ischemic insult to the chiasm is a rare event due to the fact that the chiasm is supplied by an extensive network of collateral cerebral blood vessels originating from the circle of Willis.

Our patient experienced loss of vision following AVR surgery under general anesthesia. MRI showed multiple ischemic foci in the brain, as well as a right-sided chiasmal infarct involving the prechiasmal portion of the right optic nerve. Visual field examination confirmed a right anterior junction syndrome (9). Although no definite source was found, we assume that the insult is most likely embolic in nature. Cerebral emboli have been reported to occur frequently following cardiopulmonary bypass procedures and confirmed both with fluorescein angiography (10) and autopsy studies (11,12).

Anatomic studies have detailed the complex blood supply of the chiasm and visual pathways (1,2). This rich vascular network includes 2 major components, a superior group and an inferior group. The superior group of vessels emanate from the anterior cerebral arteries and occasionally anterior communicating arteries, whereas the inferior blood supply is derived from branches of the internal carotid artery, basilar, posterior cerebral, and posterior communicating arteries. The complex nature of this network is characterized by numerous anatomical variations, collateral feeders, and crossing-over phenomenon (1). Based on the location of the chiasmatic infarct in our case, we propose involvement of branches arising from the A1 segment of the right anterior cerebral artery or from the distal right internal carotid artery.

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In conclusion, MRI, and DWI in particular, may play a valuable role in evaluating patients with perioperative visual loss due to ischemia of the anterior visual pathways.

REFERENCES

Spontaneous Resolution of Two Dural Carotid-Cavernous Fistulas Presenting With Optic Neuropathy and Marked Congestive Ophthalmopathy

Mathew Bujak, MD, FRCSC, Edward Margolin, MD, FRCSC, Andrew Thompson, MD, Jonathan D. Trobe, MD

Abstract: Two patients with dural carotid-cavernous fistulas (CCFs) presented with optic neuropathy and marked congestive ophthalmopathy, including 1 patient with a narrowed anterior chamber angle due to choroidal effusions. Endovascular intervention was planned but deferred for logistic reasons. While the patients awaited the procedures, the clinical features markedly improved, and time-resolved imaging of contrast kinetics (TRICKS) MRA was consistent with closure of the CCFs. These patients serve as a reminder that spontaneous resolution may occur in dural CCFs even when presenting clinical features are florid and vision appears to be threatened. In fact, a rapid worsening of clinical manifestations may be a sign that a dural CCF is about to close spontaneously.


Carotid-cavernous fistulas (CCFs) are typically classified into high-flow direct fistulas, which may arise after head trauma or spontaneously, and low-flow dural fistulas, which arise spontaneously, usually in elderly or postpartum women (1,2). Most high-flow direct fistulas require endovascular intervention (3). In contrast, many low-flow dural fistulas do not require intervention, as they tend to cause mild clinical manifestations and often resolve spontaneously (2–6). However, a minority of low-flow dural fistulas may cause florid signs of orbito-ocular venous hypertension, including marked vascular engorgement, proptosis, reduced eye movement, elevated intraocular pressure, retinal venous hemorrhage, optic neuropathy, and pain (7–10). In such patients, there is a temptation to intervene (2–4).

We report 2 patients whose dural CCFs caused severe clinical manifestations. One patient had a choroidal effusion with markedly narrowed anterior chamber angle and elevated intraocular pressure. Both patients had subnormal visual acuity with an afferent pupil defect indicating optic neuropathy. Before intervention, the manifestations spontaneously resolved. Time-resolved imaging of contrast kinetics (TRICKS) MRA, a noninvasive imaging technique, strongly suggested resolution of the fistulas. These patients are presented to emphasize that marked clinical manifestations are not necessarily an indication for intervention to close the fistula and may represent a harbinger of spontaneous closure.

CASE REPORTS

Case 1

A 72-year-old previously healthy woman developed a red right eye that worsened over the course of a few weeks together with recent onset of proptosis and binocular horizontal diplopia. Three weeks after the onset of symptoms, best-corrected visual acuity was 20/40 in the right eye and 20/20 in the left eye with a right afferent pupillary defect. Intraocular pressures were 26 mmHg in the right eye and 12 mmHg in the left eye. Prominent conjunctival corkscrew vessels were present in the right eye, which displayed 7 mm of proptosis and markedly reduced ocular ductions in all directions. The ocular ductions of the left eye were normal.

Biomicroscopy of the right eye disclosed a very shallow anterior chamber (Fig. 1A–B) and gonioscopy...
demonstrated a Shaffer grade 1 angle over 360. A Shaffer grade 4 angle was present in the left eye. Visante ocular coherence tomography (OCT) (Fig. 1C–D) and ultrasonic biomicroscopy (Fig. 1E–F) confirmed the anterior chamber shallowing and revealed large choroidal effusions in the right eye. The retinal veins were engorged in the right eye but not in the left eye.

CT angiography demonstrated proptosis of the right eye with enlarged extraocular muscles, edema of preseptal tissues, a dilated right superior ophthalmic vein, and early

FIG. 1. Case 1. Slit lamp biomicroscopy shows a narrow anterior chamber and dilated corkscrew conjunctival vessels in the right eye (A) and a deep anterior chamber in the left eye (B). Visante optical coherence tomography shows a closed angle in the right eye (C) and an open angle in the left eye (D). Ultrasonic biomicroscopy shows a choroidal effusion in the right eye (E) and closed anterior chamber angle in the right eye (F).

FIG. 2. Case 1. Axial (A) and coronal (B) images of a CT angiogram show proptosis on the right with preseptal soft tissue thickening (arrowheads) and early venous filling of the right cavernous sinus in the arterial phase (white arrows). Enlargement of the extraocular muscles (black arrows) is evident on the coronal scan (B).
venous filling of the right cavernous sinus (Fig. 2). There were no intracranial imaging abnormalities. A presumptive diagnosis of dural CCF was made.

Endovascular intervention was planned but delayed for logistic reasons. No medications were prescribed. Meanwhile, her manifestations began to resolve, so that intervention was further postponed.

Four weeks after initial presentation, visual acuity had improved to 20/25 in the right eye, the relative afferent pupillary defect had resolved, intraocular pressure had decreased to 16 mmHg in both eyes, and ocular ductions and venous congestive retinopathy had resolved. Ultrasonic biomicroscopy disclosed that the choroidal effusions had resolved and that the anterior chamber angle had deepened to Shaffer grade 4. TRICKS MRA performed 8 weeks after the initial CT angiogram demonstrated resolution of the dural CCF (Fig. 3).

Case 2
A 73-year-old woman with type 2 diabetes and coronary artery disease presented with the gradual onset of redness in both eyes and diplopia. Best-corrected visual acuity was 20/30 in both eyes, pupil reactions were normal, and intraocular pressure was 18 mmHg bilaterally. Prominent corkscrew conjunctival vessels were present in both eyes. Ocular ductions were normal except for 80% abduction of the left eye.

Three weeks later, she experienced severe headache and worsening of diplopia and redness in both eyes. Visual acuity had declined to 20/200 in the right eye and a right afferent pupillary defect was now present. Intraocular pressures were 30 mmHg in the right eye and 22 mmHg in the left eye. Abduction had decreased to 50% in both eyes. There was moderate retinal venous engorgement in both eyes.

CT angiography (CTA) demonstrated engorgement of both superior ophthalmic veins (Fig. 4) without intracranial abnormalities. TRICKS MRA confirmed bilateral cavernous sinus dural CCFs with intercavernous connections but no cortical venous reflux (Fig. 5).

Endovascular intervention was planned, but by the time it was to occur 2 weeks later, the patient had experienced spontaneous improvement of all clinical manifestations. Examination now demonstrated visual acuities of 20/30 in both eyes, no afferent pupillary defect, intraocular pressures of 16 mmHg bilaterally with no medications, normal ocular motility and alignment, and a normal retinal examination. TRICKS MRA demonstrated resolution of the CCF (Fig. 6).

DISCUSSION
These 2 patients are remarkable for the fact that dural CCFs gave rise to optic neuropathy and sufficiently severe orbitoocular manifestations to prompt consideration of endovascular intervention. In the interval between the intent and the readiness to intervene, however, the patients’ clinical manifestations dramatically improved, so that no procedures were necessary.

The florid and vision-threatening manifestations displayed by our patients are uncommon in dural CCF (2,5,11,12). Optic neuropathy, present in both of our patients, was reported in 13% of 80 patients with dural CCFs (13). Our first patient developed almost complete ophthalmoplegia, angle closure, and elevated intraocular pressure. We found only 1 case report (9) describing angle closure from choroidal detachment in dural CCF. Choroidal detachment in dural CCF has only been described in 3 cases (9,10,14).

The main clinical indication for endovascular treatment of dural fistulas is progressive visual loss, with other possible indications being intractable headache, elevated intraocular pressure refractory to medication, diplopia, or an intolerable cosmetic deformity (2–4). The indications for therapy found on neuroimaging include the presence of a pseudoaneurysm, large varix of the cavernous sinus, venous drainage to cortical veins, and thrombosis of venous outflow pathways distant from the fistula (15).

Endovascular intervention is usually successful in closing a dural CCF. In a review of 135 patients with dural CCFs, Meyers et al (3) showed that 97% had good recovery and 90% achieved complete cure. Such intervention may,
however, be complicated by allergic dye reactions, impairment of renal function, cranial nerve palsy, and stroke (11).

Spontaneous closure occurs with a frequency of 3.7% to 47% (2–6). Such spontaneous closure may be explained by the fact that the arteriovenous shunt elevates venous pressure within the sinus to a critical point at which stasis occurs and thrombus formation is facilitated (16–18). Thrombus formation may cause an increase in venous pressure accounting for a paradoxical worsening in clinical presentation before resolution of the fistula (5,19). Notably, both of our patients manifested significant worsening in their symptoms before spontaneous fistula closure.

Our patients demonstrated spontaneous improvement shortly after undergoing a diagnostic CTA. Other authors have noted this phenomenon (19,20). They have postulated that the change in pressure gradients during the CTA might induce stasis and local thrombosis in the region of the fistula (20). Another proposed mechanism is that the contrast material itself induces fistula closure (21). These findings have been supported by experimental evidence showing that angiographic contrast media may exaggerate the process of leukocyte accumulation and affect vascular endothelium and erythrocytes, thereby promoting thrombus formation (21).

In the diagnosis of CCF, digital subtraction angiography (DSA) has been the gold standard. This study permits temporal resolution, which allows dynamic visualization of feeding arteries, venous drainage patterns, and assessment of flow rate, factors that are important not only for definitive diagnosis but also for management strategies. The drawbacks of DSA are its invasive nature and associated complications (22). Several time-resolved MRA techniques have been introduced to allow acquisition with temporal resolution simulating DSA (23–25). One such technique, TRICKS (24), was used in both of our patients to define the location and flow characteristics of the fistula.
The form of TRICKS we used provides a whole-head 3-dimensional image at a frame rate of approximately 1 image every 2 seconds. This magnetic resonance technique exploits several data acquisition and reconstruction concepts, including variable rate k-space sampling, temporal interpolation, and zero-filling in the slice dimension (24). This allows more rapid sampling of data and temporal resolution beyond the capabilities of conventional MRI and MRA, which provide only static images. TRICKS allows dynamic visualization of contrast bolus passage from arterial to venous phases, helping to detect vascular lesions that might remain occult on static MRI or CTA. In CCF, TRICKS provides assessment of fistulous sites of early venous filling and venous drainage rates, useful in predicting outcome and directing management. Other advantages are relatively high signal-to-noise-ratio and data acquisition in any orientation, independent of direction and rate of flow (24). TRICKS has also been useful in the imaging and management of arteriovenous malformations and tumors with high flow rates such as hemangiopericytomas (26–28).

Given our experience and previous reports of spontaneous closure of dural CCFs (2,4–6,13,16–20,29–32), we suggest that endovascular intervention be deferred even in patients who have severe orbital congestion signs at presentation. Paradoxically, expectant management may be especially appropriate when CCF clinical manifestations are worsening, as this may be a sign of sinus thrombosis and impending spontaneous resolution. TRICKS MRA is a noninvasive alternative to more invasive catheter cerebral angiography.

ACKNOWLEDGMENT
We thank Dr. Iqbal Ahmed, Department of Ophthalmology, University of Toronto, for providing the images of the Visante OCT and ultrasonic biomicroscopy.

REFERENCES
Reversal of Ischemic Retinopathy Following Balloon Angioplasty of a Stenotic Ophthalmic Artery

Gyo Jun Hwang, MD, Se Joon Woo, MD, Jeong-Min Hwang, MD, PhD, Cheolkyu Jung, MD, Kyu Hyung Park, MD, PhD, O-Ki Kwon, MD, PhD

Abstract: A 65-year-old woman who had undergone internal carotid artery stenting and was being maintained on antiplatelet therapy developed features suggesting ipsilateral reduced retinal artery perfusion. Injection of urokinase into the ophthalmic artery provided temporary improvement. When manifestations of retinal arterial ischemia recurred, angiography revealed worsening stenosis at the origin of the ophthalmic artery. Balloon angioplasty at that site successfully restored visual acuity and reversed the ischemic fundus abnormalities. This is the first report of ophthalmic artery balloon angioplasty in this setting.

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Ophthalmic artery stenosis is a rare finding in patients with retinal ischemic symptoms (1). Antiplatelet agents have been a standard therapy (2,4,5). We describe a patient with ophthalmic artery origin stenosis who experienced episodic ipsilateral visual loss despite antiplatelet therapy and who achieved improvement in ischemic manifestations following balloon angioplasty of the ophthalmic artery origin, an intervention not previously reported.

CASE REPORT

A 65-year old woman presented with findings of a central retinal artery occlusion (CRAO) in the right eye (Fig. 1). Retinal fluorescein angiography revealed a patent cilioretinal artery, suggesting that the ophthalmic artery still provided some perfusion of the eye.

Two months earlier, she had undergone ipsilateral stenting for severe stenosis of the ipsilateral proximal cervical internal carotid artery. Following the procedure, she was taking aspirin, clopidogrel, and cilostazol.

Carotid angiography at the time of presentation with CRAO showed no thrombotic clot or restenosis around the carotid bifurcation. However, 70% stenosis was found at the origin of the ophthalmic artery (Fig. 2). A microcatheter was introduced into the proximal ophthalmic artery for bougination, and a fibrinolytic agent (300,000-unit urokinase) was injected into the ophthalmic artery.

Following the thrombolysis, the patient’s visual acuity gradually improved from hand motion to 20/50 in the affected eye. Antiplatelet agents were maintained.

However, 2 months after thrombolysis, she complained of gradual deterioration of visual acuity in the right eye for 3 days. Visual acuity had declined to finger counting in that eye, and ophthalmoscopy showed multiple cotton wool patches (Fig. 3A). Fluorescein angiography (Fig. 3B) showed that filling of the cilioretinal artery was more prolonged than prior to the thrombolysis (14 seconds rather than 8 seconds after dye injection). Carotid angiography revealed no remarkable findings at the carotid bifurcation but demonstrated that stenosis at the ophthalmic artery origin had increased to about 90% (Fig. 4).

Balloon angioplasty was successfully performed with a coronary balloon (1.5 × 10 mm), and tirofiban was injected at the stenotic segment. Residual stenosis amounted to 30% on the final angiogram. At 1 month following this procedure, visual acuity had improved to 20/60. The cotton wool patches had disappeared and fluorescein angiographic retinal arterial perfusion had improved (Figs. 3C, 3D).
DISCUSSION

We have described a patient with ophthalmic artery stenosis that induced sequential attacks of reduced retinal perfusion attributed to ophthalmic artery stenosis. Retinal ischemic manifestations initially improved following intra-arterial thrombolysis but recurred and later improved again following balloon angioplasty of the ophthalmic artery.

Ophthalmic artery stenosis could cause an abrupt decline of vision by acting as an embolic source or by reducing perfusion. Ophthalmic artery stenosis, without concomitant proximal carotid artery stenosis, may manifest as cotton wool patches in the ipsilateral fundus (3). In our patient, balloon angioplasty of the ophthalmic artery improved visual function and retinal perfusion. We are unaware of a previous report showing its efficacy in this setting.

REFERENCES

FIG. 3. A. Fundus photography of the right eye 2 months after thrombolysis shows multiple cotton wool spots. B. Fundus fluorescein angiography shows delayed retinal arterial perfusion. C. One month after balloon angioplasty of the right ophthalmic artery, fundus photography shows disappearance of cotton wool spots. D. Fluorescein angiogram shows improvement in retinal perfusion.

FIG. 4. Angiography of balloon angioplasty. A. Prior to angioplasty, stenosis (arrow) at the ophthalmic artery origin is estimated to be 90%. B. A coronary balloon (arrowheads) is introduced into the stenotic portion. C. Immediately after balloon angioplasty, angiography shows that stenosis (arrow) is reduced to an estimated 30%.


Cup-to-Disc Ratio in Patients With Idiopathic Intracranial Hypertension Is Smaller Than That in Normal Subjects

Brooke E. Geddie, DO, Ugur E. Altiparmak, MD, Eric R. Eggenberger, DO

Abstract: Background: A small cup-to-disc (C:D) ratio is an established risk factor for nonarteritic anterior ischemic optic neuropathy. We sought to determine if a small C:D ratio was present in patients with idiopathic intracranial hypertension (IIH) as a potential risk factor for visual loss in that disorder.

Methods: We performed a retrospective review of 52 charts of patients diagnosed with IIH at Michigan State University from 1990 to 2003. Twenty-eight patients (55 eyes) met diagnostic inclusion criteria and had undergone fundus photography of sufficient quality to allow assessment of the C:D ratio after optic disc edema had become minimal or resolved. C:D ratio was measured from the digitized photographs. The data were placed into rank order categories (0.1 unit intervals) and compared to published normative C:D data.

Results: The average vertical C:D ratio was 0.143 (SD 0.061) in the right eye and 0.127 (SD 0.056) in the left eye. The average horizontal C:D ratio was 0.145 (SD 0.053) in the right eye and 0.133 (SD 0.053) in the left eye. The IIH group rank distribution data were compared to published normative C:D ratio data (chi-square test). In each case, the IIH population had a statistically significantly smaller C:D ratio \((P < 0.0001)\) compared to normal subjects.

Conclusions: The C:D ratio in our IIH population was smaller than that in published control populations. A small C:D ratio may lower the threshold for developing optic disc edema from ischemia, increased intracranial pressure, or other mechanisms. Additional studies are needed to confirm these findings.

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A consistent risk factor for the development of nonarteritic anterior ischemic optic neuropathy (NAION) is a small cup-to-disc (C:D) ratio \((1–5)\). However, the pathogenic relationship between the C:D ratio and NAION remains unclear \((1–5)\). Proposed mechanisms include the following \((6)\):

1. Crowding causes axonal swelling secondary to mechanical obstruction to axoplasmic flow, particularly at the most crowded region, the lamina cribrosa.
2. Subclinical ischemia due to lipohyalinosis and/or other factors produces axoplasmic stasis, with swelling causing compression and further compromise of the microcirculation in the crowded laminar region.
3. Crowding may be associated with an abnormally stiff (less compliant) lamina cribrosa, exaggerating factors 1 and 2.

In this study, we focus on idiopathic intracranial hypertension (IIH), a disorder associated with optic disc edema. Although it is well known that papilledema is the result of axonal transport blockage, the pathophysiology of this cellular event is not well understood. Hayreh \((7)\) speculated that the cause is mechanical from transmission of raised intracranial pressure (ICP) to retinal ganglion cell axons in the optic nerve. Our hypothesis is that an optic disc with a small C:D ratio may be more likely to swell from increased ICP, much as it appears to be a risk factor for NAION.

METHODS

The study was approved by the Michigan State University Institutional Review Board (03-073). We performed a chart review of 52 consecutive patients from the Michigan State University Department of Neurology and Ophthalmology with a diagnosis of IIH from 1990 to 2003. Inclusion criteria \((8)\) were signs and symptoms of elevated ICP, documented elevated ICP greater than 250 mm of water (measured in the lateral decubitus position), normal cerebrospinal fluid composition, no evidence of hydrocephalus or other structural abnormality on MRI or CT, and documented optic disc photographs of sufficient quality at a point in time with minimal or resolved optic disc edema (Frisénstage 0–2) \((9)\) to allow accurate assessment of the C:D ratio.
Optic disc photographs were digitized to allow computer magnification of the optic disc (200%) and use of a pixel-measuring program (Microsoft Photo Editor) to quantify the C:D ratio. The vertical and horizontal diameter of the optic disc and cup were analyzed by one observer (B.E.G.). The diameter of the cup was divided by the diameter of the disc to derive the C:D ratio (Fig. 1). Measurements were repeated 1 month later with the observer masked to previous data for a total of 2 results per eye, which were then averaged for statistical analysis. Random confirmation was performed by a second observer (E.R.E.).

The IIH study patient C:D data were tabled in rank order categories encompassing 0.1 unit intervals. The data were then compared to published normative data. For each comparison, statistical significance was assessed with the P value determined by the chi-square test.

**RESULTS**

Of the 52 charts reviewed, 28 patients (55 eyes; 28 right and 27 left) met inclusion criteria. Among the study cohort, 96.4% (27 subjects) were women, 82.1% (23 subjects) were white, and 17.9% (5 subjects) were African American. The average age of the study patients was 28.6 (SD, 8.2) years. The average body mass index was 35.7 (SD, 6.8).

The presenting visual symptoms included blurred vision in 39.3% (11 subjects), transient visual obscurations in 21.4% (6 patients), nausea and vomiting in 14.3% (4 patients), changes in peripheral vision in 10.7% (3 patients), diplopia in 25.0% (7 patients), and tinnitus in 21.4% (6 patients). Headache was reported in all patients, with 46.4% (13 subjects) characterizing the headache as generalized.

The initial neuro-ophthalmic evaluation in all 28 subjects included visual acuity, pupil size and reactivity, Hardy-Rand-Rittler pseudosochromatic color plate testing, ocular motility and alignment measurements, kinetic visual fields, biomicroscopy, and ophthalmoscopic examinations. Best-corrected visual acuity at presentation was 20/25 or better in 47 eyes (85.5%), 20/40 or better in 53 eyes (96.4%), and worse than 20/40 in 2 eyes (3.6%). Color vision was normal (90% or better) in 45 eyes (81.8%). Initial kinetic visual field results included 18.2% (10 eyes) with full visual fields without deficits, 50.9% (28 eyes) with enlarged blind spots only, 9.1% (5 eyes) with enlarged blind spots and global constriction, 10.9% (6 eyes) with global constriction only, and 10.9% (6 eyes) with arcuate visual field defects.

All 28 subjects underwent lumbar puncture at the time of the initial diagnostic evaluation. The average opening pressure was 369 mm (SD, 93.6 mm) of water. Brain MRI was performed in 92.9% (26 subjects) and revealed a partially

<table>
<thead>
<tr>
<th>C:D Ratio</th>
<th>Normal Subjects of Kroninger and Newcomb (10), % (n)</th>
<th>Normal Subjects of Kragha (11), % (n)</th>
<th>Normal Subjects of Leibowitz et al (12), % (n)</th>
<th>Normal Subjects of Armaly and Sayegh (13), % (n)</th>
<th>Our Study, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.7 (23)</td>
<td>10.9 (550)</td>
<td>18.4 (444)</td>
<td>56.36 (31)</td>
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<td>0.1</td>
<td>38.8 (646)</td>
<td>9.54 (129)</td>
<td>14.7 (745)</td>
<td>23.5 (579)</td>
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<td>0.2</td>
<td>20.7 (345)</td>
<td>19 (257)</td>
<td>26.7 (1349)</td>
<td>23 (567)</td>
<td>40 (22)</td>
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<tr>
<td>0.3</td>
<td>18.5 (308)</td>
<td>44.45 (601)</td>
<td>26.5 (1340)</td>
<td>19.5 (481)</td>
<td>3.64 (2)</td>
</tr>
<tr>
<td>0.4</td>
<td>11.6 (193)</td>
<td>13.9 (188)</td>
<td>11.5 (562)</td>
<td>7.5 (185)</td>
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<tr>
<td>0.5</td>
<td>7.2 (120)</td>
<td>7.32 (99)</td>
<td>4.7 (236)</td>
<td>4.5 (111)</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>2.1 (35)</td>
<td>2.37 (32)</td>
<td>3.0 (154)</td>
<td>2.5 (62)</td>
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<tr>
<td>0.7</td>
<td>1.0 (17)</td>
<td>0.96 (13)</td>
<td>1.4 (71)</td>
<td>1.5 (37)</td>
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<tr>
<td>0.8</td>
<td>0.67 (9)</td>
<td>0.36 (18)</td>
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<td></td>
</tr>
<tr>
<td>0.9</td>
<td>0.07 (1)</td>
<td>0.08 (4)</td>
<td></td>
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</tr>
<tr>
<td>1.0+</td>
<td>0.08 (4)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**FIG. 1.** Calculation of the cup-to-disc ratio.
empty sella in 30.8% (8 subjects). CT was performed in 7.1% (2 subjects), yielding normal results.

Test-retest correlation (observer B.E.G.) for the horizontal and vertical C:D ratio was 0.97, with the average value of the 2 observations used in the analysis.

The average vertical C:D ratio of IIH study eyes was 0.143 (SD, 0.061) in the right eye and 0.127 (SD, 0.056) in the left eye. The average horizontal C:D ratio of IIH study eyes was 0.145 (SD, 0.053) in the right eye and 0.133 (SD, 0.053) in the left eye. The rank distribution of horizontal, vertical, and average C:D data (0.1 intervals) was compared to appropriately matched normative data (Tables 1–3) using the chi-square test.

As shown in Table 1 and Figure 2, the difference between the C:D ratio in IIH study eyes and the horizontal C:D ratio from normative data compiled by Kroninger and Newcomb (10), Kragha (11), Leibowitz et al (12), and Armaly and Sayegh (13) was statistically significant (P < 0.0001) as was the difference between the vertical C:D ratio of our IIH study eyes and the normative data from Leibowitz et al (12). For the average horizontal and vertical C:D ratio, our IIH eyes differed significantly (P < 0.001) from a normative frequency distribution ratio (Table 3 and Fig. 4) (14).

Given the C:D correlation between right and left eyes, statistical analysis was repeated using a sample of 28 patients, yielding the same results.

**DISCUSSION**

A small C:D ratio was a frequent finding in our IIH population and was more frequent than in published control populations. A small C:D ratio may lower the threshold for optic disc edema from any of several insults, including ischemia or increased ICP. The small C:D ratio may lead to diminished compensatory reserve for axoplasmic flow stasis in the setting of elevated ICP. The optic disc with a small C:D ratio may be more likely to exhibit optic disc edema compared to optic discs with larger C:D ratios.

The limitations of this study include the measurement of C:D ratio after resolution or near-resolution of optic disc edema. Based on the Frisén staging scheme (9), stage 3 optic disc edema involves increased diameter of the nerve head and stage 4 optic disc edema involves compression or obliteration of the optic cup. Because of this confounding factor, only

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**TABLE 2. Vertical cup-to-disc (C:D) ratio data from our patients in comparison to published study of normal subjects by Leibowitz et al (12)**

<table>
<thead>
<tr>
<th>C:D Ratio</th>
<th>Normal Subjects of Leibowitz et al (12), % (n)</th>
<th>Our Study, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.8 (546)</td>
<td>1.82 (1)</td>
</tr>
<tr>
<td>0.1</td>
<td>15.3 (775)</td>
<td>61.82 (34)</td>
</tr>
<tr>
<td>0.2</td>
<td>25.4 (1282)</td>
<td>32.73 (18)</td>
</tr>
<tr>
<td>0.3</td>
<td>25.4 (1281)</td>
<td>3.64 (2)</td>
</tr>
<tr>
<td>0.4</td>
<td>12.3 (619)</td>
<td>—</td>
</tr>
<tr>
<td>0.5</td>
<td>5.2 (261)</td>
<td>—</td>
</tr>
<tr>
<td>0.6</td>
<td>3.3 (168)</td>
<td>—</td>
</tr>
<tr>
<td>0.7</td>
<td>1.8 (89)</td>
<td>—</td>
</tr>
<tr>
<td>0.8</td>
<td>0.4 (20)</td>
<td>—</td>
</tr>
<tr>
<td>0.9</td>
<td>0.12 (6)</td>
<td>—</td>
</tr>
<tr>
<td>1.0+</td>
<td>0.12 (6)</td>
<td>—</td>
</tr>
</tbody>
</table>

**TABLE 3. Average horizontal and vertical cup-to-disc (C:D) ratio data from our patients in comparison to published study of normal subjects by Beck et al (14)**

<table>
<thead>
<tr>
<th>C:D Ratio</th>
<th>Normal Subjects of Beck et al (14), % (n)</th>
<th>Our Study, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0–0.09</td>
<td>4 (16)</td>
<td>21.82 (12)</td>
</tr>
<tr>
<td>0.10–0.19</td>
<td>12.5 (50)</td>
<td>67.27 (37)</td>
</tr>
<tr>
<td>0.20–0.29</td>
<td>30.75 (123)</td>
<td>9.09 (5)</td>
</tr>
<tr>
<td>0.30–0.39</td>
<td>25.5 (102)</td>
<td>1.82 (1)</td>
</tr>
<tr>
<td>0.40–0.49</td>
<td>13.75 (55)</td>
<td>—</td>
</tr>
<tr>
<td>0.50–0.59</td>
<td>10.25 (41)</td>
<td>—</td>
</tr>
<tr>
<td>0.60–0.69</td>
<td>2.5 (10)</td>
<td>—</td>
</tr>
<tr>
<td>0.70–0.79</td>
<td>0.75 (3)</td>
<td>—</td>
</tr>
<tr>
<td>0.80–0.89</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0.90–0.99</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**FIG. 2.** Horizontal cup-to-disc ratio data from our study compared to normative data from previously published studies.
those IIH eyes with Frisén stage 0 to 2 (minimal or resolved edema) were included in this study. One might question the possibility of a permanent change in C:D ratio from papilledema. While optic disc excavation and increased cup area has been reported with certain optic neuropathies (4), we are unaware of studies demonstrating a diminution of the C:D ratio.

Further data collection and analysis of a larger cohort of patients with IIH and an appropriate group of controls would be beneficial to further evaluate these preliminary results. In addition, studies in population sets with optic disc edema from other nonischemic causes would be useful to understand the potential role of optic nerve structure in the pathophysiology of optic disc edema.

REFERENCES
Scanning Laser Polarimetry Quantification of Retinal Nerve Fiber Layer Thinning Following Optic Neuritis

S. Anand Trip, PhD, Patricio G. Schlottmann, MD, Stephen J. Jones, PhD, Constantinos Kallis, PhD, Daniel R. Altmann, DPhil, David F. Garway-Heath, FRCoPhth, Alan J. Thompson, FRCP, Gordon T. Plant, FRCP, David H. Miller, FRCP

Abstract: Background: Several studies with optical coherence tomography (OCT) have demonstrated thinning of the retinal nerve fiber layer (RNFL) in patients with optic neuritis and multiple sclerosis. Similar studies have not been performed with scanning laser polarimetry (SLP), which relies on different physical phenomena. This study was designed to use SLP to measure axonal loss following a single episode of optic neuritis and to determine if there is a relationship between the degree of axonal loss and the degree of residual visual dysfunction.

Methods: Twenty-five patients with a single episode of optic neuritis and 15 control subjects were studied with SLP using the GDxVCC device to determine RNFL thickness in relation to visual acuity, visual fields, color vision, visual evoked potentials (VEPs), and previously published OCT data.

Results: SLP detected significant RNFL thinning in affected eyes compared to clinically unaffected fellow eyes in patients and in control eyes (P < 0.001). Reduced RNFL thickness was associated with significantly worse logMAR visual acuity, visual field mean deviation, and color vision. RNFL thinning correlated with reduced whole visual field and central visual field measures and VEP amplitudes. Superior and inferior quadrant RNFL thinning was related to corresponding regional visual field loss. There was a scaling factor between SLP and OCT RNFL measurements but only modest agreement.

Conclusions: SLP detected functionally relevant axonal loss in eyes affected by optic neuritis. There was a scaling factor between RNFL measurements obtained with SLP and OCT but only modest agreement. Care should therefore be taken when comparing RNFL data from studies using these different devices.

The often incomplete recovery of function from relapses in multiple sclerosis (MS) is thought to be related to axonal loss (1). Optic neuritis is a convenient model for studying relapses in MS as it is a typical first presentation of MS. Moreover, optic neuritis can occur as a relapse of MS, and the pathology found in the lesion of optic neuritis is similar to other types of central nervous system lesions found with MS relapses (2). MRI, electrophysiological and clinical measures of anterior visual pathway function have provided insights into the pathophysiological mechanisms associated with relapse and recovery in optic neuritis (3–6).

Several studies using optical coherence tomography (OCT) in patients with optic neuritis and MS have demonstrated retinal nerve fiber layer (RNFL) thinning (7–10). Some have demonstrated a relationship with visual function (8–10) and electrophysiologic measurements (7,8), indicating that the RNFL thinning is of functional relevance and represents axonal loss.

Scanning laser polarimetry (SLP) utilizes a scanning laser ophthalmoscope to determine the peripapillary RNFL thickness, pixel by pixel, by measuring the total retardation of polarized light reflected from the retina. It therefore
differs in terms of its physical basis from the interferometry method of OCT. Retardation of light reflected through the birefringent RNFL, which is measured by SLP, has been correlated with RNFL thickness determined by histology of primate retina (11,12). Therefore, SLP has the potential to be a specific measure of axonal loss. Axonal microtubules are believed to be the source of birefringence from the RNFL (13,14). The SLP measure of RNFL thinning distinguishes well between normal and glaucomatous eyes (15), and RNFL thickness measurements correlate with visual field measures in glaucoma (16,17). Previous studies have used SLP to study patients with optic neuritis and MS. One study (18) used an early model of SLP without variable corneal compensation (VCC); the second study (19) used SLP as a tool for detecting the presence of optic nerve disease in MS without presenting any quantitative RNFL data. Two recent studies employing SLP with VCC have detected RNFL thinning in patients with MS, which correlates with some aspects of visual function (20,21) and also the visual evoked potential (VEP) (21). RNFL measurements with OCT and SLP have correlated well (20,21).

In this study, we hypothesized that axonal loss of the RNFL is a major substrate of persistent visual dysfunction following optic neuritis and can be quantified by reduction of RNFL retardation using SLP. The aims of this study were to use SLP to 1) determine the extent of axonal loss following a single episode of optic neuritis with incomplete recovery compared to unaffected fellow eyes and healthy control eyes, 2) look for a relationship between the degree of axonal loss in patients and the degree of residual visual dysfunction measured clinically and electrophysiologically, and 3) compare these findings with those obtained in a previous study of the same cohort using OCT (8) and with 2 recent SLP studies in MS (20,21).

METHODS

Subjects

The patients and controls in this study were the same as those in a previous OCT study (SLP and OCT were performed on the same day) where full details of the subjects’ demographics and visual function have previously been reported (8) (Table 1). Twenty-five patients who had a single clinical attack of acute unilateral optic neuritis at least 1 year previously without recurrence were recruited from the case records of the Neuro-ophthalmology Clinic, Moorfields Eye Hospital, London, England. Fourteen had clinically isolated optic neuritis and 11 had MS (22). Appropriate tests had been performed to exclude alternative diagnoses where indicated. A selection bias was introduced toward those with incomplete visual recovery in order to study a range of visual deficits. This bias was introduced by preferentially selecting patients who had a last documented visual acuity worse than 20/20, a persisting visual field abnormality or impaired color vision on testing with Ishihara plates. Fifteen control subjects were recruited, none of whom had any ophthalmological or neurological disorder.

Approval for the study was obtained from the joint Ethics Committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery, which was accepted by the Moorfields Eye Hospital Research Governance Committee. Informed consent in writing was obtained from all subjects, in accordance with the Declaration of Helsinki.

Scanning Laser Polarimetry

SLP images were acquired with a GDxVCC device and software (Carl Zeiss Meditec, Dublin, CA; software version 5.5,0). All subjects had an ametropia <10 diopters. Scans were performed at the Glaucoma Research Unit, Moorfields Eye Hospital by an examiner who was masked to the clinical status of each subject. The GDxVCC incorporates a variable corneal compensator to achieve individualized anterior segment retardation compensation. One scan was acquired for each eye through an undilated pupil. Measurements were calculated from a measurement annulus centered on the optic disc with an internal diameter of 2.4 mm and an external diameter of 3.2 mm. The mean total RNFL thickness around the optic disc was obtained, and the RNFL thickness in quadrants (temporal, superior, nasal, and inferior) was derived for comparison with corresponding regions of the visual field. A previous study of reproducibility of GDxVCC mean RNFL measurements produced coefficient of variation values as low as 3.67% (23).

Optical Coherence Tomography

OCT images were acquired as described previously (8) with a Stratus OCT Model 3000 (Carl Zeiss Meditec, Inc). Pupils were dilated if imaging was impaired by a small pupil size. The Stratus OCT device and software were used to acquire three 3.4-mm-diameter circular scans centered on the optic disc for each eye. The mean was used to express RNFL thickness as a single average value for the whole 360° scan and also as RNFL quadrants (temporal, superior, nasal, and inferior). Macular thickness was measured once for each eye by means of 6 radial lines to compose a macular thickness/volume map.

Visual Function Testing

The visual function testing methods (8) were as follows. A retroilluminated Early Treatment Diabetic Retinopathy Study chart was used to measure visual acuity, with appropriate refractive correction, and was recorded as the 4m logMAR (minimum angle of resolution) acuity. The 30-2 program of the Humphrey field analyzer (Carl Zeiss Meditec) was used to assess the visual field and the visual field mean deviation (MD). The visual field data were divided into 4 sectors based on the relationship between the
TABLE 1. Demographic data of patients and visual function of the eyes affected by optic neuritis

<table>
<thead>
<tr>
<th></th>
<th>Clinically Isolated Syndrome</th>
<th>Multiple Sclerosis</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>14</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>6:8</td>
<td>5:6</td>
<td>11:14</td>
</tr>
<tr>
<td>Time since onset of optic neuritis, yr</td>
<td>3 [1–7]</td>
<td>3 [1–9]</td>
<td>3 [1–9]</td>
</tr>
<tr>
<td>LogMAR visual acuity</td>
<td>+0.12 [-0.08 to +0.52]</td>
<td>+0.38 [0.00 to +1.42]</td>
<td>+0.23 [-0.08 to +1.42]</td>
</tr>
<tr>
<td>Visual field mean deviation, dB</td>
<td>−6.1 [−12.9 to −2.1]</td>
<td>−8.2 [−18.5 to −0.9]</td>
<td>−7.1 [−18.5 to −0.9]</td>
</tr>
<tr>
<td>Color vision (\sqrt{FM 100-Hue score})</td>
<td>20.0 [10.2–33.1]</td>
<td>20.8 [10.4–36.6]</td>
<td>20.3 [10.2–36.6]</td>
</tr>
</tbody>
</table>

Values are mean [range].
FM, Farnsworth-Munsell; MAR, minimum angle of resolution.

optic disc and the central field, derived from a previously published optic disc–visual field map (24). The RNFL quadrants from SLP correspond to these 4 visual field sectors. One patient was unable to reliably complete automated perimetry and had high levels of fixation losses and false-negative responses, despite having near-normal acuity and normal visual fields by clinical examination. The Farnsworth-Munsell 100-hue test (25) was used to assess color vision and was scored as a square root of the error score (√/FM 100-hue score) because this follows a normal distribution in controls. Two patients with a congenital anomaly of color vision did not complete this test.

Electrophysiology

VEPs were recorded to monocular stimuli using skin-surface electroencephalographic electrodes attached over the occiput 5 cm above the inion and referred to an frontal electrode at Fz (10-20 System). The ground electrode was at Cz. The interelectrode impedance was less than 5 kohms, and the gain was 10,000. The mean luminance of the screen was 32 cd/m², and the contrast 93%. The analysis time was 250 milliseconds. Two repetitions of each VEP were recorded to ensure reproducibility and subsequently averaged together. The stimuli comprised reversal of a checkerboard pattern in the whole field and in the central field (26). Central field responses were unobtainable in 1 patient and 1 control. The pattern electroretinogram (PERG) was recorded to binocular stimulation of the whole field, subtending 28° horizontally by 20° vertically, using corneal surface electrodes (DTL Plus; Retina Technologies, Scranton, PA) referred to skin-surface electrodes over the ipsilateral outer canthus. Forty-minute check sizes were used, reversing 4.3 times per second. The luminance of the bright squares was 60 cd/m² and of the dark squares was 4 cd/m². The amplifier corner frequencies were 1 and 1,000 Hz. The sampling rate was 3 samples per millisecond, and the sweep duration was 170 milliseconds. We made 3 averages of 200 responses and subsequently averaged them together. Sweeps containing artifacts of more than 165 μV were automatically rejected.

These studies were performed in accordance with standards of the International Society for Clinical Electrophysiology of Vision (ISCEV). Analysis was performed by investigators who were masked to the status of each subject.

Statistical Analysis

SLP data were expressed as absolute values for the patient’s affected and unaffected fellow eyes and for one randomly selected eye from each control. Differences between patients and controls are reported from 2 sample t tests. Linear regression was used to confirm that there was no confounding by age or gender and to investigate possible differences between patient subgroups. Pairwise tests were used to investigate differences between affected and unaffected fellow eyes in patients.

The relationship within patients between pathologically induced changes in RNFL thickness and functional measures was studied. Because there is considerable interindividual variability in RNFL thickness within the normal population, it is better to investigate the relationships between affected eye values while adjusting for unaffected eye values as regression covariates (since the unaffected patient eye can also sometimes have subclinical abnormality (27), this approach can underestimate pathology and lead to conservative results). Accordingly, relationships between visual function (or electrophysiological variables) and SLP measures were investigated using linear regression of the affected eye visual function (or electrophysiological measure) on affected eye SLP measure, with unaffected eye visual function (or electrophysiological measure) and SLP measures as covariates. Similar regressions were used to investigate quadrant-specific relationships and with patient subgroup interaction terms to investigate whether the associations varied by clinical subgroup (clinically isolated optic neuritis or MS). Possible confounding by age and gender was investigated in the regressions, and these covariate terms were retained in models where they contributed at P < 0.05. For some relationships, 2 potentially influential outliers emerged, and results both with and without these are reported where their exclusion materially altered model conclusions. Analyses were implemented in Stata 9.2 (Stata Corporation, College Station, Tx).
SLP data from this study were compared with OCT data from the same cohort (8), using Bland-Altman plots (28), and mixed effects linear regression analysis (to allow inclusion of both patient eyes), in order to determine whether there was agreement between the 2 devices.

RESULTS

Differences in Retinal Nerve Fiber Layer Thickness Between Patients and Controls

The average RNFL thickness in affected eyes from patients was significantly reduced compared to that in clinically unaffected fellow eyes and control eyes (Table 2). There were no significant differences in visual function or RNFL thickness between the patients with MS and those with clinically isolated optic neuritis.

Relationship Between Retinal Nerve Fiber Layer Thickness and Visual Function in Affected Patient Eyes

Reduced RNFL thickness was associated with significantly worse visual function in terms of logMAR visual acuity, visual field (MD), and color vision (\(\sqrt{FM} 100\)-Hue score) (Table 3). These relationships, which remained significant whether or not 2 outliers were included, are graphically represented in Figure 1 (in order to simplify graphical presentation of these fellow eye–adjusted associations, the corresponding affected minus unaffected fellow eye values are illustrated).

Relationship Between the Retinal Nerve Fiber Layer Quadrant Thicknesses and Their Corresponding Visual Field Sectors in Affected Patient Eyes

A 1-\(\mu\)m reduction in superior and inferior RNFL quadrant thickness was related to a \(-0.17\) dB (95% confidence interval [CI], \(-0.22\) to \(-0.11\); \(P < 0.001\)) and a \(-0.10\) dB reduction in nasal and temporal visual RNFL quadrant thicknesses and their corresponding visual field sectors' MDs, respectively. There was no association between the nasal and temporal RNFL quadrants and their corresponding visual field sectors.

| TABLE 2. Scanning laser perimetry measurement of retinal nerve fiber layer (RNFL) thickness in control eyes, patient unaffected eyes, and patient affected eyes |
|-----------------|-----------------|-----------------|
|                 | Control Eyes | Patient Unaffected Eyes | Patient Affected Eyes |
| n = 15          | n = 25        | n = 25            |
| Average RNFL thickness, \(\mu\)m | 57.9 (8.1) | 55.5 (6.3) | 44.4 (8.4) |
| \(P_c = 0.37\) | \(P_c < 0.001\) | \(P_f < 0.001\) |

Values are mean (SD). \(P_c\) values are comparisons between control eyes and patient eyes. \(P_f\) values are comparisons between unaffected fellow eyes and affected eyes in patients. RNFL, retinal nerve fiber layer.

DISCUSSION

SLP using the GDxVCC device was able to detect mean reductions in RNFL thickness in affected patient eyes of 23% and 20% compared to that in control eyes and unaffected patient eyes, respectively, values that were highly statistically significant (Table 2). The mean decrease of 4% in RNFL thickness in unaffected patient eyes relative to control eyes was not statistically significant.
The first study to employ SLP in patients with optic neuritis (18) used an early commercially available model, which had fixed corneal compensation (FCC) rather than the VCC used in the present study. The disadvantage of FCC compared to VCC is that it does not permit individualized correction of anterior segment birefringence, resulting in inaccurate RNFL measurements. Accordingly, we cannot use that study for comparison (29).

Two recent studies have used SLP with VCC to study patients with MS (20,21). Zaveri et al (20) studied 155 eyes from 80 patients with MS and 85 eyes from 43 controls. RNFL thickness in the 68 eyes affected by optic neuritis was reduced by 14% compared to that in control eyes. Pueyo et al (21) studied 100 eyes from 50 patients with MS and 85 eyes from 43 controls. RNFL thickness in the 68 eyes affected by optic neuritis was also reduced by 14% compared to that in control eyes. Given that the same GDxVCC technology was used in these studies, the greater reduction in RNFL thickness in our study can be explained by the deliberate bias toward incomplete visual recovery.

In our study, RNFL thinning was significantly related to measures of visual acuity, visual fields, and color vision, replicating the findings of the previous OCT study of this cohort (8). As for OCT, the SLP-measured superior and inferior RNFL quadrants (but not the temporal or nasal quadrants) were related to their corresponding visual field sector measures, supporting a structure-function relationship with both devices. The lack of correlation in the temporal and nasal quadrants in this study and the previous OCT study could be explained by the fact that the nasal and temporal RNFL are thinner than the superior and inferior RNFL (30) and the OCT and SLP devices may be less sensitive in detecting change in these thinner sectors. Also, these RNFL quadrants are responsible for a relatively smaller area of the central visual field (24), and the number of perimeter test points in the nasal and temporal sectors is significantly less than in the superior and inferior sectors—

<table>
<thead>
<tr>
<th>Linear Coefficients*</th>
<th>95% Confidence Intervals</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity, logMAR</td>
<td>+0.025</td>
<td>+0.007 to +0.04</td>
</tr>
<tr>
<td>Visual field mean deviation, dB</td>
<td>-0.28</td>
<td>-0.44 to -0.11</td>
</tr>
<tr>
<td>Color vision (F M 100-Hue score)</td>
<td>+0.75</td>
<td>+0.48 to +1.03</td>
</tr>
<tr>
<td>Whole field VEP amplitude, μV</td>
<td>-0.21</td>
<td>-0.33 to -0.10</td>
</tr>
<tr>
<td>Central field VEP amplitude, μV</td>
<td>-0.11† [-0.07]</td>
<td>-0.20 to -0.02</td>
</tr>
<tr>
<td>PEG P50 amplitude, μV</td>
<td>+0.01</td>
<td>-0.05 to +0.07</td>
</tr>
<tr>
<td>PEG N95 amplitude, μV</td>
<td>-0.06</td>
<td>-0.14 to +0.02</td>
</tr>
</tbody>
</table>

*Interpreted as the estimated worsening of vision function or electrophysiological measure for each micrometer decrease in RNFL thickness.

†This result was substantially different when 2 outliers were excluded: square brackets contain the outlier excluded coefficient and P value.

PERG, pattern electroretinogram; VEP, visual evoked potential.
tissue as it moves from the RNFL to deeper retinal layers. However, the definition of the bottom of the RNFL measurement has not been rigorously proven (32). SLP utilizes the ability of a birefringent structure, in this case, the RNFL, to retard 1 vector of polarized light that passes through it. The amount of retardation is used to calculate the thickness of the RNFL. Retardation correlates with histological RNFL thickness in primate retina (11,12). The absolute RNFL thickness values produced by either device have not been definitively validated in postmortem human studies. A problem of such an investigation is the propensity for the RNFL to swell or shrink after fixation (33). It is therefore unclear at this time what the true in vivo values are for RNFL thickness.

The ability of Stratus OCT and GDxVCC to discriminate between normal and glaucomatous eyes has been studied (34,35), but there are few data directly comparing the relationship between RNFL values produced by the 2 devices. Leung et al (36) studied healthy controls and patients with glaucoma using Stratus OCT and GDxVCC. They found that RNFL thickness measured by the 2 devices correlated well together with $r = 0.852$ using linear regression analysis. The analysis looked at the strength of the relationship between the 2 measures but not assess the agreement between them. The latter requires the construction of Bland-Altman plots (28). Shewry et al (37) also attempted to address the issue of agreement between Stratus OCT and GDxVCC by studying normal, ocular hypertensive, and glaucoma subjects. They used linear regression analysis and Bland-Altman plots to investigate the relationship and agreement between the devices. The data have only been published in abstract form, and only the regression data were presented. When the regression was forced through the origin, the equation $\text{oct} = 1.8 \times \text{slp}$ was produced ($P < 0.001$ for the regression coefficient), which suggested that there was a scaling factor of 1.8 between the 2 devices.

As the present SLP study and previously published OCT study (8) both used the same patient and control eyes studied at the same time, there was an opportunity to study the relationship between RNFL values measured by the 2 devices in optic neuritis, although the study was not

FIG. 1. Interocular difference in scanning laser perimetry (SLP) retinal nerve fiber layer (RNFL) thickness plotted against interocular differences in visual acuity (A), visual field (B), and color vision (C).

FIG. 2. Regression plot for optical coherence tomographic (OCT) RNFL thickness against scanning laser perimetry (SLP) retinal nerve fiber layer (RNFL) thickness.
specifically designed and powered to evaluate this relationship. Using the linear regression method employed by Shewry et al (37), a similar equation was produced: \( \text{oct} = 1.93 \times \text{slp} - 12.8 \) \((P < 0.001\) for the regression coefficient). Furthermore, the relationship was not affected by subject status or disease status of the eye, suggesting that there is a true scaling factor between the measurements produced by the 2 devices. However, the observed regression coefficient can only be a rough guide to the true relationship because of measurement error in both variables. Agreement was assessed with Bland-Altman plots, which produced oct:slp ratios in the same order of magnitude to the scaling factor produced by linear regression but with wide 95% limits of agreement. This suggests that the 2 devices have only a modest level of agreement when applied to the subjects in this study despite producing RNFL values showing a good relationship with regression analysis. This may be partly explained by the low subject numbers in this study.

Zaveri et al (20) have previously compared OCT and SLP RNFL measurements in the same patients using linear correlation and stated that there was a significant yet moderate relationship \((r = 0.67; P < 0.001)\). Pueyo et al (21) also found a similar degree of correlation \((r = 0.60; P < 0.0005)\). Neither study specifically looked at agreement between the measurements from the 2 devices. New generation OCT uses techniques with higher sensitivity, for example, spectral domain OCT (38). These contemporary OCT techniques may provide different results to Stratus OCT, and further comparison of SLP with spectral domain OCT will be informative.

This study has shown that SLP using GDxVCC is able to detect functionally relevant axonal loss in the RNFL of eyes affected by optic neuritis and thus replicates the findings of a previous OCT study of the same cohort and replicates the findings of 2 recent SLP studies in patients with MS (8). In addition, there appears to be a scaling factor between the RNFL values produced by the 2 devices, but there is only modest agreement between OCT and SLP in this study. SLP may have similar potential to OCT in the study of axonal loss in optic neuritis and MS and could be used to monitor the efficacy of future neuroprotective therapies in clinical trials.

REFERENCES


Original Contribution


22. Posner CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH.


Rarebit Perimetry for Bedside Testing: Comparison With Standard Automated Perimetry

Samuel K. Steven Houston, BS, Eric D. Weber, MD, Sebastian F. Koga, MD, Steven A. Newman, MD

Abstract: Background: Rarebit perimetry (RBP), a technique developed for the detection of early damage to the afferent visual system, has not been extensively tested at the bedside. This study was designed to test the feasibility of bedside testing with RBP in comparison with standard automated perimetry (SAP) performed in the clinic.

Methods: We tested 29 eyes of 15 subjects admitted with neurologic or neurosurgical diseases affecting the afferent visual system. RBP was performed on a laptop computer at the bedside. SAP (Humphrey field analyzer) testing was performed later in the clinic. Results were evaluated by a masked neuro-ophthalmologist.

Results: Visual fields corresponded between RBP and SAP in 24 (72%) of the 29 tested eyes. RBP detected defects in 5 subjects who had normal visual field results on SAP. All subjects preferred RBP for convenience.

Conclusion: RBP is a convenient method of bedside visual field testing and is no less sensitive to visual field defects in this role than SAP.

Methods: We tested 29 eyes of 15 subjects admitted with neurologic or neurosurgical diseases affecting the afferent visual system. RBP was performed on a laptop computer at the bedside. SAP (Humphrey field analyzer) testing was performed later in the clinic. Results were evaluated by a masked neuro-ophthalmologist.

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Conclusion: RBP is a convenient method of bedside visual field testing and is no less sensitive to visual field defects in this role than SAP.

D etecting and monitoring early visual field damage is important in lesions of the afferent visual pathways. Standard automated perimetry (SAP) utilizes white-on-white threshold testing that measures the presence of a visual defect and compares results with a normative database (1). The test targets are large and stimulate adjacent receptive fields, often underestimating the amount of damage (2). A large proportion of ganglion cells may be lost before SAP generates an abnormal result (3–6).

Rarebit perimetry (RBP), developed by Frisén in 2002 for the detection of early visual field damage, utilizes briefly exposed microdots to test the presence of vision or completeness of the neuroretinal architecture. Any defects in the architecture produce sieve-like visual field defects that maintain their retinotopic features. RBP reports mean hit rate (MHR), which should be 100% if the neuroretinal matrix is intact (7). However, as a result of the physiological blind spot, angioscotomata, blinks, and attention lapses, values for normal individuals may vary (8–9). Values for normal subjects and the effect of age on MHR (Table 1) have been reported, including test-retest variability, learning effect, influence of optical defocus, and cataract extraction in normal subjects (2,7,10–12), but an extensive normative database is lacking. Promising results have been reported for RBP in detecting early damage from glaucoma and neuro-ophthalmologic disorders as compared to frequency-doubling technology and SAP (2,7,10,13).

Ophthalmologists are frequently consulted to evaluate visual disorders in inpatients. Visual fields are an important component of the examination, but bedside testing is usually limited to the use of finger confrontation or projection techniques that are highly variable and have been shown to detect only dense defects (14). More quantitative assessment is desirable, but many patients are unable to undergo formal visual field testing because they are bedridden, unable to sit up or be transported, are continuously monitored, or otherwise unstable. A bedside visual field test must be convenient, portable, and comparable to SAP.

RBP is an easy patient-friendly option that can be carried out on a personal computer with a liquid crystalline display (LCD). Unlike automated perimetry, RBP is portable and easily administered with the patient lying in bed. Testing provides a quantitative and topographic picture of the visual field, making this method far superior to confrontation testing. Studies have also shown that RBP is comparable to SAP and may even be superior at detecting subtle damage. Previous studies have recognized the practical role of RBP in testing at the bedside (2,7,12,13). The purpose of this study was to test the feasibility of RBP in the inpatient setting.

METHODS

Test Subjects
Our study included 29 eyes from 15 consecutive ophthalmology consultations. Following investigational review board approval and informed consent, all patients underwent testing of their visual acuity at near using their own...
TABLE 1. Normal values of rarebit perimetry

<table>
<thead>
<tr>
<th>Author</th>
<th>Age, Mean (Range)</th>
<th>MHR</th>
<th>Number of Locations &lt; 90%</th>
<th>Effect of Age on MHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frisén 2002 (7)</td>
<td>27 (20–70)</td>
<td>96%</td>
<td>88–100</td>
<td>0.1%/y</td>
</tr>
<tr>
<td>Frisén 2003 (8)</td>
<td>27 (20–70)</td>
<td>96%</td>
<td>88–100</td>
<td>0.1%/y</td>
</tr>
<tr>
<td>Brusini 2005 (2)</td>
<td>41 (35–72)</td>
<td>88.6% (SD = 4.8%)</td>
<td>78–98</td>
<td>1–21</td>
</tr>
<tr>
<td>Martin 2005 (11)</td>
<td>21 (6.5–12)</td>
<td>93% (95% CI = 90–95)</td>
<td>78–100</td>
<td>0–21</td>
</tr>
<tr>
<td>Martin 2005 (11)</td>
<td>30 (14–20)</td>
<td>97% (95% CI = 96–98)</td>
<td>89–100</td>
<td>0–10</td>
</tr>
<tr>
<td>Martin and Wagner 2004 (10)</td>
<td>54 (17–88)</td>
<td>97% (95% CI = 94.5–96.7)</td>
<td>78–100</td>
<td>0–18</td>
</tr>
<tr>
<td>Salvetat 2007 (12)</td>
<td>71 (24–79)</td>
<td>91.3% (95% CI = 80–98.2)</td>
<td>78–99</td>
<td>0–21</td>
</tr>
</tbody>
</table>

CI, confidence interval; MHR, mean hit rate; SD, standard deviation.

Test Procedure

RBP has been described in detail elsewhere (7); software can be obtained from lars.fisene@neuro.gu.se. It utilizes a dark background and briefly exposed high-contrast probes or points. These test points are shown simultaneously for 200 milliseconds and consist of 2 microdots separated by 4° angle and measuring one half the minimum angle of resolution in diameter (1/100th the size of the test point in SAP). The paired dots appear randomly within 20 peripheral rectangular areas (0.5-m test distance) and 4 central areas (1-m test distance) inside 30° angle of eccentricity. Each of the 24 rectangular positions is probed twice for each pass, and the minimum of 5 passes for each test is utilized, resulting in 10 presentations per area. Ten percent of the test points consisted of one or no dots that serve as control. The target and background luminances are set at 150 cd/m² and 1 cd/m², respectively. The results of RBP consist of the MHR (sum of microdots seen divided by sum of microdots shown), number of locations with less than a 90% hit rate and percent miss rates for each of the 24 rectangular areas tested. Results also include a topographic display of the visual field for each eye (2,7,12).

RBP utilizes a personal computer with a 15” LCD display. The pupils are undilated, and a correction of 2 diopters (D) at the 0.5-m test distance and 1 D at the 1.0-m distance is made. A patch is used to test each eye separately.

In this study, the subject’s bed was elevated to 45° angle, and the laptop was placed on a Mayo table at eye level. The subjects used a computer mouse to indicate a response. As mouse position is irrelevant for this testing, it was held on the subject’s lap or hand. Lights were turned off, and window blinds were closed to minimize glare. The subjects received instructions on the test procedure and were shown a test demonstration before starting. A questionnaire was answered on completion of testing.

RESULTS

The analysis included the visual fields of 29 eyes from 15 subjects. There were 4 men and 11 women, ranging in age from 20 to 63 years. RBP and SAP were analyzed and classified separately and randomly. Visual field defect classifications, chosen from a list, included arcuate, altitudinal, central scotoma; left or right homonymous; cecocentral scotoma; diffuse depression; enlarged blindspot; bitemporal; and normal. Corresponding RBP and SAP visual fields were then compared side by side to determine whether defects were correlated.

Figures 1–3 demonstrate some examples of RBP and the corresponding SAP. Figure 1 is of a 53-year-old woman with optic neuropathy of unknown etiology and visual acuity of 20/20 in the right eye and 20/15 in the left eye. Visual fields showed an inferior arcuate defect in the right eye and a superior arcuate defect in the left eye. The patient had asymmetric nerve fiber layer thinning on optical coherence tomography. Figure 2 is of a 58-year-old woman who presented with an ischemic stroke. Visual fields illustrate a dense right homonymous hemianopia. Figure 3 is of a 22-year-old man with a left frontal glioma who presented with the acute onset of seizures. Visual acuity was 20/20 in both eyes, and ophthalmoscopy showed bilateral papilledema. Visual fields disclosed enlarged blind spots.

There was correspondence between RBP and SAP in 21 (72%) of 29 visual fields. RBP detected a defect in 5 (17%) of 29 visual fields in which SAP was normal. SAP detected 2 defects not detected by RBP. One visual field defect did not show correspondence between the 2 tests. RBP showed diffuse depression in 3 visual fields that was not detected with SAP. RBP test time averaged 4 minutes and 48 seconds per visual field; SAP test time averaged 3 minutes and 16 seconds. Table 2 displays subject demographics, diagnosis, and visual field classifications.
In completing the questionnaire regarding the ease and convenience of testing with both RBP and SAP, subjects used a scale of 1 (easy) to 5 (difficult). They were then asked which test they preferred. Despite the fact that RBP test time was slightly longer than SAP test time, all 15 subjects preferred RBP because it was more convenient. But they agreed that the ease of the testing was the same for RBP and SAP.

**DISCUSSION**

In this study, RBP was comfortably carried out at the bedside. Testing conditions could be accommodated to the subject. The mouse facilitated testing as it only required the function of one finger, eliminating the need to be able to grip a device. The laptop computer was easily portable, fitting nicely in a carrying case or backpack.

RBP produced results comparable to those of SAP, with 72% of visual fields exhibiting corresponding defects. Five visual fields (17%) showed defects on RBP that were not evident on SAP, consistent with the increased sensitivity of RBP in detecting subtle damage. However, 3 visual fields performed by RBP showed diffuse depression, potentially masking defects.

Although RBP test times were slightly longer than SAP test times, when transportation time and clinic wait time is included, RBP is much less time consuming. Moreover, RBP, unlike SAP, is applicable to subjects who are medically unstable, need continuous monitoring, or have multiple access lines or monitors.

The disadvantage of RBP is the use of suprathreshold testing, which may produce excess noise. On SAP, the problem of diffuse depression is resolved by analyzing the pattern deviation, which sets the 7th highest value (85th percentile best point) as a new baseline sensitivity (1). RBP does not have a built-in algorithm to account for diffuse depression, and some subtle defects may be lost. However, studies have shown that the effectiveness of suprathreshold testing is comparable to that of full-threshold testing (15). RBP also differs from SAP in that the fixation target moves, a feature that may promote subject confusion. However, our subjects reported that the moving fixation target helped maintain attention. Moving fixation targets have not altered diagnosis in other studies (16).

There have been questions regarding the reliability of RBP as compared with SAP. Studies by Brusini et al (2) and Gedik et al (13) have shown that the MHR and mean deviation were strongly correlated. However, further studies will need to be performed to investigate the reproducibility and utility of RBP in tracking visual defects over time.

**FIG. 1.** A patient with bilateral optic neuropathy. Rarebit perimetry (top) and standard automated perimetry (bottom) show corresponding arcuate defects in both eyes.
FIG. 2. A patient with left occipital lobe infarction. Rarebit perimetry (top) and standard automated perimetry (bottom) reveal a right homonymous hemianopia.

FIG. 3. A patient with increased intracranial pressure from a frontal lobe glioma. Rarebit perimetry (top) and standard automated perimetry (bottom) show enlargement of the blind spot in each eye.
TABLE 2. Patient demographics, diagnosis, and visual field classification

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age</th>
<th>Sex</th>
<th>RBP (OD:OS)</th>
<th>SAP (OD:OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary mass</td>
<td>51</td>
<td>F</td>
<td>Normal:arcuate</td>
<td>Normal:arcuate</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>49</td>
<td>F</td>
<td>Normal:normal</td>
<td>Normal:normal</td>
</tr>
<tr>
<td>Optic neuropathy</td>
<td>53</td>
<td>F</td>
<td>Arcuate:arcuate</td>
<td>Arcuate:arcuate</td>
</tr>
<tr>
<td>Ocular ischemic syndrome</td>
<td>59</td>
<td>M</td>
<td>Diffuse depression</td>
<td>Diffuse depression</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>55</td>
<td>M</td>
<td>Left homonymous:Left homonymous</td>
<td>Left homonymous:Left homonymous</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>40</td>
<td>F</td>
<td>Arcuate:arcuate</td>
<td>Arcuate:arcuate</td>
</tr>
<tr>
<td>Pseudotumor cerebri</td>
<td>20</td>
<td>F</td>
<td>Diffuse depression:Diffuse depression</td>
<td>Diffuse depression:Diffuse depression</td>
</tr>
<tr>
<td>Meningioma</td>
<td>54</td>
<td>F</td>
<td>Diffuse depression:arcuate</td>
<td>Arcuate:arcuate</td>
</tr>
<tr>
<td>Visual changes</td>
<td>47</td>
<td>F</td>
<td>Normal:arcuate</td>
<td>Normal:arcuate</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>63</td>
<td>F</td>
<td>Normal:arcuate</td>
<td>Normal:cocentral scotoma</td>
</tr>
<tr>
<td>Orbital tumor</td>
<td>50</td>
<td>M</td>
<td>Normal:normal</td>
<td>Normal:normal</td>
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<tr>
<td>Stroke</td>
<td>58</td>
<td>F</td>
<td>Right homonymous:Right homonymous</td>
<td>Right homonymous:Right homonymous</td>
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<td>Pseudotumor cerebri</td>
<td>22</td>
<td>F</td>
<td>Diffuse depression:arcuate</td>
<td>Diffuse depression:diffuse depression</td>
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<tr>
<td>Cerebral tumor</td>
<td>22</td>
<td>M</td>
<td>Enlarged blindspot:enlarged blindspot</td>
<td>Enlarged blindspot:enlarged blindspot</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>30</td>
<td>F</td>
<td>Arcuate:arcuate</td>
<td>Normal:normal</td>
</tr>
</tbody>
</table>

OD, right eye; OS, left eye; RBP, rarebit perimetry; SAP, standard automated perimetry.

ACKNOWLEDGMENT

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Mitochondrial Pseudomyasthenia

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Abstract: The classic ocular motor presentation of mitochondrial disorders is chronic, symmetric, and diffuse weakness. We describe a man with 25 years of asymmetric ptosis, ophthalmoparesis, and facial weakness that partially responded to steroid therapy. Serologic and electrophysiological investigations for myasthenia gravis were negative, but muscle biopsy confirmed a mitochondrial myopathy. This case illustrates the potential of mitochondrial ophthalmoparesis to mimic the features of ocular myasthenia.

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A classic ocular motor presentation of mitochondrial myopathy is a chronic progressive external ophthalmoplegia (CPEO), a slowly worsening weakness of all extraocular muscles, eyelids, and the orbicularis oculi. While asymmetric ptosis in CPEO is not uncommon, most patients do not experience diplopia because dysfunction of the extraocular muscles is symmetric (1). Markedly asymmetric ophthalmoparesis is rare (2), and when present may suggest an alternative diagnosis of ocular myasthenia gravis. We describe a man with long-standing asymmetric ptosis and ophthalmoparesis in whom ocular myasthenia was initially considered, whose signs partially responded to prednisone, but whose investigations revealed a mitochondrial myopathy.

CASE REPORT

A 63-year-old man developed vertical diplopia and right ptosis abruptly at age 38. The ptosis and diplopia persisted and over the next 25 years slowly worsened, with gradually increasing separation of images. He was not aware of any diurnal variation or fatigability and denied symptoms of dysarthria, dysphagia, and limb weakness. He had complex partial seizures that began at age 25. These typically began with left facial tingling, followed by tinnitus, visual hallucinations, and senses of déjà vu and de-realization. Electroencephalogram demonstrated sharp waves in the right central temporal region. The seizures ceased with the use of carbamazepine and lamotrigine. There was no family history of seizures or ocular disorders.

His initial examination showed best-corrected visual acuity of 20/20 in both eyes, with no retinal abnormalities. Pupils were symmetric in light and dark. There was 4 mm of ptosis and partial limitations of abduction in the right eye and of adduction and depression in the left eye (Fig. 1). Measurements showed 18 prism-diopters (PD) of left hypertropia in primary position and downgaze, decreasing to 5 PD in upgaze, and a small exotropia in right gaze. There was subtle weakness of left lid closure (Fig. 2) but no other evidence of facial or extremity weakness.

The patient was given a trial of pyridostigmine that had no effect and was then prescribed 20 mg prednisone daily. Four months after the initial prescription, he had 3 mm of right ptosis. Abduction of the right eye and depression of the left eye had greater range. The left hypertropia had decreased from 18 to 6 PD in primary position, and in downgaze, his left hypertropia had decreased to 5 PD.

Two assays for acetylcholine receptor antibodies were negative. Single-fiber electromyography of the right and left frontalis muscles was performed on 2 separate occasions and was normal. Repetitive stimulation of the left facial nerve at 3 Hz did not show any decrement of the compound muscle action potential. A CT of his chest and MRI of the brain were unremarkable.
One month later, prednisone was stopped because of confusion and depression. Four months after stopping steroid therapy, examination showed 4 mm of right ptosis; diminished abduction of the right eye; and limited adduction, abduction, and depression of the left eye. The left hypertropia now measured 20 PD in primary position. A biopsy of the left vastus lateralis was performed. Ragged red fibers were noted with modified Gomori trichrome stain, and ragged blue fibers in the nicotinamide adenine dinucleotide hydrogen (NADH) and succinic acid dehydrogenase (SDH) stains. Many cytochrome oxidase-negative muscle fibers were identified (Fig. 3). There was no evidence of inflammation. Electron microscopy showed subsarcolemmal accumulations of mitochondria with focal subsarcolemmal splitting; mitochondria displayed considerable pleomorphism and most contained rectangular crystalline inclusions. Mitochondrial DNA analysis was negative for deletions or point mutations of MELAS 3243, 3271 or MERFF 8344, and nuclear DNA analysis was negative for POLG and Twinkle mutations. Free and total carnitine levels were very low, at 3 and 4 μmol/L, respectively, and he was started on carnitine supplementation. Electrocardiogram was normal.

On 3 examinations over the subsequent 2 years, his right ptosis varied slightly from 3 to 5 mm and he remained with a 16–20 diopter left hypertropia in primary position, with exotropia varying from 0 to 18 PD in right gaze. He had occasional complaints of right leg weakness but no clear evidence of paresis in his limbs.

**DISCUSSION**

Our patient presented with weakness of the levator palpebrae superioris and lateral rectus muscle of the right eye and of the medial rectus, inferior rectus, and orbicularis oculi of the left eye. Prednisone improved his ptosis by history, and examination confirmed better abduction of the right eye and depression of the left eye during treatment, which deteriorated again when prednisone was stopped. Subsequent examinations also showed variability of right ptosis and extraocular movement, notably his exotropia in right gaze.

About half of the patients with CPEO have asymmetric ptosis (1,3), with a few having unilateral ptosis (1,4–6). While minor asymmetries in ophthalmoparesis can occur, reflected in a 40% incidence of disconjugacy and transient or persistent diplopia (1), marked asymmetry is highly unusual. There is one report of a woman who presented with marked weakness of the right medial rectus and mild paresis of the left lateral rectus and right inferior rectus, without ptosis, combined with a right facial palsy (2). This patient showed no decremental response on nerve conduction studies, but myopathic features on electromyography prompted muscle biopsy, ultimately leading to the finding of a mitochondrial DNA deletion, establishing the diagnosis of CPEO (7).

![FIG. 1. Photographic documentation of right ptosis and decreased abduction in the right eye and decreased adduction and depression in the left eye.](image1)

![FIG. 2. With forced lid closure, there is mild weakness of the orbicularis oculi muscle on the left.](image2)
The patient we describe did not have myopathic features on electromyography but then neither do a third of patients with mitochondrial myopathy (1). He did not have mitochondrial DNA deletions but not all cases of CPEO do: some can have point mutations (8,9) and sometimes with overlapping features of other mitochondrial syndromes, such as MELAS or MERRF (10–12). Our patient’s complex partial seizures differed from the epilepsies of these classic mitochondrial syndromes, but mitochondrial dysfunction may be a contributing factor in some cases of temporal lobe epilepsy (13). Regardless, his muscle biopsy showed clear features of a mitochondrial myopathy, and his metabolic assays revealed a carnitine deficiency, a secondary phenomenon in some mitochondrial myopathies (1,14,15) but not in myasthenia.

Response to prednisone is typical of inflammatory or autoimmune muscle disorders, including myasthenia gravis. However, in other disorders, such as Duchenne muscular dystrophy, prednisone can also improve muscle function (16). The effect of steroids in mitochondrial myopathies is less clear. In vitro studies have suggested possible beneficial effects of methylprednisolone on mitochondrial function (17). Anecdotal reports suggest that steroids improve weakness in some patients with mitochondrial myopathy (14,18,19) but not others (2,3,20). In addition, there are descriptions of mitochondrial damage and CPEO-like signs evolving in patients on chronic steroid therapy (21). Whether our patient truly improved on prednisone can be questioned as some of his signs fluctuated without treatment. However, his left hypertropia was a relatively stable deficit that did show a documented decrease during the time he was taking prednisone and deterioration after he stopped.

Clinically, a steroid-responsive pattern of highly asymmetric lid with facial and ocular motor weakness with variable signs between examinations strongly suggests myasthenia gravis. Negative results of antibody testing and

FIG. 3. Muscle biopsy. A. Modified Gomori trichrome–stained section showing ragged red fibers, ×400. B. Succinic acid dehydrogenase stain showing numerous fibers with increased subsarcolemmal enzymatic staining (“ragged blue” fibers), ×100. C. Cytochrome oxidase study (COX) showing “ragged brown” fiber with increased subsarcolemmal enzymatic staining and COX negative fibers, ×400. D. Electron photomicrograph showing pleomorphic elongated mitochondria containing intramitochondrial inclusions, ×43,000.
electrophysiology should not dissuade one from the diagnosis, given the high rate of false-negative results when myasthenia is purely ocular (22,23). Our case illustrates the potential of mitochondrial myopathy to simulate features of myasthenia, including marked asymmetry, variability, apparent response to steroid therapy, and lack of myopathic signs on electromyography.

REFERENCES
Cancer-Associated Retinopathy in Neuroendocrine Carcinoma of the Fallopian Tube

Anitha Raghunath, MD, Grazyna Adamus, PhD, Diane C. Bodurka, MD, Jinsong Liu, MD, PhD, Jade S. Schiffman, MD

Abstract: A 70-year-old woman developed progressive visual loss with compromised visual acuity and visual fields, cells in the anterior chamber and vitreous, attenuated retinal arterioles, and macular edema. She had undergone right oophorectomy and partial salpingectomy nearly 50 years earlier. Full-field and multifocal electroretinography showed waveforms of markedly attenuated amplitudes, findings consistent with cancer-associated retinopathy (CAR). Positron emission tomography revealed a nodule in the anterior wall of a right hydrosalpinx. Total laparoscopic hysterectomy yielded a neuroendocrine fallopian tube malignancy. She underwent partial treatment with paclitaxel and carboplatin that was aborted because of the development of herpes zoster infection. At 15 months following diagnosis, her ophthalmic status was stable. This is the first report of CAR in neuroendocrine carcinoma of the fallopian tube.

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Although paraneoplastic syndromes affecting vision, including cancer-associated retinopathy (CAR), are well documented in patients with small cell carcinomas, fallopian tube neuroendocrine carcinoma causing CAR has not been reported. We report such a case.

CASE REPORT

A 70-year-old woman reported progressive worsening of vision in both eyes (left eye more than right eye) for approximately 18 months. The patient had undergone bilateral cataract surgery 18 months earlier with a temporary improvement in vision. She described intermittent diarrhea for 2 years for which evaluation had been unrevealing. Nearly 50 years earlier, she had been diagnosed with an ovarian cyst and had undergone right oophorectomy and partial salpingectomy in conjunction with an incidental appendectomy. Although the cyst was benign, it had been necessary to remove part of the adjoining fallopian tube for complete excision of the ovarian cyst. She also had a history of hypothyroidism and excision of basal cell carcinoma of the nose.

Three months before she presented to us, she had been evaluated by a neuro-ophthalmologist who had recorded visual acuities of 20/20 in the right eye and 20/25 in the left eye. Color vision had been severely impaired, but no afferent pupillary defect had been found. Posterior segment examination had revealed vitreous cells, mild retinal arteriolar attenuation, and normal optic discs. Intraocular pressures had been 32 mm Hg in the right eye and 19 mm Hg in the left eye.

Brain MRI had disclosed mild white matter signal abnormalities. Full-field electroretinography had shown extinguished or attenuated responses in nearly all photopic and scotopic conditions (Fig. 1). Negative tests had included serology for paraneoplastic neuronal and antiretinal antibodies, fluorescent treponemal antibody absorption test, rapid plasma reagin, angiotensin-converting enzyme, anti-neutrophil cytoplasmic antibody, Borrelia burgdorferi antibody, and spinal fluid examination. The patient had been treated with bimatoprost eyedrops to lower intraocular pressure but was distressed by deteriorating vision and glare.

Two months before consulting us, a second neuro-ophthalmologist recorded that visual acuities had deteriorated to 20/40 in the right eye and 20/50 in the left eye. Color vision had been severely impaired, but no afferent pupillary defect had been found. Posterior segment examination had revealed vitreous cells, mild retinal arteriolar attenuation, and normal optic discs. Intraocular pressures had been 32 mm Hg in the right eye and 19 mm Hg in the left eye.

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Two months before consulting us, a second neuro-ophthalmologist recorded that visual acuities had deteriorated to 20/40 in the right eye and 20/50 in the left eye. Color vision had been reduced in both eyes, and vitreous cells and slight pallor of both optic nerves were observed. Visual field examination showed enlargement of the blind spots with constricted isopters along the
horizontal meridian. A retinal fluorescein angiogram was suggestive of vasculitis. Optical coherence tomography showed subfoveal fluid bilaterally. Multifocal electroretinography showed bilateral near flattening of the waveforms. The patient was diagnosed with bilateral chronic posterior uveitis, retinal vasculitis, and macular edema. No treatment was instituted.

On our examination, best-corrected visual acuities were 20/25 in the right eye and 20/60 in the left eye. She was able to identify 4/14 Ishihara color plates with the right eye and 0/14 with the left eye. There was a left afferent pupillary defect of 0.6–0.9 log units. There were 2+ cells in the anterior chamber and 3+ cells in the vitreous in both eyes. Optic discs appeared normal, but macular edema was seen in the left eye. Amsler grid testing showed a dense ring scotoma with minimal central preservation in both eyes. With automated visual fields (Fig. 2), a dense ring scotoma was present in the right eye and severe constriction in the left eye.

Further investigations revealed a negative collapsing response-mediating protein 5 antibody but positive serum anti-retinal antibodies against carbonic anhydrase II, alpha-enolase, and a 97 kDa protein. Immunohistochemistry, performed at the Ocular Immunology Laboratory at Oregon Health and Science University, Portland, Oregon (G.A.), showed strong cytoplasmic staining of the outer nuclear layer and diffuse staining of the ganglion cell layer and neuronal fibers of human retina.

The patient underwent investigations to exclude lymphoma and other malignancies. Gastrointestinal system evaluation to exclude Whipple disease and neoplasia with
endoscopy and colonoscopy showed only diverticular disease. A whole-body fluorodeoxyglucose positron emission tomography (with noncontrast CT for attenuation correction) showed a nodular area in the anterior wall of a right hydrosalpinx. This finding was confirmed by ultrasound, which also showed a thickened endometrial stripe suspicious for endometrial malignancy. CA-125 measurement was 12.9 U/mL (within normal limits).

Over the next 4 months, the hydrosalpinx grew, so the patient underwent a total laparoscopic hysterectomy. After an intraoperative frozen section reported a fallopian tube malignancy, a bilateral salpingo-oophorectomy, pelvic lymph node dissection, and omentectomy were completed. Low-power histopathology showed extensive necrosis (Fig. 3A). High-power histopathology (Fig. 3B) showed hyperchromatic nuclei and scant indistinct cytoplasm, numerous mitoses, and great variation in tumor cell size with focally irregularly shaped nuclei.

Immunohistochemical staining was positive for epithelial membrane antigen (Fig. 3C), cytokeratin, chromogranin, synaptophysin, and neurofilament and negative for leukocyte common antigen, placental alkaline phosphatase, and alpha-fetoprotein. The morphology and immunohistochemical profiles supported a diagnosis of high-grade neuroendocrine carcinoma with small cell features. No tumor was found in the ovaries, endometrium, lung, or gastrointestinal tract.

The patient did not receive any immunosuppressive medication, but completed 2 of 6 planned cycles of paclitaxel and carboplatin. She failed to complete chemotherapy due to an outbreak of herpes zoster in the right lower back.

She has no evidence of malignancy at 15 months following surgical treatment. At the most recent ophthalmological evaluation, visual acuities were 20/30 in the right eye and 20/40 in the left eye. Previous binocular vitrectomies had revealed no evidence of malignancy or infection. She continues to have mild panuveitis for which she has been receiving periocular corticosteroid injections. Secondary to the corticosteroid injections, she has developed uncontrolled glaucoma.

**DISCUSSION**

We believe this to be the first reported case of CAR in the context of a neuro-endocrine carcinoma of the fallopian tube. Such cancers account for only 1% of all gynecologic malignancies (1). Neuroendocrine carcinoma—which is more common in the lung, gastrointestinal tract, and genitourinary tract—is rare in the fallopian tube, where adenocarcinoma is much more likely (2). The first primary neuroendocrine tumor of the fallopian tube was reported in 2004 by Dursun et al (2).

Neuroendocrine carcinomas of the gynecologic tract are associated with poor prognosis (3). However, the patient with fallopian tube neuroendocrine carcinoma reported by Dursun et al (2) was alive at 16 months with no evidence of disease. Our patient is also doing well at 15 months after treatment.

**REFERENCES**

Orbital Involvement in Bing-Neel Syndrome

Rebecca C. Stacy, MD, PhD, Frederick A. Jakobiec, MD, Fred H. Hochberg, MD, Ephraim P. Hochberg, MD, Dean M. Cestari, MD

Abstract: Bing-Neel syndrome (BNS) is defined as intracranial involvement of Waldenström macroglobulinemia (WM). Few cases of orbital involvement have been reported. A 51-year-old man with a history of WM developed bilateral orbitopathy and optic neuropathy. Orbital biopsy, cerebrospinal fluid studies, and neuroimaging confirmed the diagnosis of BNS involving the orbital soft tissues, optic nerves, meninges, and cauda equina. The neuro-opthalmic manifestations resolved after parenteral and intrathecal chemotherapy in addition to autologous stem cell transplantation. The rare neuro-opthalmic manifestations of BNS may require a multifaceted approach to therapy.

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Waldenström macroglobulinemia (WM) is a lymphoproliferative disease characterized by clonal lymphoplasmacytoid cells and immunoglobulin M (IgM) heavy chain production (1). Neurologic and ocular involvement can occur by infiltration of WM cells or deposition of IgM in tissues, formation of amyloid deposits, or transformation to more aggressive forms of lymphoma. More than 50% of patients with WM have peripheral nerve involvement. Rarely, WM cells and tissue-bound IgM can involve the lacrimal gland and retina (2) or be associated with discrete masses within the orbit (3–5). Less commonly, WM affects the intracranial tissues. A decade before Waldenström characterized his eponymous disease, Bing and Neel (6) and Bing et al (7) reported 3 patients with intracranial lymphoplasmyctic proliferation without bone lesions. The Bing-Neel syndrome (BNS) designates the intracranial manifestations in patients with WM.

We describe a patient with BNS with diffuse, bilateral infiltration of the orbital fat and optic nerves that preceded the identification of involvement of the meninges, cauda equina, and cerebrospinal fluid (CSF). The orbital infiltrates were nontumefactive and did not produce proptosis. Treatment with intravenous and intrathecal chemotherapy was followed by autologous stem cell transplantation. This case extends the spectrum of manifestations of BNS.

CASE REPORT

A 47-year-old man was found to have anemia, but an evaluation was unrevealing. Two years later, abdominal CT demonstrated retroperitoneal lymphadenopathy and a CT-guided biopsy showed kappa-restricted small lymphocytes expressing CD19 and CD20 but not CD5, CD10, or CD23. Based on an IgM of 1820 mg/dL, the diagnosis of WM was made. He was treated with rituximab, cyclophosphamide, vincristine, and prednisone without response. He was then treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, leading to a partial remission. Four years after the diagnosis of WM, he developed decreased eye movements in both eyes and was referred to our neuro-ophthalmology service.

The patient reported that for the past year he had experienced intermittent “pressure sensations” behind both eyes. He denied diplopia or other pertinent symptoms. Visual acuity was 20/20 in both eyes with normal color vision (by Ishihara plates), Amsler grid testing, and pupillary reactions. There was no proptosis and the globes were nontender to palpation but slightly resistant to retropulsion symmetrically. Adduction was slightly reduced bilaterally without misalignment on alternate cover testing in primary gaze position. Automated perimetry showed a superior nasal defect in the right eye and a superior arcuate defect in the left eye (Fig. 1). The biomicroscopic and ophtalmoscopic examinations were normal except for an operculated retinal hole in the left eye.

Orbit and brain T1 MRI revealed heterogeneous hypointensity of orbital fat (Fig. 2A). Scattered areas of
abnormal hyperintensity on T2 sequences were present in both orbits (Fig. 2B). Postcontrast fat-suppressed T1 images revealed dense diffuse bilateral enhancement of the orbital fat and optic nerves (Fig. 2C, D). The leptomeninges also enhanced (Fig. 2D, arrow).

Right orbitotomy and biopsy of the orbital fat demonstrated a dense infiltrate composed of lymphocytes and lymphoplasmacytoid cells that invaded but did not destroy the septal and lobular architecture of the orbital fat (Fig. 3A). The infiltrating lymphoplasmacytoid cells had small, round, and dark nuclei and surrounded by rims of eosinophilic cytoplasm. Electron microscopy confirmed the presence of mitochondria and many strands of rough endoplasmic reticulum, consistent with antibody production (Fig. 3B). The lymphocytes stained positively for CD20 (a B-cell marker) (Fig. 3C) and BCL-2 (a marker for many non-Hodgkin lymphomas). In situ hybridization showed IgM-positive cells and many scattered kappa cells (Fig. 3D), which also coexpressed the Mu heavy chain. Stains for CD10 (a marker for precursor B-lymphoblastic leukemias and follicular lymphomas) and CD23 (a marker for follicular lymphomas) were negative.

Six weeks later, the patient described episodes of vision loss in the left eye lasting 10–30 seconds. Visual field deficits in both eyes had enlarged, and optic discs had become swollen (Fig. 4A). The MRI was unchanged. Due to the progression in symptoms and worsening visual field deficits, the patient was admitted the next day and treated with methylprednisolone, 1

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**FIG. 1.** Automated visual fields show superior nerve fiber bundle defects in both eyes.

**FIG. 2.** A. Precontrast T1 axial MRI shows heterogeneous hypointensity of the orbital fat bilaterally. B. On T2 axial MRI there is heterogeneous hyperintensity of the orbital fat. C. Postcontrast fat-suppressed T1 axial MRI shows diffuse enhancement of the optic nerves and orbital fat. D. Postcontrast coronal T1 MRI demonstrates enhancement of the orbital fat and interhemispheric leptomeninges (arrow).
g/day for 2 days. A lumbar puncture the same day yielded spinal fluid containing 255 mg/dL of protein and 6 white blood cells. When examined by flow cytometry, 30% of CSF cells were marked with CD19 and 20 but none with CD23, CD5, or CD10. Palliative orbital radiation was started one day later in 10 fractions to a total dose of 20 Gy.

These findings were consistent with WM without transformation into a large B-cell lymphoma. Spine MRI demonstrated enhancement in the cauda equina and meninges (Fig. 4B). Parenteral intravenous methotrexate (8 g/mm² every 10 days) was then administered for 5 cycles. One month after the fifth cycle, visual acuity, pupillary...
responses, and color testing remained normal and there were no further episodes of transient visual loss. Visual fields had improved, and optic disc edema had resolved without pallor. At this time, a bone marrow biopsy contained 5% lymphoma cells by flow cytometry.

To consolidate the systemic WM response, the patient underwent an in vivo rituximab-purged autologous hematopoietic stem cell transplant. Conditioning chemotherapy 9 days before his procedure began with intravenous bolus of 250 mg/m² thiotepa per day for 3 days, followed by 0.8 mg/kg intravenous busulfan every 6 hours for 3 days, followed by 60 mg/kg intravenous cyclophosphamide for 2 days.

Seventy-seven days after the transplant, orbit/brain MRI demonstrated stable infiltration of the orbital fat, optic nerves, and meninges. Eighty days after transplantation, CSF had improved, showing a protein of 102 mg/dL and 2 white blood cells. However, neuro-ophtalmic examination revealed worsening of the visual field defects. A single dose of intrathecal cytarabine liposome injection with systemic dexamethasone abolished CSF lymphocytes and reduced protein concentration to 57 mg/dL. No malignant CSF cells were identified on flow cytometry. One month after intrathecal chemotherapy, visual fields had improved and no lymphoma was present on bone marrow biopsy. Six months after transplantation, the patient remains on maintenance cytarabine liposome injection therapy without reappearance of WM and no new visual problems. His last IgM level was 127 mg/dL, within the normal range.

**DISCUSSION**

BNS, a rare complication of WM, results from tumor cell infiltration of the CSF or the deposition of WM-associated IgM within the brain and spinal cord. It was first described in 1936 in a patient with infiltration of the spinal cord and medulla by lymphoplasmacytoid cells (6). In the past 70 years, various definitions and classifications of BNS have been proposed. In 1960, Logothetis et al (8) refined the classification of BNS into 5 different subtypes: focal, diffuse, peripheral, subarachnoid hemorrhage, or mixed. Patients with diffuse disease have been classified by us (9) into 2 groups of patients: Group A, those with WM cells invading the brain or CSF, and Group B, a smaller population with WM-associated IgM damage to the white matter of the brain.

Many reports erroneously apply the term BNS to describe focal deficits caused by malignant transformation events of WM. It is important to distinguish Group A presentations from transformation of WM into diffuse large B-cell lymphoma with intracranial involvement, which presents with distinct tumor masses, focal neurological deficits, or seizures. Brain biopsies from transformed patients demonstrate focal neoplastic lymphocytic infiltration of the brain parenchyma (10,11). This was not the case in our patient. His Group A BNS appears to have consisted of WM cells infiltrating the orbital fat and optic nerves. Patients in Group A can have diffuse WM infiltrates into brain or meninges and can present with confusion, fatigue, and personality changes. Neuroimaging in these cases shows meningeal enhancement (12) or white matter changes. Histologic studies from Group A demonstrate lymphocytes or lymphoplasmacytoid cells in the brain stem and meninges (8,13–16). Group B patients have cells in the brain or CSF in numbers insufficient to explain diffuse neurologic impairment, suggesting a causative role for WM-associated IgM, a role analogous to WM-IgM deposition on peripheral nerves.

The reported ocular complications of WM have usually reflected hyperviscosity in the setting of excessive quantities of pentameric IgM, resulting in vaso-occlusive conditions with associated flame-shaped retinal hemorrhages and optic disc edema (5). Rare reports note tumors within the orbit (17), lateral orbital wall (18), eyelid, bulbar conjunctiva (19), and lacrimal gland (2). Histology in these cases has been consistent with WM. Karimi et al (20) reported a case of biopsy-confirmed WM complicated by multiple discrete masses in the soft tissue of both orbits that had infiltrated and replaced normal orbital fat.

Less common than orbital WM cases are those with WM and orbital and intracranial involvement. Kim et al (21) reported such a patient with headache and a cavernous sinus mass. The dura and CSF contained WM cells, but no ophthalmic data were provided. Another patient complained of cloudy vision, confusion, and headaches in advance of decreased acuity, keratic precipitates, vitreous debris, chorioretinitis, and optic disc edema from intracranial hypertension (22). Biopsied brain tissue contained vascular infiltrates of lymphoplasmacytoid cells, consistent with WM. The pathological features of the chorioretinitis are unknown. A similar example (13) was a 68-year-old woman with WM and a right sixth cranial nerve palsy, who had enhancement of the leptomeninges and elevated protein in the CSF.

Our patient had histological evidence of WM involving the orbit and CSF with extensive MRI involvement of optic nerves, spinal cord, and meninges. He represents Group A cellular infiltration of BNS, and his cellular form of BNS is characterized by infiltration of the optic nerves, cauda equina, spinal cord and brain meninges, Virchow-Robin spaces, and CSF. This case extends the prior limited definition of BNS, which included only discrete lesions within the intracranial space (23).

Our case is unusual in several regards. Orbital WM has previously been described as discrete masses on imaging, which were associated with proptosis and restricted eye movement (17,18). In contrast, our patient had no discrete tumor mass or evidence of transformation into a higher-grade tumor. Instead, there was diffuse infiltration of the orbital fat without complete obliteration of its constituent lobules. The absence of proptosis suggests an almost equal
volumetric replacement of fat by tumor. This pattern of diffuse infiltration has not yet been reported in WM; but this pattern has been documented with non-Hodgkin lymphoma in a patient with multiple myeloma (24) and has been seen in some of our other patients with primary ocular lymphoma. The patient of Karimi et al (20) had multiple discrete bilateral tumor masses. It is possible that our patient represents a later stage of a similar process, as the biopsy in the case of Karimi et al (20) showed patchy deposits of tumor cells in nonobiterated fat.

Our case extends the signs, symptoms, and examination of Group A patients with BNS to include ophthalmic manifestations (9). The process developed with asymptomatic visual field defects and MRI evidence of infiltrative optic neuropathy. With progression, the visual field defects worsened and transient visual loss occurred. The diffuse enhancement of the optic nerve from the globe to the orbital apex, beyond the intraconal fat, suggests an infiltrative process, which may have been ameliorated by treatment. Alternatively, we cannot exclude the possibility of nerve compression by infiltrates within the orbital fat.

Once diagnostic criteria for BNS have been accepted, more rigorous trials of treatment methods may proceed. To date, clinicians have explored intravenous and intrathecal chemotherapy and whole-brain radiation, with varying results (11–13,21). Treatment with high-dose methotrexate, orbital radiation, and corticosteroids resulted in reduction of visual symptoms in our patient. The intracranial component of the disease responded to high-dose conditioning regimens prior to autologous stem cell transplantation. However, complete response was elusive. Worsening visual field defects and persistent CSF tumor cells prompted therapy with intrathecal cytarabine liposome injection, which led to a favorable response.

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MRI Restricted Diffusion in Optic Nerve Infarction After Autologous Fat Transplantation

Yoo Jin Lee, MD, Hak Jin Kim, MD, PhD, Kwang-Dong Choi, MD, PhD, Hee-Young Choi, MD, PhD

Abstract: A 24-year-old woman reported blindness in the left eye upon awakening from fat autotransplantation to her forehead for soft tissue augmentation in the face. Clinical findings on the third postoperative day suggested ipsilateral ophthalmic artery occlusion with infarction of the optic nerve and retina. There were also clinical manifestations of a mild right hemiparesis. MRI diffusion-weighted imaging (DWI) revealed restricted diffusion of the left optic nerve and left middle cerebral artery domain indicative of the cytotoxic edema of infarction. This is the second report of optic nerve infarction after fat autotransplantation to the forehead and the first report of DWI restricted diffusion in this setting.

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A part from pain at the puncture sites, autologous fat injection for soft tissue augmentation in the face is reported to be a safe procedure (1). However, patients have rarely had acute visual loss and cerebral infarction (2–6). Fluorescein angiography, brain MRI, and cerebral angiography have been used in diagnosis of these events (2–4,6), but diffusion-weighted imaging (DWI) has not been described.

First described in 1986 (7), DWI is most commonly used to identify acutely infarcted cerebral tissue, which has an increased intracellular fraction of water. Owing to the availability of higher magnet strength MRI scanners and improvement in software, DWI can now be applied to smaller structures. Indeed, this MRI pulse sequence, which measures changes in water diffusion during acute stroke related to cytotoxic edema (8), is now being reported in optic nerve infarction (9–12).

We present a patient who developed acute optic nerve infarction and cerebral infarction after autologous fat transplantation documented by DWI restricted diffusion for the first time in this setting.

CASE REPORT

A 24-year-old woman presented with swelling and blindness in the left eye for 2 days. Three days earlier she had received an injection of autologous fat in her forehead under intravenous anesthesia.

On the day of the procedure she was unable to open both eyes due to the swelling of her eyelids. On the first postoperative day she became aware of visual loss in the left eye, decreased sensation on the forehead and scalp, and paresthesias of the right leg. She still could not open her left eye and dragged her right leg on walking.

On our examination on the third postoperative day, blood pressure was 110/70 mm Hg, pulse was 68/min, and temperature was 36.1°C. Blood count, erythrocyte sedimentation rate, C-reactive protein, and electrocardiogram were normal. She had no history of trauma, diabetes, or hypertension.

She was alert and mental status was intact. The left eye had no light perception, ptosis, and restricted extraocular motility in all directions. The left pupil did not constrict to direct light, and there was an afferent pupillary defect in the left eye. Ophthalmoscopy was normal in the right eye but showed pallid optic disc swelling and widespread retinal whitening in the left eye.

Pain, touch, and temperature senses were reduced in the left forehead and scalp. Motor function was intact in the upper and lower extremities. Deep tendon reflexes were increased in the right side. There was no Babinski sign.
Brain and orbit MRI at 5-mm slice thickness performed on the third postoperative day revealed hyperintensity in the left middle cerebral arterial territory and subtle hyperintensity in the left optic nerve on DWI and subtle hypointensity in corresponding regions on the apparent diffusion coefficient (ADC) map (Fig. 1). The ADC values were $2.75 \times 10^4$ in the affected optic nerve and $14.6 \times 10^4$ in the unaffected optic nerve, confirming markedly restricted diffusion in the affected optic nerve and normal diffusion in the unaffected optic nerve. T2 MRI did not show any signal abnormality in the affected optic nerve (Fig. 1C).

A follow-up DWI MRI at 3-mm slice thickness performed on the fourth postoperative day revealed an increase in the hyperintensity in the left middle cerebral arterial territory and the left optic nerve (Fig. 2A). The ADC map showed more prominent hypointensity of the corresponding regions (Fig. 2B). The ADC values were $2.37 \times 10^4$ in the affected optic nerve and $12.6 \times 10^4$ in the unaffected optic nerves.

The patient was treated with 1 g/day intravenous methylprednisone for 3 consecutive days. Five months later she still had no light perception in the left eye. Ophthalmoscopy disclosed severe retinal fibrosis in that eye. A relative afferent pupillary defect persisted in that eye, but ocular motility was normal except for a mild adduction deficit.

DISCUSSION

Our patient experienced complete visual loss in the left eye shortly after the injection of autologous fat into her forehead. Clinical findings on the third postoperative day suggested ipsilateral ophthalmic artery occlusion with infarction of the optic nerve and retina. There were also clinical manifestations of a mild right hemiparesis. DWI obtained on the third and fourth postoperative days revealed restricted diffusion of the left optic nerve and left middle cerebral artery domain indicative of the cytotoxic edema of infarction.

Ours is not the first report of acute visual loss and cerebral infarction after fat injection into the face (2–5). Mori et al (2) reported immediate onset of infarction of the ophthalmic artery during the time of injection of autologous fat in the glabellar area. Obstruction of the ophthalmic artery was irreversible. Feinendegen et al (3) described a patient with acute blindness in the left eye and right hemiplegia and global aphasia immediately after autologous fat injection into the periorbital areas. Ophthalmoscopic examination and carotid angiography revealed findings consistent with ipsilateral occlusion of the retinal and carotid arteries. It was assumed that intravasated fat reached the ophthalmic artery and the middle cerebral artery through the arteries on the forehead and led to immediate vessel occlusion. Egido et al (4) reported a case of sudden visual loss with hemiplegia immediately after autologous fat injection into the glabellar area. Brain CT showed embolic infarction in the right middle cerebral artery territory 8 days later. It was thought that fat material had been injected into a distal branch of the ophthalmic artery such as the supratrochlear artery. Dreizen and Framm (5) reported a similar patient showing permanent visual loss. Lee et al (6) reported a patient with central retinal arterial occlusion and unconsciousness. The patient recovered consciousness within a week but did not recover vision in the affected eye. The injection forces were postulated to have been strong enough to allow fat to reach the internal carotid artery, with embolism occurring to the ophthalmic artery and a branch of the middle cerebral artery (6).

Our contribution is to present DWI documentation of such an event for the first time. As in previous reports, we presume that the pressure of fat injection was high enough to reverse the flow through a branch of facial artery and force fat into the ophthalmic and distal internal carotid arteries (3,4). To avoid this problem, the physician must be careful to exert minimal force while injecting the fat into the facial tissue and to inject slowly (3).

There were 4 previous reports of restricted diffusion in DWI of acute ischemic optic neuropathy (9–12). The causes were rhinocerebral mucormycosis (9), nonarteritic posterior ischemic optic neuropathy (10), thrombotic arterial occlusion with underlying cavernous sinus thrombophlebitis (11), and thromboembolism with underlying arterial thrombosis (12). In these cases, restricted diffusion, which occurs

![FIG. 1. A. Axial diffusion-weighted MRI of the brain performed on the third postoperative day reveals abnormally high signal in the left optic nerve (arrow). B. Apparent diffusion coefficient map shows a corresponding low signal (arrow), indicating restricted diffusion. C. Axial T2 MRI does not show high signal in the corresponding region of the optic nerve (arrow), indicating its insensitivity to damage at this early stage.](image-url)
promptly as in other ischemic strokes, is critical in demonstrating optic nerve infarction, especially when other MRI pulse sequences show no abnormalities (9,12) and in distinguishing infarction from inflammation (10).

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MRI and Positron Emission Tomography Findings in Heidenhain Variant Creutzfeldt-Jakob Disease

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Abstract: The typical presentation of Heidenhain variant Creutzfeldt-Jakob disease (CJD) is a rapidly progressive visual loss in the setting of a relatively normal ophthalmologic examination. At presentation, patients with this uniformly fatal illness frequently demonstrate only minor cortical abnormalities on MRI. Here, we document the clinical presentation and imaging results of a patient with

FIG. 1. A. Automated visual fields reveal rapidly worsening bilateral homonymous defects. B. MRI abnormalities were subtle and included slight hyperintensity on FLAIR imaging and restricted diffusion on diffusion-weighted imaging within the occipital cortical ribbon (arrows). A magnetic resonance perfusion study (using the unenhanced arterial spin labeling technique) revealed slightly reduced occipital blood flow (arrow). Fluorodeoxyglucose-positron emission tomography (shown in axial, sagittal, and coronal views) revealed marked occipital and parietotemporal hypometabolism (arrows). These regions included striate cortex, color processing area V4, and motion processing area V5. C. Pathologic examination at autopsy revealed marked neuronal loss, gliosis, and spongiform vacuolization (arrows) within the occipital neocortex while other cortical and subcortical regions were relatively spared.

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Heidenhain variant CJD in whom abnormalities on positron emission tomographic imaging were more evident than changes on MRI. These changes were present in striate cortex and visual association areas, providing clinical-anatomical correlation with our patient’s visual deficits. Nuclear imaging provides a considerably more sensitive measure of neural dysfunction early in the course of this disease.

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A 66-year-old woman noticed slowly progressive blurred vision in the left inferior visual field. There were no headaches or other accompanying symptoms. An ophthalmologic examination revealed a homonymous left inferior field cut and no other abnormalities. Brain MRI was normal.

Over several weeks, visual loss gradually extended into the right inferior visual field (Fig. 1). She was referred for neuro-ophthalmic consultation. The patient described visual hallucinations in the form of shimmering orange lights in her peripheral vision along with palinopsia. Knitting had become difficult because of impaired depth perception. She had developed mild gait unsteadiness. There were no deficits of memory, language, or behavior, nor was there weakness or numbness.

On examination, she was alert and fully oriented. She named 28 of 30 items on the Boston naming task and comprehended complex verbal commands. She was fluent, and she could repeat normally. On memory testing the patient recalled 10 of 10 elements in a story after a 5-minute delay. Visuospatial testing revealed difficulty copying a cube, although she drew a clock face correctly. On testing of executive functions, she named 18 words beginning with the letter F in 1 minute. She completed oral trials successfully, performed simple calculations, and demonstrated normal praxis.

Corrected visual acuity was 20/25 in each eye. The patient correctly named colors but reported desaturation of blue and yellow. She identified the control Ishihara color plate but none of the test plates and made numerous errors arranging the desaturated L’Anthony D-15 color panel. She was unable to perceive a stereoscopic image with the Titmus stereotest (3,000 arcsec retinal disparity). Confrontation visual fields demonstrated a dense left inferior quadrant scotoma and a partial right inferior quadrant scotoma. Within the blind field, however, she correctly discriminated motion cues (the Riddoch phenomenon). The patient reported persistence of visual images a few moments after shifting gaze but correctly described all elements of both the “cookie-theif” picture and a Navon figure. Pupillary responses, ocular motility, and fundus examinations were normal.

Strength was normal. There was no myoclonus, numbness, or dysmetria. She reached for objects accurately, without past-pointing or tremor. Tandem gait was mildly impaired. Reflexes were normal, and symmetric and plantar responses were flexor.

A repeat brain MRI revealed slight abnormalities of the occipital cortical ribbon, including hyperintensity on FLAIR imaging and diffusion-weighted imaging that was more prominent on the right (Fig. 1). In addition, there were nonspecific white matter hyperintensities, consistent with small vessel ischemia. The basal ganglia and thalami were normal. An MRI perfusion study (using the unenhanced arterial spin labeling technique) revealed slightly decreased occipital blood flow. Fluorodeoxyglucose-positron emission tomography, in contrast to the MRI studies, revealed striking abnormalities, with severe hypometabolism of the bilateral occipital and parieto-temporal cortices (right greater than left) (Fig. 1).

Cerebrospinal fluid analysis showed no cells, protein 52 mg/dL, glucose 56 mg/dL, and normal cytology. The 14-3-3 immunoassay revealed only weak immunoreactivity and was considered an ambiguous result. CT of the chest and abdomen were normal. Testing for paraneoplastic antibodies was negative. An electroencephalogram (EEG) revealed a normal posterior dominant rhythm, without focal slowing or paroxysmal sharp waves. Visual evoked responses were normal (P100 latency, 103 milliseconds in the right eye, 101 milliseconds in the left eye).

The patient went completely blind over a period of 8 weeks. She died 12 weeks from the onset of symptoms and terminally she had myoclonus and impaired arousal and orientation. At autopsy, there was severe neuronal loss and gliosis with spongiform vacuolization that predominantly affected the occipital lobes (Fig. 1). Western blot analysis demonstrated accumulation of protease-resistant PrP\(^{\text{res}}\) (type 1), and genetic sequencing revealed the homozygous methionine polymorphism at codon 129 of the PrP gene.

The Heidenhain variant of sporadic Creutzfeldt-Jakob disease (CJD) describes a rare rapidly progressing dementia in which prominent visual changes constitute the initial symptoms. In 1929, Heidenhain first described this entity, reporting 3 cases sharing this striking clinical presentation in whom histopathological analysis revealed severe abnormalities including neuronal loss, gliosis, and vacuolization that were most prominent in the occipital lobes (1). Publication of cases with similar clinical and pathological features led to the proposal that this entity be named the Heidenhain variant (2). After several decades without insight into the pathogenesis of these disorders, Stanley Prusiner (3) advanced the prion hypothesis, which implicates the misfolding of the normal PrP protein into the protease-resistant PrP\(^{\text{res}}\) isoform. Almost all cases of Heidenhain variant CJD (including our patient) are homozygous for methionine at codon 129 of the PrP gene, but the significance of this association remains unclear (4).

The clinical diagnostic features of Heidenhain variant CJD have been well characterized (5–15). In comparison to
patients with ataxia-predominant CJD. Heidenhain patients have a similar age at onset, although they have a more rapid deterioration (mean disease duration, 5.7 vs 7.5 months) (7). Heidenhain patients commonly report a variety of visual symptoms, including blurring, field constriction, metamorphopsia, visual hallucinations, or visual neglect. In our patient, widespread posterior metabolic abnormalities in striate cortex and visual association areas (including color processing area V4 and motion processing area V5) accounted for the patient’s bilateral homonymous visual field defects, impaired color processing, and palinopsia.

It is common for the brain MRI in Heidenhain variant CJD to be normal or show only minimal changes, particularly early in the disease course (8). As our case demonstrates, severe progressive cortical visual loss may occur with only minimal structural changes identified by MRI. On the other hand, several recent reports of Heidenhain variant CJD have demonstrated that nuclear imaging studies may reveal conspicuously abnormal areas of hypometabolism (9–12). Reduced occipital blood flow has also been reported using nuclear imaging techniques, including Xe-133 SPECT (5), 99mTc-SPECT (13), and [15O]H2O PET (11). In many of these cases, however, Heidenhain variant CJD was suspected without pathological confirmation (9–12).

The case illustrated here demonstrates pathologically confirmed Heidenhain variant CJD with prominent focal hypometabolism observed on brain PET scan. In contrast, other ancillary tests (including standard MRI sequences, magnetic resonance perfusion, CSF 14-3-3, and EEG) demonstrated only mild abnormalities during the disease course and provided only limited clinical-anatomical correlation with our patient’s visual complaints. Nuclear imaging is a particularly sensitive indicator of the extent of neural dysfunction early in the course of Heidenhain variant CJD, demonstrating severe posterior hypometabolism in cortical regions that correlate with the visually predominant clinical deficits in these patients.

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Abducens Ocular Neuromyotonia in a Patient With Nasopharyngeal Carcinoma Following Concurrent Chemoradiotherapy

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Abstract: We describe a case of ocular neuromyotonia (ONM) following concurrent chemoradiotherapy for nasopharyngeal carcinoma (NPC). During an episode of neuromyotonia, the patient developed involuntary contraction of the left lateral rectus muscle and globe retraction with downshoot movement in the left eye. In the quiescent period, ocular motor examination revealed a partial left sixth nerve palsy. While diplopic complaints in patients with NPC raise suspicion of tumor recurrence or radiation-related cranial neuropathy, ONM must also be kept in the differential diagnosis.

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CASE REPORT

A 47-year-old woman was referred with a 3-year history of intermittent diplopia. Six years previously she had been treated for nasopharyngeal carcinoma (NPC) with concurrent chemoradiotherapy (cisplatin and fluorouracil for 4 courses and radiotherapy of 7,440 cGy in 62 fractions) with complete remission. She had not experienced diplopia before, during, or after these treatments. At presentation, her visual acuity was 20/20 in each eye. Pupillary function was normal. Both anterior segment and funduscopic findings were normal. Ocular motility examination revealed a left esotropia of 14 prism diopters in primary position, increasing in left gaze and decreasing in right gaze. Other cranial nerve function was unremarkable except for diminished sensation on left side of the chin. Brain MRI and endoscopic nasopharyngeal examination showed no evidence of tumor recurrence.

Three months later, the patient had a left esotropia of 6 prism diopters in primary position that increased to 10 prism diopters in left gaze. Leftward saccades were disconjugate, with a slower velocity in the left eye. After sustaining in left gaze for more than 1 minute, she reported a pulling sensation in left eye. When asked to move her eyes back to primary position, the patient developed a large left exotropia of more than 50 prism diopters. When she looked to the right, her left eye demonstrated globe retraction, palpebral fissure narrowing, and a downshoot movement. (See Video, Supplemental Digital Content 1, http://links.lww.com/WNO/A9, which demonstrates the ocular movement during the quiescent period and the ocular neuromyotonia [ONM] attack.) The patient was intolerant of carbamazepine, but with institution of 200 mg phenytoin daily, she reported fewer episodes of diplopia.

DISCUSSION

NPC is a tumor of the epithelial cells that cover the surface and line the nasopharynx. Because of the proximity of nasopharynx to the skull base and cavernous sinus, cranial nerve deficits occur in approximately 20% to 25% of such cases, with the sixth nerve being most commonly involved. Isolated sixth nerve palsy is a common finding of both new onset and recurrent disease. Cranial nerve palsies are also a well-known complication of radiation therapy for NPC. Therefore, diplopic complaints in treated NPC patients inevitably raise suspicion of tumor recurrence or radiation-related cranial neuropathy. A brief ocular motility test

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might overlook the possibility of ONM, which requires prolonged eccentric gaze.

Compared to radiation-related cranial neuropathy, ONM is very rare and has been reported previously in only 2 patients with NPC (1,2). These patients shared several features in common with our case, including ONM of the lateral rectus muscle, favorable response to membrane-stabilizing medication, and the coexistence of radiation-related neuropathy and ONM.

Our patient was treated with cisplatin and fluorouracil while receiving radiation. Both medications have been reported to cause cranial nerve toxicity (3). The concurrent use of these drugs during radiotherapy might increase tissue sensitivity to radiation and increase the likelihood of developing ONM. The effect of chemotherapy on the occurrence of ONM warrants further study.

We observed a down-shoot movement in adduction of the left eye of our patient during an episode of ONM. To our knowledge, this finding has not been previously reported. It may have occurred due to simultaneous cocontraction of medial and lateral rectus muscles with the lateral rectus sliding under the globe, producing an anomalous vertical movement as seen in Duane syndrome (4).

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Selective Saccadic Palsy After Cardiac Surgery

Eui-Jung Kim, MD, Sun-Young Oh, MD, Ha-Cheol Choi, MD, Byoung-Soo Shin, MD, Man-Wook Seo, MD, Jong-Bum Choi, MD

Abstract: We report a patient who showed a selective deficit of voluntary saccades and quick phases of nystagmus after cardiac surgery. Voluntary saccades in the horizontal plane were very slow, while vertical saccades, vestibular and optokinetic nystagmus, were absent. However, smooth pursuit, the vestibulo-ocular reflex, and the ability to hold steady eccentric gaze were preserved.

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To maintain optimal visual acuity, we use voluntary saccades to move the eyes rapidly from one point of visual fixation to the next (1). Loss of voluntary saccades may occur with brainstem strokes, although other types of eye movements are usually affected. Cases of selective saccadic palsy as a complication of cardiac surgery have been previously described (2–4). However, the pathogenesis of the disorder is unclear, and few reports have clearly defined the nature of the ocular motor deficit. Here, we report a patient with selective saccadic palsy after a cardiac operation and characterize and quantify the defect of the ocular motor disorder.

CASE REPORT

A 43-year-old man with chest pain underwent repair of an aortic dissection. The procedure was complicated by massive bleeding. On awakening from anesthesia, the patient had difficulty shifting his gaze and complained of vertical diplopia in primary position, which worsened in downward gaze. He also had difficulty walking because of an inability to alter his direction of gaze voluntarily.

On neurologic examination, the patient was alert and fully oriented. He had no dysarthria or dysphagia. He showed mild dysmetria of upper extremities and truncal ataxia with a tendency to fall.

Abnormalities on neuro-ophthalmic examination were limited to his eye movements. The patient had a right hypertropia, worse on looking down and to his left. Three-dimensional recording of eye motion with oculography (SMI, Teltow, Germany) was performed (see Video, Supplemental Digital Content 1, http://links.lww.com/WNO/A8). Horizontal and vertical saccades were profoundly slowed and hypometric. Optokinetic responses were absent. However, smooth pursuit, vergence, horizontal and vertical VOR, and the ability to hold the eye in an eccentric position were preserved. Eye movements and the ability to hold steady gaze were evaluated during attempted fixation of visual targets located centrally or eccentrically (±30° horizontally and ±20° vertically). There was no spontaneous or gaze-evoked nystagmus. Horizontal saccades were generated by a target moving pseudorandomly on a light bar with a range of ±16.7°. The range of target amplitude was 5°–30°. The patient had slowed and hypometric voluntary horizontal saccades (Fig. 1). Vertical saccades were completely paralyzed. Quick phases of nystagmus (reflexive saccades) were also reduced or absent during optokinetic nystagmus. Smooth pursuit (Fig. 1) and vergence eye movement were preserved. The vestibulo-ocular reflex (VOR), evaluated during passive or active head rotations, was normal in the horizontal and vertical planes while optokinetic stimuli elicited no horizontal or vertical movements (see Video, Supplemental Digital Content 1, http://links.lww.com/WNO/A8).

Bithermal caloric tests showed bilateral weak responses (less than 4° per second) (Fig. 2). Sinusoidal harmonic accelerations (peak velocity: 50° per second; frequency range: 0.02–0.32 Hz) showed decreased gains of the VOR and visual-enhanced VOR.

No brainstem abnormalities were detected on MRI (Fig. 3). Somatosensory and brainstem auditory-evoked potentials and audiogram were normal.
During 2 years of follow-up, our patient experienced no improvement in either his saccadic palsy or his truncal ataxia with gait instability.

**FIG. 1.** Three-dimensional recording of eye movements with video-oculography. A. Horizontal saccades are slow and hypometric B. Smooth pursuit is preserved. LH: left eye position, horizontal; LV: left eye position, vertical; RH: right eye position, horizontal; RV: right eye position, vertical.

**DISCUSSION**

Our patient showed abnormalities of saccades and quick phases of nystagmus including slowing, hypometria, and limited range. In contrast, smooth pursuit, VOR, vergence, and the ability to hold the eye in an eccentric position were preserved. Review of several anatomic structures within the brainstem may help explain this dichotomy. Premotor burst neurons and omnipause neurons lie within the reticular formation of the brainstem. Excitatory burst neurons generating horizontal saccades are located in the paramedian pontine reticular formation (PPRF), at the level of the abducens nuclei, and extend rostrally (1,5). Experimental bilateral lesions in the PPRF selectively abolish horizontal saccades, leaving other eye movements intact (6). Excitatory burst neurons for vertical and torsional saccades and quick phases are located in the rostral interstitial nuclei of the median longitudinal fasciculus (riMLF) (1,7). Bilateral lesions of riMLF abolish vertical and torsional rapid eye movements (8). However, it would be difficult to conceive a process causing selective impairment of burst neurons for horizontal and vertical saccades located in the pons and midbrain.

The omnipause neurons (OPNs) are another important component of the brainstem saccade generator and lie close to the midline in the raphe interpositus nucleus (1,9). OPNs are glycinergic and project to burst neurons in both the pontomedullary reticular formation, which directly controls horizontal fast eye movements, and the riMLF, which contains vertical eye movement–related burst neurons. OPNs are tonically active and make inhibitory connections with burst neurons directly controlling motorneurons for vertical and horizontal eye movements but pause before saccades in any direction. Chemical lesions of OPNs cause saccades to become slow (10). Recently, it has

**FIG. 2.** Quick phases of nystagmus (reflexive saccades) are reduced or absent during bithermal caloric stimulation. Peak slow phase of nystagmus (circled triangles) was less than 5% of normal velocity bilaterally. Positive sign indicates eye movement to the right, and negative sign to the left. SPV = slow phase velocity.
been proposed that OPNs also have a neuromodulatory function, to increase the responsiveness of saccade-related neurons when they receive a trigger signal (11–13). Therefore, the effect of OPNs on burst neurons may be 2-fold: inhibition when no saccade is planned, but enhancement of glutaminergic mechanisms when a saccade is triggered. So, a possible explanation of selective saccadic palsy in our patient is that OPNs might be damaged, in which case, both horizontal and vertical saccades would be expected to be slow.

The small vertical deviation in our patient suggests that structures adjacent to the brainstem reticular formation concerned with saccade generation may also have been affected. Yet, the pathogenesis of our patient’s mild dysmetria and gait instability remains unclear. These findings could be explained by cerebellar damage as would decreased saccadic acceleration and deceleration and saccadic hypometria (14). However, MRI failed to demonstrate any abnormalities of the cerebellum.

It is likely that ischemia to the brainstem reticular formation was responsible for saccadic palsy in our patient. Hypotension, intraoperative hypothermia, or microemboli are all potential contributing factors (2). Over a 2-year period, our patient showed no clinical improvement. This is consistent with other reports that patients with this ocular motor disorder may remain permanently visually disabled after cardiac surgery (2,3).

REFERENCES


Reversible Blindness: Simple Partial Seizures Presenting as Ictal and Postictal Hemianopsia

Pritha Ghosh, MD, Gholam Motamedi, MD, Benjamin Osborne, MD, Carlos A. Mora, MD

Abstract: A 34-year-old woman developed a sustained right homonymous hemianopia and episodic visual hallucinations 8 days after liver transplant surgery. Neuro-ophthalmologic examination and perimetry confirmed a right homonymous hemianopia with macular sparing. The patient’s vital signs and laboratory values, including a comprehensive metabolic panel and drug levels, were unremarkable. Brain MRI with and without contrast was also unremarkable. A video electroencephalogram revealed frequent, recurrent, left occipitoparietotemporal simple partial seizures associated with episodes of eyelid fluttering, right gaze preference, visual hallucinations, and a dense right hemianopia that persisted interictally. After treatment of the seizures with levetiracetam, perimetry showed resolution of the right homonymous hemianopia. This case demonstrates many classic features of occipital and parietal seizures. It also suggests that, unlike previously reported cases of enduring visual field deficits after cessation of seizures, early diagnosis and management of visual seizures may prevent permanent visual field deficits.

CASE REPORT

A 34-year-old woman with a history of ulcerative colitis and primary sclerosing cholangitis was admitted for elective liver transplantation. On hospital day 2, the patient had surgery without any complications. Postoperatively she was started on mycophenolate mofetil, tacrolimus, and prednisone for immunosuppression.

On postoperative day (POD) 8, the patient complained of spells of changes in her vision. The spells began with a sensation of vertigo, followed by spots of light or “sparkles” on the right side of her binocular peripheral vision. She was then overcome by a cold chill followed by a hot flash. The entire episode would last for less than 2 minutes and would occur between 5 and 20 times per day. Over the next 3 days, she began experiencing complex visual hallucinations. In addition to phosphenes, she would see false images of nurses walking along her right side as if they were coming to fix her intravenous line. There was no auditory component to these hallucinations, and the patient was aware that these images were not real.

On POD 13, she reported decreased peripheral vision on her right side and an intermittent, throbbing, left temporal headache. Her neuro-ophthalmologic examination revealed visual acuities near 20/20 bilaterally with normal pupillary responses, full extraocular movements, and unremarkable funduscopic exam. Automated perimetry demonstrated a right homonymous hemianopia with macular sparing (Fig. 1A). The remainder of her physical exam was unremarkable.

The etiology for the patient’s hemianopsia was unclear. She had no personal or family history of seizures. Vital signs, serum electrolytes, and liver function tests were normal, and tacrolimus levels were within therapeutic range. Brain MRI

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with and without contrast was unremarkable. Despite the lack of radiological or serological evidence suggesting tacrolimus neurotoxicity, the patient’s tacrolimus was discontinued and replaced with cyclosporine on POD 15. There was no immediate improvement in her symptoms following this change of medication.

Video electroencephalogram (EEG) monitoring on POD 15 revealed 22 events within a 24-hour period. These consisted of simple partial seizures originating in the left occipitoparietotemporal head regions with maximal surface negative discharges recorded from the occipital electrodes. The ictal activity rapidly spread to the immediate parietal and temporal leads but remained confined to electrodes P3-O1 and T5-O1 with no secondary generalization. Clinically, the patient had a right gaze deviation with brief eyelid fluttering at the seizure onset. She then described phosphenes and complex visual hallucinations of people walking in her right visual field, followed by sensations of cold chills and hot flashes rising in her upper body. She remained conscious and coherent throughout each event. The EEG and clinical presentation were consistent, lasting about 140 seconds (Fig. 2). Interictally, she complained of a persistent right homonymous hemianopia.

The patient was started on 500 mg oral levetiracetam twice daily on POD 15 but continued to have seizure activity. By POD 16, the levetiracetam increased to 1,000 mg twice a day, and no further epileptiform activity was recorded. The patient also reported a cessation in her visual hallucinations, although her hemianopia persisted. However, by POD 19, the patient had complete resolution of her hemianopia (Fig. 1B).

DISCUSSION

Our patient had frequent cryptogenic occipitoparietotemporal simple partial seizures that resulted in ictal and postictal right homonymous hemianopia with macular sparing. This case demonstrates several classic clinical findings associated with parietal and occipital seizures. For example, eyelid fluttering is a known presentation in

FIG. 1. A. Perimetry performed initially revealed right homonymous hemianopia with macular sparing. B. Repeated testing after treating the seizure disorder showed resolution of the hemianopia.
occipital seizures (1,5). Elementary visual hallucinations of phosphenes are also common in occipital seizures, particularly when seizure discharges originate from the lateral convexity of the occipital lobe (1). Typically, the phosphenes of occipital seizures are described as multicolored circles or spots, but as with our patient, some have reported achromatic flashing lights as well (3,4). The location of ictal phosphenes is classically in the contralateral

![FIG. 2. A. Partial seizure starts with right gaze deviation. Fast low-voltage spike activity builds in left parietal-occipital, maximum in occipital (P3-O1) and temporo-occipital (T5-O1) leads (arrows). B. Sixty seconds later, ictal activity remains confined to same leads (arrows); total seizure duration, 140 seconds.](image)
hemifield. In 18 patients with occipital epilepsy reported by Panayiotopoulos (3), 13 patients characterized their elementary hallucinations to be located in the contralateral, monocular, temporal hemifield. Although our patient also experienced phosphenes in the contralateral hemifield, she distinctly described it as a binocular phenomenon.

The formed visual hallucination that our patient described, that is, seeing people moving from the periphery to the midline of her hemianopic field, is a characteristic example of complex visual hallucinations associated with occipitoparietal seizures. As with our case, patients with complex ictal hallucinations frequently have a gaze preference in the direction of the hallucination but are usually aware that their hallucinations are not real (1).

During the final moments of her epileptic events, our patient reported thermal fluctuations. Thermal sensations, although less common than other sensory findings of pain or paresthesias, have been observed in occipitoparietal seizures. Prior studies suggest that fluctuation in thermal perception may originate from the perisylvian region (1). However, in our patient, the thermal fluctuations did not correlate with a perisylvian electrographic spread pattern.

In this case, all of the events were brief and were followed by postictal headaches, both of which are common features of occipital seizures (3,4). Our patient also experienced ictal and postictal right homonymous hemianopia with macular sparing. Her postictal EEG showed brief delta activity, most prominently in the left temporal lobe. Postictal hemianopia, a type of Todd’s phenomenon, has been previously reported (2,6,7). In this case, our patient had macular sparing of her visual field. Although macular sparing would suggest an isolated occipital ictus, the EEG demonstrated that she had an occipitoparietal ictus. This discrepancy may be secondary to the limited sensitivity of scalp leads, which may not record the weaker electrical field of simple partial seizures. Given the maximum negativity over the O1 electrode, it is possible that our patient’s seizure originated in the occipital lobe but was better detected by the scalp leads after it had spread to the parietal lobe.

Despite a comprehensive workup, the etiology of our patient’s seizures remains unknown. MRI revealed no focal lesions. Further evaluation with a single photon emission computed tomographic scan or cerebral angiogram could not be performed as the patient’s liver transplant began to fail shortly after cessation of her seizures.

Seizures are a known complication of liver transplantation. They usually occur in a bimodal distribution at 1 week and 5–16 weeks after surgery and are usually generalized (8). Infection, stroke, central pontine myelinolysis, and drug toxicity are among the different etiologies for posttransplant seizures(9). Of the medications that can induce seizures in transplant patients, calcineurin inhibitors, like tacrolimus, are a potential cause (10,11). In a retrospective study of tacrolimus-related seizures by Sevmis et al (11), 9% of liver transplant patients receiving tacrolimus developed seizures within the first 2 weeks of surgery, despite therapeutic levels. All these patients had generalized tonic-clonic seizures, and about 40% of them had evidence of posterior reversible encephalopathy syndrome on MRI.

This case demonstrates many of the classic findings of parietal and occipital seizures, including eyelid fluttering, gaze preference, and elementary and complex visual hallucinations. In addition, this case illustrates that ictal homonymous visual field defects may occur, and if recognized and treated promptly, these field defects may resolve.

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The Neural Mechanism for Latent (Fusion Maldevelopment) Nystagmus

Lawrence Tychsen, MD, Michael Richards, MD, Agnes Wong, MD, PhD, Paul Foeller, MS, Dolores Bradley, PhD, Andreas Burkhalter, PhD

Abstract: Latent nystagmus (LN) is the by-product of fusion maldevelopment in infancy. Because fusion maldevelopment—in the form of strabismus and amblyopia—is common, LN is a prevalent form of pathologic nystagmus encountered in clinical practice. It originates as an afferent visual pathway disorder. To unravel the mechanism for LN, we studied patients and nonhuman primates with maldeveloped fusion. These experiments have revealed that loss of binocular connections within striate cortex (area V1) in the first months of life is the necessary and sufficient cause of LN. The severity of LN increases systematically with longer durations of binocular decorrelation and greater losses of V1 connections. Decorrelation durations that exceed the equivalent of 2–3 months in human development result in an LN prevalence of 100%. No manipulation of brain stem motor pathways is required. The binocular maldevelopment originating in area V1 is passed on to downstream extrastriate regions of cerebral cortex that drive conjugate gaze, notably MSTd. Conjugate gaze is stable when MSTd neurons of the right and left cerebral hemispheres have balanced binocular activity. Fusion maldevelopment in infancy causes unbalanced monocular activity. If input from one eye dominates and the other is suppressed, MSTd in one hemisphere becomes more active. Acting through downstream projections to the ipsilateral nucleus of the optic tract, the eyes are driven conjugately to that side. The unbalanced MSTd drive is evident as the nasalward gaze-holding bias of LN when viewing with either eye.

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Latent nystagmus (LN) is a common subtype of pathologic nystagmus observed in human and nonhuman primates (1). It is linked strongly to binocular maldevelopment in infancy, from either strabismus or deprivation of monocular spatial vision (amblyopia).

LN is characterized by a conjugate horizontal slow-phase drift of eye position that is directed nasalward with respect to the viewing eye (2,3). When viewing switches from one eye to the other, the direction of the slow-phases reverses instantaneously: leftward when the right eye (RE) is fixating and rightward when the left eye (LE) is fixating (Fig. 1). The severity of the nystagmus (and its conspicuity during clinical examination) increases when one eye is covered, hence the term latent. When the nystagmus is evident with both eyes open, it is called manifest LN.

LN is distinguished easily during clinical examination from congenital nystagmus, also called the infantile nystagmus syndrome (INS), by the fact that LN has instantaneous reversal of direction with alternating fixation. By eye movement recording, it is distinguished also in waveform. The waveform of LN is always that of decreasing velocity and linear trajectory, whereas that of INS is of increasing velocity and pendular trajectory (2). Eye movement recordings or high magnification clinical inspection with a slit-lamp biomicroscope or ophthalmoscope frequently reveals a superimposed small torsional movement.

Seminal contributions to our understanding of the clinical features of LN have been made by Dell’Osso et al (2,4), who have also clarified the historical origins of LN’s various terms. In 1872, Faucon (5) first described what we now appreciate as manifest LN. In 1912, Fromaget and Fromaget (6) introduced the term nystagmus latent. These early reports of LN were reviewed by Sorsby (7) in 1931.
The oxymoron manifested latent nystagmus was introduced by Kestenbaum (8) in 1947, who emphasized that LN is often observed in patients with strabismus when they view with both eyes open.

Although infantile esotropia is the leading association with LN, any disorder that perturbs development of binocular fusion in infancy, such as monocular or severe binocular deprivation, will produce LN and manifest LN (9,10). The National Institutes of Health Committee on Eye Movement and Strabismus classification (11) has therefore recommended that the terms LN/manifest LN be replaced by the etiologic descriptor fusion maldevelopment nystagmus.

**DEVELOPMENT OF FUSION ELIMINATES NASALWARD VISUAL CORTEX BIASES**

Behavioral studies have shown that the postnatal development of binocular sensory and motor functions in normal infant monkeys parallels that of normal infant humans but on a compressed time scale: one week of monkey development approximates 1 month of human (12–15). Binocular disparity sensitivity and binocular fusion are absent in human and monkey neonates. Stereopsis emerges abruptly in humans during the first 3–5 months of postnatal life (16–20) and in monkeys, during the first 3–5 weeks (14), achieving adult-like levels of sensitivity.

V1 horizontal axonal connections are key components of fusion development and maldevelopment (Fig. 2). Binocularity in primates begins with horizontal connections between V1 ocular dominance columns (ODCs) of opposite ocularity (21–23). These connections are immature in the first weeks of life, conveying crude weak binocular responses (24–26). Maturation of binocular connections requires correlated (synchronous) activity between right eye and left eye geniculostriate inputs (27,28). Decorrelation of inputs (Fig. 3), produced by binocular noncorrespondence, causes loss of horizontal connections over a period of days in V1 of kittens (27,29). The inference from our experimental results and clinical studies is that similar losses occur over a period of weeks in V1 of monkeys and over a period of months in V1 of children. Binocular decorrelation also promotes interocular suppression (Fig. 4) as a further hindrance to fusion (1).

In the first months of life in humans and weeks of life in monkeys, monocular motion visual evoked potentials reveal a nasotemporal asymmetry (30–33). Monocular preferential looking testing reveals greater perceptual sensitivity to nasalward motion (34). Monocular pursuit and optokinetic tracking reveal biases favoring nasalward target motion (12,35–38). These nasolateral motion biases are pronounced before onset of sensorial fusion and stereopsis but systematically diminish thereafter. They are retained in subtle form in normal adult humans and can be unmasked using
contrived monocular stimuli (39,40). If normal maturation of binocularity is impeded by eye misalignment or monocular deprivation, the nasalward biases persist and become pronounced (34,41–47). The nasalward gaze bias is the key feature of the fusion maldevelopment syndrome. Other common findings are loss of stereopsis, interocular suppression, strabismus, and smaller amplitude torsional/vertical oscillations of the eyes.

**BINOCULAR DECORRELATION FROM VARIOUS CAUSES BEGINS THE LN CASCADE**

Clinical studies of children (43) and adults (2,4,44,48) with LN have inspired a series of behavioral, physiological, and neuroanatomic studies in nonhuman primates (NHPs) who had LN associated with naturally occurring (22,23,49–55) or experimentally induced (1,10,56–65) infantile strabismus. The common finding of these experiments is that the prevalence and severity of LN correlate systematically with the age of onset and duration of binocular decorrelation in infancy.

The most common clinical cause of binocular decorrelation is strabismus, which in human infants is overwhelmingly esotropic (convergent) (66). Early onset esotropia exceeds exotropia by a ratio of 9:1. Esotropia is also the most common form of naturally occurring strabismus in NHPs (67,68). It may therefore be considered the paradigmatic form of strabismus in primates. However, any prolonged deprivation of normal binocular experience in early infancy can cause binocular decorrelation (e.g., monocular congenital cataract, uniocular high ametropia in hyperopia or myopia, uniocular neonatal vitreous hemorrhage, uniocular corneal clouding, dense bilateral cataracts). In NHP models, monocular deprivation (uniocular amblyopia) or severe binocular deprivation (bilateral amblyopia) (10,57,63) produced by eyelid suturing (the thin translucent eyelid of NHPs mimics a congenital cataract, allowing diffuse luminance to the retina but blocking spatial vision) is also used to generate LN. But an important fact to note is that loss of spatial vision is not required; the majority of human and NHP infants with strabismus alternate fixation initially and have no amblyopia (69). The necessary and sufficient factor is binocular decorrelation, not lack of sharp visual acuity.

Decorrelation durations that exceed the equivalent of 3 months in human infant development result in an LN prevalence of 100% (1,65,70). Perturbing these inputs from the first week of life causes LN, but delaying the perturbation to the time of onset of normal fusion and stereopsis (the equivalent of age 2–4 months in human) is equally effective (71). The severity of the resultant LN corresponds
to the severity of loss of binocular connections between ODCs of opposite ocularity in visual area V1 and the severity of interocular suppression (1,72). Area V1 feeds forward to extrastriate areas MT/MST known to be important for gaze holding and gaze tracking, such as smooth pursuit, optokinetic nystagmus (OKN), and the short-latency ocular following response (73–76).

MALDEVELOPMENT IN V1 IS PASSED ON TO MEDIAL TEMPORAL AND MEDIAL SUPERIOR TEMPORAL AREAS

Visual areas V1, V2 (prestriate cortex), medial temporal (MT), and medial superior temporal (MST) of the cerebral cortex are major components of the conjugate gaze pathway (77). Each of these areas in normal primates contains directionally selective binocular neurons (78–81). MST in each cerebral hemisphere encodes ipsiversive gaze (74,82–84). MST in turn projects downstream to the brain stem visual motor nuclei that generate eye movements, including the nucleus of the optic tract (NOT), medial vestibular nucleus, and interconnected abducens and ocular motor nuclei (77,85). In primates, subcortical inputs to NOT may play a minor role (for reviews of the physiology of NOT and its role in LN see the work of Mustari and colleagues, as well as Hoffmann) (9,10,86). But the dominant pathway is from MST to brain stem. The dominant role of the cortical pathway, and the minimal role of a subcortical pathway, is reinforced by studies of children. Neuroimaging of visual cortex, combined with eye movement recordings, has shown absence of visually driven pursuit or OKN in cerebrally blind infants (87,88).

One mechanism for the gaze-holding asymmetry would be overrepresentation of nasalward neurons within visual areas V1 through MT in the immature/strabismic cortex. However, directionnal and binocular responses of neurons in V1, V2, and MT have been investigated in infant monkeys, as well as in monkeys with early onset strabismus, and no overrepresentation of neurons selective for nasalward motion has been found (26,61,89,90). Rather than overrepresentation of nasalward neurons, the mechanism appears to lack of connectivity of and suppression of temporalward neurons. In strabismic animals, binocular (excitatory) responses are reduced and interocular suppression is increased (89–91). These physiological abnormalities have neuroanatomic correlates. In V1 of strabismic monkeys, binocular connections are deficient (22,23) and interocular metabolic activity is suppressed (53,92,93).

BINOCULAR DECORRELATION UNMASKS AN INNATE NASALWARD MONOCULAR BIAS

LN is always linked to abnormal binocular development in infancy. This important clinical observation motivated the studies of NHPs, which have provided the functional-structural correlations needed to explain the pathophysiology. The translational value of NHP studies cannot be overstated. The NHP studies have provided the pivotal facts necessary to explain one of the most common clinical ocular motor disorders. The NHP studies have also motivated repair of fusion earlier in infancy (94), thereby preventing LN or reducing its severity.

LN is caused by an afferent binocular visual pathway defect. The binocular defect un masks a directional bias encoded in the cerebral gaze pathways. Normal binocular development (fusion) in the first months of life eliminates the directional bias; abnormal development (maldeveloped fusion) exaggerates the bias. If fusion goes unrepaired in infancy, the directional bias persists permanently throughout adult life (1,95).

A key implication emerging from the NHP studies is that the visual cortex in each cerebral hemisphere is wired innately for nasaldward motion. The innate wiring is monocular. To generate temporalward gaze holding, signals must traverse binocular connections, unimpeded by interocular suppression. If normal binocularity fails to develop, the system remains predominantly monocular and asymmetric, incapable of driving temporalward gaze holding or robust temporalward pursuit/OKN (10,43,44,61,66,90). LN is an abnormal monocular bias added on to a normal ipsiversive hemispheric gaze bias.

HYPOTHETICAL SIGNAL FLOW FOR LN

Figure 5 illustrates the mechanism for LN, showing the circuit mediating gaze holding in primates and the role of binocular connections. Shaded structures indicate less active visual and motor neurons caused by occlusion of one eye or interocular suppression. The circuit on the right depicts the pathways and visuomotor component structures in a primate with LN.

The flow is from top to bottom, starting from the monocular visual field (VF) of the fixating (or viewing) RE. The nasal and temporal VFs in primates are unequal in area, with a bias favoring the larger temporal hemifield. Retinal ganglion cell fibers (RGC) from the nasal and temporal retinas decussate at the optic chiasm, synapse at the lateral geniculate nucleus (LGN), and project to alternating monocular RE and LE ODCs in V1. During development, RGCs from the nasal retina outnumber and establish connections earlier than those from the temporal retina. The LGN lamina corresponding to the nasal retina (laminas 1, 3, and 5) contain more neurons and develop earlier than those from the temporal hemiretina (laminas 2, 4, and 6). Within the LGN, the neurons remain monocular, with no binocular interlaminar interaction.

The monocular bias, favoring nasal hemiretinal inputs, is passed on to the ODCs of area V1. In each V1, ODCs representing the nasal hemiretina (temporal visual hemifield) occupy slightly more cortical territory than those...
FIG. 5. Neural network diagrams showing visual signal flow for pursuit and gaze holding in strabismic and normal primates. A paucity of mature binocular connections explains behavioral asymmetries evident as asymmetric pursuit/optokinetic nystagmus and latent fixation nystagmus. In all primates, pursuit area neurons in each hemisphere encode ipsilaterally directed pursuit. Signal flow is initiated by a moving stimulus in the monocular visual field (VF), which evokes a response in visual area neurons V1 and MT. Each eye at birth has access, through innate monocular connections, to the pursuit area neurons in MSTd of the contralateral hemisphere. Access to pursuit neurons of the ipsilateral hemisphere requires mature binocular connections. In fusion maldevelopment (right column), retinal ganglion cell fibers from the nasal and temporal hemiretina (eye) decussate at the optic chiasm (chi), synapse at the lateral geniculate nucleus (LGN), and project to alternating rows of ODCs in V1 (visual area rectangles). In each V1, ODCs representing the nasal hemiretina (temporal visual field) occupy slightly more cortical territory than those representing the temporal hemiretina (nasal hemifield), but each ODC contains neurons sensitive to nasally directed and temporally directed motion (half circles shaped like the matching hemifield; arrows indicate directional preference). Visual area neurons, including those beyond V1 in area MT, encoding nasally directed motion are wired innately—through monocular connections—to the pursuit area. In normal primates, access to MSTd for temporalward gaze requires binocular connections to homoversive neurons within neighboring ODCs that have opposite ocularity (LE ODC neurons when viewing with the RE). The pathway from V1/MT to MSTd requires efferent projections through the splenium of the corpus callosum (96,97).

MSTd efferents project to the ipsilateral brain stem NOT (85,98) and to ipsiversive-related brain stem structures (medial vestibular nucleus, dorsolateral pontine nucleus, and ocular motor nuclei of cranial nerves 3 and 6).

RECONCILING CURRENT KNOWLEDGE WITH PREVIOUS LN HYPOTHESES IN HUMANS

Based on clinical observations and eye movement recordings in humans, several mechanisms have been proposed as the cause of LN. Ishikawa (99) thought that LN could be explained as a hyperactive stretch reflex of the medial rectus muscles, which drove the viewing eye nasally. Although the muscular basis is untenable, he drew further attention to the linkage of LN with other nasalward visuomotor biases, notably infantile esotropia.

Dell’Osso et al (2,4) hypothesized that LN arose from a confusion of egocentric direction caused by strabismus. Patients with unilateral or alternating strabismus view at any given moment with one eye predominantly. The viewing eye is displaced laterally with respect to the midline of the head. This displacement is not present with binocular fusion. With fusion, the perceptual center (cyclopean eye) coincides with midline. The incongruity between the body midline and the laterally displaced monocular view was representing the temporal hemiretinas (nasal hemifield), but each ODC contains neurons sensitive to nasalward (leftward) versus temporalward (rightward) visual motion. Receptive field neurons in V1 and MT are simplified here as half circles to match their corresponding hemifields. The arrows indicate the directional preference of the neurons. The visual area neurons (including those beyond V1 in area MT) are sensitive to both nasalward and temporalward motion (26,61,89), but only those encoding nasalward motion are wired innately through monocular connections to gaze (eye motion) neurons in the MST area (congregated in the dorsal-medial portion or MSTd). MSTd in each cerebral hemisphere encodes ipsiversive gaze (74,82–84), which is nasalward gaze in relation to the contralateral eye (leftward for MST in the left cerebral hemisphere and rightward for MST in the right hemisphere) (90).

The only difference between the LN primate’s visual cortex and the normal primate’s visual cortex is a paucity of binocular horizontal connections (23,72) (compounded by interocular suppression (53,92,93)). The paucity is depicted as a lack of diagonal RE ODC to LE ODC connections, absent in the LN cortex (right side of figure), and present in the normal cortex (left side of figure). In the cortex of normal primates, access to MSTd for temporalward gaze requires binocular connections to homoversive neurons within neighboring ODCs that have opposite ocularity (LE ODC neurons when viewing with the RE). The pathway from V1/MT to MSTd requires efferent projections through the splenium of the corpus callosum (96,97).

MSTd efferents project to the ipsilateral brain stem NOT (85,98) and to ipsiversive-related brain stem structures (medial vestibular nucleus, dorsolateral pontine nucleus, and ocular motor nuclei of cranial nerves 3 and 6).
believed to generate a neural command driving the viewing eye toward midline, that is, nasward. By revising confusion of egocentric direction to unbalanced, infantile, monocular interhemispheric MST'd drive, the hypothesis of Dell’Osso et al (2,4) can be updated to fit well with current biology. Volitional manipulation of interhemispheric activity can also alter LN direction. Dell’Osso et al (100) reported a monocular patient with LN who could do so by imagining viewing through the lost eye (replaced by an ocular prosthesis).

The notion of unbalanced cerebral hemisphere activity as a cause of nystagmus was emphasized by Sharpe et al (101,102), and by Zee (103). They proposed an imbalance of pursuit tone to explain a linear conjugate slow-phase drift of the eyes toward the more active hemisphere in adult patients with unilateral parietooccipital damage and normal binocular vision. Although they did not extrapolate their hypotheses to include a mechanism for LN, their insights may be considered important contributions.

van Dalen (39) pointed out that a subtle form of LN can be evoked in normal adult humans when viewing monocularly by flashing light in a Ganzfeld at high temporal frequencies. A current interpretation would be that by eliminating all gaze-stabilizing and fusional cues, while simultaneously activating visual motion neurons, the Ganzfeld unmask the vestiges of the infantile nasward bias. Kommerell and Mehdorn (48) emphasized the association of LN with impairment of temporalward OKN under conditions of monocular viewing. The nasotemporal OKN asymmetry was postulated to cause LN through mechanisms that remained to be worked out. Tychsen and Lisberger (44) postulated a defect in nasotemporal motion sensitivity within extrastriate visual areas MT/MST as the cause of both LN and pursuit/OKN asymmetries in humans with maldeveloped fusion. The work in humans by each of these investigators motivated the NHP experiments reviewed here that have helped to reveal the biology of LN.

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Blurred Vision and Eye Pain in a Middle-Aged Woman

Joseph Chacko, MD, Wade Brock, MD, Harry Brown, MD, Patrick Luetmer, MD, Caterina Giannini, MD, PhD

Dr. Chacko:

A 48-year-old white woman complained of worsening blurry vision in both eyes lasting 1 year and pain in both eyes for the previous month, which worsened with eye movements. She had experienced frequent headaches and transient visual obscurations during the preceding month, but she denied nausea, vomiting, and diplopia. Her medical history was significant for hypertension, acid reflux, anemia, and retroperitoneal fibrosis requiring ureteral stenting in the past year. She had undergone hysterectomy 13 years earlier. Her family history was significant for leukemia in her father. Social history revealed that she was an 18 pack-year smoker, but had quit 16 years earlier. Her only medication was valsartan. She denied any use of methysergide.

On examination, the patient’s blood pressure was 160/88 and her weight was 216 pounds. Visual acuity with correction was 20/20 in each eye. Color vision was normal, and pupils were brisk in each eye without a relative afferent pupillary defect. Intraocular pressure measured 18 mm Hg in each eye. Visual fields were full to confrontation, and slit-lamp examination was unremarkable.

There was slight ptosis of the left upper lid, and xanthelasmae were present (Fig. 1). There was no proptosis. Ocular motility revealed mild bilateral limitation of upgaze. The optic discs were mildly swollen (Fig. 2), and the fundi otherwise were normal. Neuroimaging was obtained (Fig. 3A–E).

Dr. Luetmer:

MRI of the brain and orbits (Fig. 3) demonstrates sharply marginated, bilaterally symmetric, uniformly enhancing masses filling and mildly expanding the intraconal spaces. The masses are isointense to the optic nerves on T1 images (Fig. 3A, 3C, 3D) and demonstrate markedly low signal on T2 images (Fig. 3B). Despite the size of the masses and mild displacement of the extraocular muscles, there is no deformity of the globes and no obvious proptosis. The optic nerves are encased without displacement or evidence of infiltration. The fat planes at the orbital apex are preserved, and there is no evidence of intracranial extension. No additional masses are seen, and the imaging including the intracranial contents is otherwise negative.

Dr. Chacko:

At this point, the differential diagnosis of bilateral, symmetric, and enhancing intraconal orbital masses was broad. The diagnostic categories of inflammatory, neoplastic, and infectious were entertained. Inflammatory conditions in the differential included sarcoidosis, Wegener granulomatosis, thyroid eye disease, and idiopathic orbital inflammation (i.e., orbital pseudotumor). Neoplastic
processes include lymphoma, sarcoma, meningiomas, and neurofibromas. Infectious entities such as syphilis and tuberculosis needed to be ruled out. Less common entities considered were eosinophilic granuloma, Waldenstrom macroglobulinemia, polyarteritis nodosa, and Erdheim-Chester disease.

Dr. Chacko:

A battery of laboratory tests were performed. Triiodothyronine, thyroid stimulating hormone, thyroxine, angiotensin-converting enzyme, antinuclear antibodies, perinuclear antineutrophil cytoplasmic antibodies, cytoplasmic antineutrophil cytoplasmic antibodies, SS-A, SS-B, rapid plasma reagin, and purified protein derivative (tuberculin) were all normal. Abnormal values were erythrocyte sedimentation rate: 44 mm/h; C-reactive protein: 59.2 mg/L (normal: 0–10 mg/L); lysozyme: 25 μg/mL (normal: 9–17 μg/mL); and rheumatoid factor: 33 IU/mL (normal 0–14 IU/mL). These abnormal values suggested an inflammatory process. A lumbar puncture was also performed. The opening pressure was 14 cm of water. Cerebrospinal fluid composition was normal, with no cells being present. A left anterior orbitotomy was performed with biopsy.

Dr. Giannini:

The orbital biopsy specimen showed dense fibrosis with a sparse polymorphous inflammatory cell infiltrate, mostly, lymphocytes (Fig. 4). These findings are nonspecific.

Dr. Chacko:

In reviewing the patient’s history, she had undergone a needle biopsy in the past year to make a diagnosis of retroperitoneal fibrosis. The orbital and retroperitoneal biopsy findings (Fig. 5) were very similar.

Dr. Giannini:

The retroperitoneal needle biopsy specimen also shows fibrosis with a marked polymorphous inflammatory cell infiltrate, composed of lymphocytes as well as histiocytes and eosinophils (Fig. 5A). Staining with CD-68, an immunohistochemical stain that highlights macrophages, revealed marked
positivity (Fig. 5B) as did staining with CD-45, an immunohistochemical stain for lymphocytes (Fig. 5C). The findings are consistent with “idiopathic retroperitoneal fibrosis.”

**Diagnosis**

Multifocal fibrosclerosis consisting of bilateral sclerosing orbital pseudotumor and retroperitoneal fibrosis.

**Dr. Chacko:**

Multifocal fibrosclerosis is a rare idiopathic autoimmune disorder characterized by fibrous lesions at multiple sites. The link between retroperitoneal fibrosis, Riedel thyroiditis, and idiopathic orbital inflammation was first suggested by Barrett in 1958 (1). The literature since has greatly expanded the number of locations in the body where the fibrous lesions may occur (Table 1) (2–6). A few cases have been familial, suggesting a genetic factor (2).

When involving the orbit, multifocal fibrosclerosis is indistinguishable from a solitary sclerosing orbital pseudotumor. It can affect intraconal and/or extraconal compartments, extraocular muscles, and the lacrimal gland. Symptoms and signs include pain, proptosis, ptosis, diplopia, and visual loss. Orbital infiltration can lead to visual loss from optic nerve compression or, rarely, from serous detachment of the retina or retinal pigment epithelium (7).

Pathology specimens show a predominance of fibrous connective tissue, active fibroblasts, and a leukocytic infiltrate consisting of lymphocytes, plasma cells, and eosinophils. The hyalinized fibrous tissue and chronic inflammatory cell infiltrate are sometimes arranged in concentric whorls around attenuated blood vessels (5). The lack of Touton giant cells and foamy lipid-laden macrophages distinguishes this disorder from Erdheim-Chester disease.

Our patient was treated initially with 80 mg prednisone daily with a slow taper. She reported some subjective improvement in vision. Her neuro-ophthalmic examination has shown resolution of the disc swelling with resultant mild pallor of both optic discs. Rheumatology started her on mycophenolate mofetil as a steroid-sparing agent, but she discontinued it after 2 months due to expense. Unfortunately, she has developed congestive heart failure, pedal edema, and renal insufficiency due to the multifocal fibrosclerosis. Radiographs of the knee have shown bony sclerosis, which was noted by Richards et al (3) in their case as well. We also suspect that the “xanthelasmas” of her eyelids are actually subcutaneous fibrosis, as she has no history of hyperlipidemia. Her vision of 20/20 in both eyes

<table>
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<tr>
<th>TABLE 1. Systemic involvement with multifocal fibrosclerosis</th>
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<td>Retroperitoneal fibrosis</td>
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with full visual fields has been preserved for more than 9 months using varying doses of prednisone.

Patients with bilateral orbital pseudotumor should be evaluated systemically for multifocal fibrosclerosis. Renal function should be checked. Patients found to have renal insufficiency should be investigated for a treatable urinary obstruction due to retroperitoneal fibrosis. The prognosis for multifocal fibrosclerosis is quite variable (6). Treatment options include observation, steroids, steroid-sparing (antineoplastic) agents, radiation, and surgery.

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Abstract: This Hoyt lecture is composed of 2 topics. First, a series of patients with idiopathic intracranial hypertension (IIH) is presented, emphasizing the importance of magnetic resonance venography (MRV). Study of the cerebral venous sinuses in IIH may demonstrate focal stenosis or venous gaps and represent a manifestation of elevated intracranial pressure. Conversely, the clinical picture of IIH may occur following cerebral venous sinus thrombosis, and MRV may be essential in establishing this diagnosis. In the future, evaluation of flow in the cerebral venous sinuses may play an important role in determining the potential for visual failure. Second, I will review patients with visual cognitive changes, which often go unrecognized. These patients suffer from visuo-perceptual disturbances, recognizing parts of visual scenes but not the entire picture and are unable to comprehend their visual environment. These findings are often part of the syndrome of posterior cortical atrophy characterized by parieto-occipital atrophy, enlargement of the atrial portion of the ventricular system, and diminished metabolic activity in the posterior portion of the brain demonstrated with positron emission tomography.

I would like to thank the North American Neuro-Ophthalmology Society for this invitation to speak in honor of William F. Hoyt, MD. Bill has been a great influence in my career, and I am grateful for his wisdom and guidance. I would like to discuss 2 intriguing problematic neuro-ophthalmic conditions and hopefully will provide some new insights into these disorders.

Idiopathic intracranial hypertension (IIH), a condition of increased intracranial pressure (ICP), is also known as pseudotumor cerebri (PTC) because it may be associated with signs and symptoms that suggest the presence of a brain tumor. IIH occurs primarily in obese women during their childbearing years. Symptoms often worsen during and after a period of weight gain. The disease is rare in thin men, suggesting a hormonal connection. Although no other specific risk factor other than obesity has been identified, a number of other conditions have been linked to high ICP. For example, any disorder that blocks the flow of cerebrospinal fluid (CSF) between the brain and its drainage system can cause raised pressure. Other clinical associations include withdrawal from systemic corticosteroids, large doses of vitamin A, the use of anabolic steroids, and probably the use of tetracycline and lithium. The precise cause of IIH remains unknown (1,2).

Updated Dandy criteria for the diagnosis of IIH have been proposed (3).

1. If symptoms present, they may only reflect those of generalized intracranial hypertension or papilledema.
2. If signs present, they may only reflect those of generalized intracranial hypertension or papilledema.
3. Documented elevated ICP measured in the lateral decubitus position.
5. No evidence of hydrocephalus and mass, structural, or vascular lesion on MRI or contrast-enhanced CT for typical patients and MRI and magnetic resonance venography (MRV) for all others.
6. No other cause of intracranial hypertension identified.

William F. Hoyt, MD
The clinical manifestations of IIH include headache in 75%–99% of cases (4). The headaches are usually generalized, worse on awakening or with Valsalva maneuver. Visual loss is mild in 50%–90% of patients and severe in 10%–25%. Visual field defects are a result of papilledema and are attributed to axoplasmic stasis with axonal attrition, leading to optic atrophy, as well as vascular compromise associated with central or branch retinal artery occlusion; nerve fiber layer hemorrhages; and infarctions, chorioidal folds, and subretinal fluid in the peripapillary or macular area. Transient visual obscurations occur in up to 75% of patients usually related to changes in posture and may represent intermittent axoplasmic stasis secondary to CSF pressure waves. Pulsatile tinnitus occurs in approximately 60% of patients possibly due to transmission by CSF under increased pressure of intensified vascular pulsations to the walls of venous sinuses converting laminar to turbulent flow. Other clinical features include back and neck pain, radiating paresthesias, seventh nerve palsies, and diplopia, generally due to sixth nerve palsy and rarely due to third or fourth cranial nerve involvement.

Treatment of IIH is determined by the presence or absence of visual loss. Patients with no visual impairment are managed with weight loss and symptomatic treatment of headaches until resolution of symptoms. Those with visual loss should be put on a program of weight loss and acetazolamide. If visual loss is progressive, systemic corticosteroids or optic nerve sheath fenestration should be considered (5). Progressive visual failure or intractable headaches may also be treated with a CSF diversion procedure (6).

In the presence of papilledema, MRI (Fig. 1) may demonstrate flattening of the posterior wall of the globe, empty sella, distention of the perioptic nerve sheaths, and enhancement of the optic disc within the globe (7). The use of contrast with MRI is essential as unenhanced imaging may fail to detect venous sinus thrombosis, meningeal infiltration, and isodense brain tumors.

Cerebral venous sinus thrombosis may cause increased ICP as its sole manifestation. Bioussé et al (8) reported 160 patients with cerebral venous sinus thrombosis, 59 (37%) of whom presented with a syndrome of isolated intracranial hypertension. In distinguishing these patients from those with IIH, data regarding CSF and neuroimaging proved critical. Eleven patients (25%) had abnormal CSF composition, an important distinguishing feature from IIH. Neuroimaging showed involvement of more than 1 venous sinus in more than 54% of this patient cohort. The authors emphasize the challenges in identifying venous sinus thrombosis and point out in some instances that cerebral angiography may be warranted to establish this diagnosis.

While cerebral venous sinus thrombosis is clearly a cause of raised ICP, the relationship of other venous sinus abnormalities detected with MRV remains problematic. Increased ICP may lead to narrowing and stenosis of the venous sinuses. Conversely, abnormalities in cerebral venous sinus drainage may lead to elevated ICP and clinical findings simulating IIH. Higgins et al (9) reviewed MRV studies from 20 patients with IIH and compared them with 40 controls. Patients underwent evaluation with either phase-contrast or time-of-flight MRV. In 13 of the 20 patients with IIH, focal narrowings and/or signal gaps were detected in the transverse sinuses and in none of the controls. However, the MRV technology used in this study has limitations, which may lead to misinterpretation. For example, time-of-flight MRA is subject to artificial signal loss due to in-plane flow and turbulence. The transverse and sigmoid sinuses are locations in the dural venous system subject to such artifacts. Farb et al (10) employed ATECO MRV (auto-triggered elyptic-centric-oriented 3-dimensional gadolinium-enhanced MRV) in the study of transverse and sigmoid sinuses in patients with IIH. The factors leading to artificial signal loss with time-of-flight MRV are greatly reduced with ATECO MRV. These investigators found bilateral sinus venous stenosis in the transverse and sigmoid sinuses in 27 of 29 patients with IIH and only 4 of 59 controls. In addition, manometric measurements have shown a venous pressure gradient between the proximal and distal segments of the transverse sinus in patients with IIH. With cervical puncture, these pressure gradients are no longer present (11,12). Similarly, transverse sinus narrowing detected in patients with IIH has resolved following lumboperitoneal shunt (13). King et al (12) found that in patients with IIH and increased intracranial venous sinus pressure, reduction of CSF pressure following removal of CSF lowered venous sinus pressure.
This study suggests that increased venous sinus pressure is actually caused by elevated ICP. As Corbett and Digre (14) point out that the report by King et al provides one answer to this "chicken or the egg" controversy. With these facts in mind, let us now look at some illustrative cases.

**Case 1**

A 12-year-old girl weighing 160 pounds complained of intermittent headaches of 3-month duration, increasing in intensity and associated with vomiting. More recently, she developed horizontal double vision. Visual acuity was 20/20 in each eye, visual fields revealed nasal loss bilaterally, and bilateral papilledema was present. MRV showed no abnormalities. An opening pressure of 500 mm of water was found on lumbar puncture, and the patient was treated with acetazolamide.

**Comment:** This case is an example of how cerebral venography may be normal with markedly elevated ICP.

**Case 2**

A 32-year-old woman presented with severe headaches. When initially evaluated, her vision was 20/20 in each eye and she was found to have bilateral papilledema. Brain MRI was normal, and lumbar puncture revealed an opening pressure of 550 mm of water. The patient was treated with acetazolamide but developed left face and arm numbness and was unable to walk. Repeat MRI and MRV demonstrated right transverse sinus thrombosis (Fig. 2) and multiple right hemispheric infarctions. Laboratory studies revealed a protein S level of 12% (normal: 60%–140%), and the patient was treated with heparin and then switched to Coumadin.

**Comment:** This patient presented with headaches and papilledema without localizing neurologic signs. After progressive neurologic deficits developed, a diagnosis of venous sinus thrombosis and cerebral infarction was established and appropriate treatment instituted.

**Case 3**

A 19-year-old obese woman presented with a 2-year history of headaches and progressive worsening of vision in both eyes. A diagnosis of IIH was established, and she was treated with acetazolamide for a brief period. The patient did not lose weight and headaches continued. After a year of medical management, vision deteriorated and a lumboperitoneal shunt was performed with improvement of vision. Headaches and visual loss recurred, but shunt revision was delayed.

Neuro-ophthalmic evaluation revealed vision of 20/200 in the right eye and 20/400 in the left eye. Pupils were sluggish in their response to light with a left relative afferent pupillary defect. Visual fields were severely constricted, and both optic nerves showed chronic atrophic papilledema. A right optic nerve sheath fenestration was performed, and the patient was started on acetazolamide. In addition, the lumboperitoneal shunt was found to be obstructed and was revised. Two months postoperatively, the patient was free of headaches and vision improved to 20/40 in the right eye and 20/60 in the left eye, with expansion of the visual fields.

**Comment:** This case demonstrates how visual function can be improved despite long-standing diminished visual acuity and chronic swelling of the optic discs.

**Case 4**

A 17-year-old boy with a 6-month history of frontal headaches reported seeing “black spots” for 3 weeks and diminished vision for 1 week. Visual acuity was found to be 20/70 in the right eye and counting fingers in the left eye. The right visual field demonstrated mild nasal constriction, and there was severe bilateral papilledema. Brain MRI was

![FIG. 2. Right transverse sinus thrombosis (arrows) is demonstrated on contrast-enhanced T1 coronal MRI (A) and magnetic resonance venography (B).](image-url)
normal. Opening pressure on lumbar puncture was 490 mm of water, and the CSF composition was normal. Laboratory studies were unremarkable with the exception of a platelet count of 883,000 (normal: less than 450,000). Bone marrow biopsy was negative, and the hematology consultant felt that the thrombocytosis was unrelated to increased ICP. Brain MRI was normal, but MRV demonstrated bilateral transverse sinus stenosis with normal jugular venous flow (Fig. 3). The patient was treated with acetazolamide, intravenous Solu-Medrol, and bilateral optic nerve sheath fenestrations. He reported diminished headaches, vision improved to 20/50 in the right eye 20/200 in the left eye, and papilledema resolved.

Comment: This is an example of IIH in which the cerebral venous system revealed transverse sinus narrowing without thrombosis, consistent with elevated ICP.

Case 5

A 46-year-old woman complained of headaches and was found to have a left homonymous hemianopia and papilledema. Brain MRI revealed a meningioma involving the posterior aspect of the superior sagittal sinus and right occipital lobe (Fig. 4). She was treated with radiosurgery.

Comment: This case illustrates that partial compression of the cerebral venous sinuses by a neoplasm can lead to signs and symptoms of increased ICP including headaches and papilledema.

It should be apparent that evaluation of the cerebral venous sinuses is an essential part of the workup of IIH. This is done first to exclude cerebral venous sinus thrombosis and also to monitor external venous sinus compression. Future studies may demonstrate a correlation between venous sinus compromise and the threat to vision in the setting of raised ICP.

I would now like to review posterior cortical atrophy (PCA), a dementia syndrome characterized by signs and symptoms of cortical visual dysfunction (15). First characterized by Benson et al (16), at onset the visual complaints of patients with PCA are often vague and nonspecific and patients may initially present to an ophthalmologist.

Clinical features of PCA include Balint syndrome and often various aspects of Gerstmann syndrome, visual agnosia, alexia, agraphia, and transcortical sensory aphasia. In contrast to typical Alzheimer disease, patients with PCA often retain memory, insight, and judgment until late in the course of their illness (16).

Diagnostic criteria for PCA have been proposed (Table 1). Both clinical findings and neuroimaging abnormalities indicate involvement of the posterior visual association cortices. Patient evaluation consists of 3 types of studies. First, neuropsychological testing will demonstrate

![FIG. 3. Magnetic resonance venography demonstrates stenosis (arrows) of both transverse sinuses.](image1)

![FIG. 4. Contrast-enhanced T1 sagittal (A) and axial (B) MRI shows a meningioma (arrow) compressing the right occipital lobe and the superior sagittal sinus. On magnetic resonance venography (C), there is narrowing (arrow) of the posterior portion of the superior sagittal sinus.](image2)
dysfunction in the occipitoparietal (dorsal) or occipitotemporal (ventral) visual streams or both. The former will give rise to Balint syndrome, Gerstmann syndrome, dressing apraxia, and aphasia, while the latter to alexia without agraphia, visual object agnosia, and prosopagnosia. Second, neuroimaging studies demonstrate atrophy of the parietal

TABLE 1. Proposed diagnostic criteria for posterior cortical atrophy

<table>
<thead>
<tr>
<th>Core features</th>
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<tr>
<td>Insidious onset and gradual progression</td>
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<td>Presentation of visual complaints in the absence of significant primary ocular disease explaining the symptoms</td>
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<td>Relative preservation of anterograde memory and insight early in the disorder</td>
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<td>Disabling visual impairment throughout the disorder</td>
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<td>Absence of stroke or tumor</td>
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<td>Absence of early parkinsonism and hallucinations</td>
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<tr>
<td>Any of the following findings:</td>
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<td>Simultanagnosia with or without optic ataxia or ocular apraxia</td>
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<tr>
<td>Constructional dyspraxia</td>
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<tr>
<td>Visual field defect</td>
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<tr>
<td>Environmental disorientation</td>
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<tr>
<td>Any of the elements of Gerstmann syndrome</td>
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<tr>
<th>Supportive features</th>
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<tbody>
<tr>
<td>Alexia</td>
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<tr>
<td>Presenile onset</td>
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<tr>
<td>Ideomotor or dressing apraxia</td>
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<td>Prosopagnosia</td>
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<tr>
<th>Investigations</th>
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<tr>
<td>Neuropsychological deficits referable to parietal and/or occipital regions</td>
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<tr>
<td>Focal or asymmetric atrophy in parietal and/or occipital regions on structural imaging</td>
</tr>
<tr>
<td>Focal or asymmetric hypoperfusion/hypometabolism in parietal and/or occipital regions on functional imaging</td>
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FIG. 5. T1 axial (A), coronal (B), and sagittal (C) MRI reveal cortical atrophy most marked in the parieto-occipital regions bilaterally with enlargement of the atrial portion (arrow) of the occipital horn of the lateral ventricles.
and/or occipital regions and, at times, more generalized cortical atrophy. There is often enlargement of the lateral ventricles with focal enlargement of the atrial region. Third, with the use of PET, there is hypometabolism and with SPECT hypoperfusion in the parietal and/or occipital regions of the brain (17).

The most frequent pathological findings of PCA are senile plaques and neurofibrillary tangles primarily affecting the visual association areas. The cause for this focal involvement with PCA is unknown. No specific environmental or genetic factor has yet been identified. Given the current lack of understanding regarding the etiology of PCA, no treatment has proven effective, and the prognosis for these patients remains poor as shown in the following cases.

Case 1
A 64-year-old woman complained of visual difficulties for 5 years. She could not recognize objects and had trouble reading and calculating. There was increased memory disturbance, and she was unable to copy geometric figures. On brain MRI, the frontal horns and the frontal area of the brain showed moderate cortical atrophy and severe bilateral parieto-occipital cortical atrophy, enlargement of the atrial portion of the ventricular system, and enlarged occipital horns (Fig. 5). PET demonstrated markedly reduced metabolic activity in the parieto-occipital regions.

Comment: This case illustrates the typical presenting signs and symptoms of a patient with PCA.

Case 2
A 62-year-old man reported problems with reading for 1.5 years. He would lose his place and stated that there was a “cloud” in front of both eyes. He also noted difficulty with colors, and he misplaced objects. He often could not find food on his plate and was becoming forgetful of names and dates. Although an accountant, he was unable to perform even simple calculations. Visual acuity was 20/25 in the right eye and 20/30 in the left eye. Visual fields demonstrated a right homonymous hemianopia and hemiachromatopsia, but the patient could detect motion in the right homonymous visual fields. He could count fingers if...
they were moving, but when stationary, they would disappear (Riddoch phenomenon). He could not detect angles or determine the distance of an object before him and was unable to interpret pictures.

Over the ensuing year, the patient experienced increasing difficulty dressing himself, became disoriented to time and person, and developed left homonymous superior visual field extinction. Brain MRI revealed enlargement of the posterior horns of the lateral ventricles with associated cortical atrophy. There was diminished parieto-occipital metabolic activity bilaterally on PET (Fig. 6).

Comment: Early in the clinical course, this patient's visual complaints suggested a primary ophthalmologic disorder, but further evaluation pointed to more widespread neurologic involvement.

Case 3
A 73-year-old woman had difficulty with reading. Visual acuity was 20/70 in the right eye and 20/40 in the left eye. Letters tended to disappear, and sentences made no sense. She had mild general confusion but could read numbers better than letters. Her interpretation of pictures for content was difficult. For example, in the "cookie theft picture" (Fig. 7), the patient could see the boy, but not interpret the scene. She could not do serial 7 subtractions, 1-minute recall was defective, and she could not copy geometric figures. There was a Riddoch phenomenon in the left homonymous hemifields. Brain MRI demonstrated mild parieto-occipital cortical atrophy with enlargement of the atrial portions of the ventricular system, and PET showed hypometabolism in both parieto-occipital areas, greater on the right.

Comment: Simultanagnosia was a striking feature of this patient's findings consistent with PCA.

Case 4
A 59-year-old woman with cardiomyopathy underwent heart transplantation. On the fourth postoperative day, the patient noted that the vision was dim as if "looking through a shade." Visual acuity was 20/50 in both eyes for isolated letters, but she could not identify letters embedded in words. Pupils, eye movements, and fundi were normal. Visual fields were intact but revealed left hemifield Riddoch phenomenon. The patient mislocated objects when reaching for them in space (see the video on the Neuro-Ophthalmology Virtual Education Library [NOVEL] Web site at http://content.lib.utah.edu/u7/jno1370). Brain CT showed biparietal wedge-shaped infarctions.

Comment: watershed infarctions of the parieto-occipital region can produce a clinical picture indistinguishable from PCA, but neuroimaging will make the cause clear.

The clinician should be highly suspicious of the diagnosis of PCA in the patient with persistent yet nonspecific visual complaints in the setting of a normal eye examination. By testing higher visual cortical function, one’s index of suspicion will be raised further. Finally, employing neuropsychological testing and a combination of structural and functional neuroimaging modalities, the diagnosis of PCA can be established.

REFERENCES
Literature Commentary


A chronic state of impaired venous drainage from the central nervous system, termed chronic cerebrospinal venous insufficiency (CCSVI), is claimed to be a pathologic phenomenon exclusively seen in multiple sclerosis (MS). This has invigorated the causal debate of MS and generated immense interest in the patient and scientific communities. A potential shift in the treatment paradigm of MS involving endovascular balloon angioplasty or venous stent placement has been proposed as well as conducted in small patient series. In some cases, it may have resulted in serious injury. In this point of view, we discuss the recent investigations that led to the description of CCSVI as well as the conceptual and technical shortcomings that challenge the potential relationship of this phenomenon to MS. The need for conducting carefully designed and rigorously controlled studies to investigate CCSVI has been recognized by the scientific bodies engaged in MS research. Several scientific endeavors examining the presence of CCSVI in MS are being undertaken. At present, invasive and potentially dangerous endovascular procedures as therapy for patients with MS should be discouraged until such studies have been completed, analyzed, and debated in the scientific arena.

Poor drainage from the internal jugular vein (IJV) and azygos vein (AV) cause multiple sclerosis? Studies from Italy and Buffalo, NY have suggested a strong association between CCSVI and MS. To support this association, selective catheterization has shown that approximately 90% of patients with MS have IJV and AV stenosis. An unmasked, uncontrolled study of IJV and AV angioplasty in 65 MS patients showed improved clinical and MRI outcomes (1). However, there was a high rate of restenosis leading the investigators to suggest stent placement into the IJV or AV. The proposed theory is that poor venous drainage leads to iron accumulation in the brain, which causes an inflammatory response. MR spectroscopy studies have shown increased iron in MS brains compared to controls.

This point-of-view article argues strongly against the idea that CCSVI causes MS. I would have to agree. It certainly appears that CCSVI occurs in MS, but I have trouble believing that CCSVI causes MS for many of the reasons outlined in this article. I wonder if, instead, MS causes CCSVI, and this may be another chicken vs. egg issue like transverse venous sinus stenosis and idiopathic intracranial hypertension (2). It appears that the excitement over this is likely to lead to a clinical trial of angioplasty or stenting. If a rigorous study is performed, I will be amazed if it turns out to be beneficial.

—Michael S. Lee, MD

CCSVI is currently a very hot topic in MS. The person at the forefront of this is Dr. Paolo Zamboni, an Italian vascular surgeon who began studying the venous drainage issue in an attempt to find a cure for his wife’s MS. His findings have not been replicated by others (3) and venous anomalies are frequently found in people without MS.

Perhaps, venous drainage issues do play some role. For instance increased iron deposition, which may be related to MS disability, has been correlated with venous drainage abnormalities (4). CCSVI may also be an epiphenomenon or actually secondary to the MS. The so-called “liberation procedure,” with angioplasty and stenting, is not without risk. In fact, the procedure has been abandoned at Stanford University after a fatal intracranial hemorrhage and a complication requiring open heart surgery from stent movement into the right ventricle (5). I agree with Michael, and am “cautiously pessimistic” that CCSVI really plays a role in the pathogenesis of MS.

—Mark L. Moster, MD

Complex visual hallucinations (VHs) occur in several pathologic conditions; however, the neural mechanisms underlying these symptoms remain unclear. Although dopamine may have a role, indirect evidence indicates that serotonin may also contribute to the pathogenesis of complex VHs, probably via involvement of the serotonin 2 receptor.

**Objective:** To examine for the first time in vivo changes in serotonin 2A receptor neurotransmission among patients having Parkinson disease (PD) with VHs.

**Design:** Case-control study.

**Setting:** Academic research.

**Patients:** Seven patients having PD with VHs and 7 age-matched patients having PD without VHs were recruited.

**Main Outcome Measures:** We used the selective serotonin 2A receptor ligand setoperone F18 during positron emission tomography among nondemented patients having PD with VHs.

**Results:** Patients having PD with VHs demonstrate increased serotonin 2A receptor binding in the ventral visual pathway (including the bilateral inferooccipital gyrus, right fusiform gyrus, and inferotemporal cortex) as well as the bilateral dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula.

**Conclusions:** This pilot study provides the first in vivo evidence suggesting a role for serotonin 2A receptors in mediating VHs via the ventral visual pathway in PD. Treatment studies should be performed using selective serotonin 2A receptor antagonists, which have important implications for the clinical management of VHs and psychosis in PD.

It is very likely that various mechanisms underlie the different situations in which we see VHs (Bonnet syndrome, dementia with Lewy bodies, schizophrenia, seizures, PD, posterior cortical atrophy, etc.). This article demonstrates increased serotonin 2A binding in patients with PD who have VHs and would therefore suggest the possibility of benefit of serotonin 2A antagonists, such as clozapine. Elucidating mechanisms of VH in the above conditions will benefit a large population of patients suffering from VH. The assurance of “not being crazy,” not going blind, and that the condition is not medically important helps patients but not nearly as much as eliminating the symptoms altogether.

—Mark L. Moster, MD

Pretty cool article. It would have been cooler if the investigators had given the patients a selective serotonin 2A receptor antagonist, made the VHs go away, and showed reduced binding on a subsequent PET scan. This would convince me of a likely pathogenic basis and effective treatment instead of “important implications” in the conclusion.

—Michael S. Lee, MD
clear that this is better than the patient moving his/her eye, but the outcomes are extremely positive. I have already talked to my low vision provider about starting this, and we’ll see how they do. If a patient cannot see a low vision provider, it is a nice tip for a patient to try to improve their reading proficiency.

—Michael S. Lee, MD

One of the most important features that contributed to the success of this program was the choice of trainer. The trainer was a seasoned adult literacy tutor with experience in motivating students, who acted as a “coach.” Patients were elderly and the training was non-threatening. In fact, a major reason for exclusion (58 patients) was that these were anxious or reluctant patients, who felt threatened by formal testing.

Additionally, because of the individual personal attention and the lack of a control group, this study may lend more support to the way a visual rehabilitation program is administered than to the actual visual technique employed.

—Mark L. Moster, MD


We conducted a masked, crossover, therapeutic trial of gabapentin (1,200 mg/day) vs memantine (40 mg/day) for acquired nystagmus in 10 patients (aged 28–61 years; 7 female; 3 multiple sclerosis [MS]; 6 post-stroke; and 1 post-traumatic). Nystagmus was pendular in 6 patients (4 oculopatatal tremor; 2 MS) and jerk upbeat, hemi-seesaw, torsional, or upbeat-diagonal in each of the others. For the group, both drugs reduced median eye speed ($P < 0.001$), gabapentin by 32.8% and memantine by 27.8%, and improved visual acuity ($P < 0.05$). Each patient improved with 1 or both drugs. Side effects included unsteadiness with gabapentin and lethargy with memantine. Both drugs should be considered as treatment for acquired forms of nystagmus.

This is a small study of patients with acquired symptomatic (oscillopsia or blurred vision) nystagmus. It reinforces the benefits of both gabapentin and memantine for pendular nystagmus. Six patients had pendular and the other 4 had different types of jerk nystagmus. Patients with jerk nystagmus had variable responses from no improvement to improvement but symptomatic side effects. The benefits reported for jerk nystagmus are more encouraging than I have seen in my practice. When actually reading the individual clinical reports, the benefits seem mild, and the side effects concerning. I have not used memantine at 10 mg QID in these patients and will consider increasing the dose.

—Mark L. Moster, MD

The article does not mention how the acuity was measured (e.g., Snellen vs. ETDRS). The mean improvement in visual acuity was logMAR 0.084. As a reminder, a visual acuity of 20/20 is logMAR 0.00 and 20/25 is logMAR 0.10. So, on average, these patients gained ≤ 1 line of acuity, which could simply represent normal fluctuation especially in unmasked patients and examiners. I will continue to try gabapentin and memantine in patients with acquired nystagmus since the eye speed improved and the oscillopsia is often the worst symptom for patients. The authors note, and I think it is important to highlight here, the importance of avoiding memantine in patients with MS since it can lead to increased relapses (1).

—Michael S. Lee, MD


**Objectives:** To determine whether lateral occipital complex (LOC) activation with functional magnetic resonance imaging (fMRI) predicts visual outcome after clinically isolated optic neuritis (ON). To investigate the reasons behind good recovery following ON, despite residual optic nerve demyelination and neuroaxonal damage.

**Methods:** Patients with acute ON and healthy volunteers were studied longitudinally over 12 months. Structural MRI, evoked potentials (VEPs), and optical coherence tomography (OCT) were used to quantify acute inflammation, demyelination, conduction block, and later to estimate remyelination and neuroaxonal loss over the entire visual pathway. The role of neuroplasticity was investigated using fMRI. Multivariable linear regression analysis was used to study associations between vision, structure, and function.

**Results:** Greater baseline fMRI responses in the LOCs were associated with better visual outcome at 12 months. This was evident on stimulation of either eye ($P = 0.007$ affected; $P = 0.020$ fellow eye) and was independent of measures of demyelination and neuroaxonal loss. A negative fMRI response in the LOCs at baseline was associated with a relatively worse visual outcome. No acute electrophysiological or structural measures, in the anterior or posterior visual pathways, were associated with visual outcome.

**Interpretation:** Early neuroplasticity in higher visual areas appears to be an important determinant of recovery from ON, independent of tissue damage in the anterior or posterior visual pathway, including neuroaxonal loss (as measured by MRI, VEP, and OCT) and demyelination (as measured by VEP).

One of the clinical challenges in neuro-ophthalmology is determining which patient with optic neuritis will have poor visual recovery. Although no current treatment has been
shown to affect the ultimate outcome, identifying patients with poor visual prognosis is important in order to develop effective interventions. To date, the main predictor of poor outcome has been poor visual acuity at baseline (1). Thinning of RNFL on OCT or GDx has correlated with poor outcome, but this occurs after months, likely at a time too late for effective intervention.

Prior reports have found fMRI evidence of adaptive neuroplasticity after a bout of ON. The current study tested the hypothesis that after accounting for markers of anterior and posterior visual pathway damage, early LOC activation would be associated with better visual outcome and found it to be the case. This provides another glimpse into the crystal ball of decreased recovery. Besides determining a poorer prognosis, it might eventually provide an avenue for treatment with CNS manipulations in addition to the approach of protecting the optic nerve and ganglion cells.

—Mark L. Moster, MD

It will be interesting to see if others find a similar association. There were only 7 patients in the “poor” vision outcome, and the authors defined poor vision as worse than logMAR 0.2 (equivalent to Snellen 20/32). Personally, I would consider “less than desirable” visual outcome as worse than 20/40 (logMAR 0.3). Using that cutoff, there were only 2 patients in that category and one of them had acuity of logMAR 0.32, which is approximately 20/42. Given the lack of moderate or severe vision loss in this study, it is hard to know how predictive fMRI of the LOC really is.

—Michael S. Lee, MD


Objective: To evaluate implant and prosthesis movement after myoconjunctival enucleation and subsequent polymethyl methacrylate (PMMA) implantation, compared with the traditional enucleation with muscle imbrication using a PMMA implant and with enucleation accompanied by porous polyethylene implantation.

Design: Randomized, controlled, observer-masked, interventional study.

Participants: One hundred fifty patients, equally and randomly allocated to the 3 groups.

Intervention: Group 1 consisted of patients in whom a PMMA implant was used after enucleation with muscle imbrication (traditional PMMA group). Group 2 consisted of patients in whom a PMMA implant was used after enucleation with a myoconjunctival technique (myoconjunctival PMMA group). Group 3 consisted of patients in whom a porous polyethylene implant was used after enucleation by the scleral cap technique (porous polyethylene group). Fifty patients were included in each group. Patients were allocated to 1 of the 3 groups using stratified randomization. Informed consent was obtained. Acrylic prostheses custom made by a trained ocularist were fitted 6 weeks after surgery in all patients. A masked observer measured implant and prosthesis movement 6 weeks after surgery using a slit-lamp device with real-time video and still photographic documentation. Analysis of implant and prosthesis movement was carried out using the Mann-Whitney U test, and a P value of ≥0.03 was considered significant. Complications including implant displacement and exposure also were noted.

Main Outcome Measures: Implant and prosthesis movement.

Results: Myoconjunctival PMMA implant movement was better than the traditional PMMA implant (P = 0.001), but was similar to that of the porous polyethylene implant. Prosthesis movement with the myoconjunctival PMMA implant was better than that of either the traditional PMMA (P = 0.001) or the porous polyethylene (P = 0.002) implants.

Conclusions: Myoconjunctival enucleation technique with a PMMA implant provides statistically and clinically significantly better implant and prosthesis movement than the traditional PMMA implant and better prosthesis movement than the porous polyethylene implant.

After enucleation, an implant is placed intraconally to provide orbital volume, and then, Tenon capsule and conjunctiva were sutured closed over the implant. Later, a cosmetic prosthetic shell is placed over the conjunctiva. When the patient moves his/her contralateral eye, the desired outcome is for the prosthesis to move as much as possible. There are essentially two kinds of implants: a porous implant that allows in-growth of tissue into the implant and a nonintegrated implant. Two of the most common implants are the nonintegrated PMMA implant (cost ~$2–10) and the porous polyethylene implant (cost ~$300).

The authors randomized patients to one of 3 groups and used a masked observer to measure prosthesis movement. The traditional PMMA group sutured the extraocular muscles (EOM) to each other. The myoconjunctival PMMA group sutured the EOM to the closest fornix. The porous polyethylene group sewed a scleral cap to the implant and then sutured the EOM to the wrapping. Evaluators were masked to surgical technique. The authors show that the cheaper PMMA implant had better prosthesis movement with the myoconjunctival technique than the traditional surgical technique with PMMA and the more expensive porous implant. This is a great study that represents not only substantial cost savings but also better outcome.

—Michael S. Lee, MD

Ditto.

—Mark L. Moster, MD
Diagnostic Neuroradiology
Valery N. Kornienko, MD, PhD,
Igor Nikolaevich Pronin, MD, PhD
2009, 1228 pp, Hard cover, 16 chapters
Price: $339.00

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

The authors of this large textbook draw on their long-standing experience at the N.N. Burdenko Neurosurgical Institute in Moscow. The book begins with a review of modern neuroimaging techniques. Chapters include history and new research technologies, congenital malformations of the brain and skull, cerebrovascular diseases and malformations of the brain, supratentorial tumors, pineal region tumors, sellar and parasellar tumors, infratentorial tumors, tumors of the meninges, head trauma, hydrocephalus, intracranial infections, toxic and metabolic disorders, demyelinating diseases of the central nervous system, neurodegenerative disorders of the central nervous system, spine and spinal cord disorders, subject index.

This publication is printed on glossy paper with 1,905 high-quality images (angiography, CT and MRI) with 22 tables. Given the quantity of the illustrative material, this text serves as an atlas as well as a comprehensive review of neuroradiology.

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ISBN: 0195366743
Price: $125.00

Intended audience: Neurologists, neurosurgeons, oncologists, neuro-opthalmologists, and radiation oncologists as well as internists.

This book is a practical approach to the diagnosis and management of patients with cancer who develop neurologic complications.

It is divided into 3 sections:
1. General principles of oncology, which include the pathophysiology of nervous system metastases, blood-nervous system barrier dysfunction; pathophysiology and treatment, and supportive care of its complications.
2. Metastases including intracranial, spinal, leptomeningeal, and cancer involving cranial and peripheral nerves and muscles.
3. Nonmetastatic complications of cancer including vascular disorders, CNS infections, delirium and metabolic and nutritional complications of cancer, side effects of chemotherapy, side effects of radiation therapy, neurotoxicity of surgical and diagnostic procedures, and paraneoplastic syndromes.

The text is printed on glossy paper, illustrated in both color and black-and-white, with high-quality photographs, tables, and illustrations. It serves as an authoritative reference in the field of neuro-oncology.

Neurology and Systemic Disease: Neurologic Clinics
Alireza Minagar, MD
2009, 337 pp, Hard cover,
17 chapters (articles)
ISBN13: 9781437719185,
ISBN: 143771918X
Price: $105.00

Intended audience: Neurologists, ophthalmologists, neuro-opthalmologists, and internists.

This issue of Neurologic Clinics features 17 chapters that address the neurologic complications of systemic illnesses. Articles include neurologic presentations of infectious endocarditis, acid-base imbalance and electrolyte abnormalities, endocrine emergencies, systemic lupus erythematosus in children and adults, respiratory disease, nutritional deficiencies, gastrointestinal disease, radiation therapy, lyme disease and syphilis, drug abuse, transplant complications, sarcoidosis, fungal infections, cardiac disease, AIDS, systemic vasculitis, and hepatic disease. There are several black-and-white tables and MRI scans. There are a few color photographs that are printed on glossy paper. This monograph is invaluable to physicians who treat patients with neurologic problems stemming from systemic disease.

Neuroradiology: The Requisites
David M. Yousum, MD, Robert I. Grossman, MD, Robert D. Zimmerman, MD
2009, 619 pp, Hard cover, 18 chapters
ISBN-13: 9780323045216,
ISBN: 0323045219
Price: $99.00

Intended audience: Radiologists, neurologists, neurosurgeons, neuro-opthalmologists, residents, and fellows.
In this large textbook, the authors cover topics ranging from imaging basics to neurodegenerative disorders. They address the conceptual, technical, and interpretive core knowledge needed for imaging the brain, spine, head, and neck and discuss all the high-tech imaging modalities available including diffusion-weighted imaging, CT angiography, and magnetic resonance spectroscopy. Chapters include techniques in neuroimaging, cranial anatomy, neoplasms of the brain, vascular diseases of the brain, head trauma, infectious and noninfectious inflammatory diseases of the brain, white matter diseases, neurodegenerative diseases and hydrocephalus, congenital disorders of the brain and spine, orbit, sella and central skull base, temporal bone, sinonasal disease, mucosal disease of the head and neck, extramucosal diseases of the head and neck, anatomy and degenerative diseases of the spine, nondegenerative diseases of the spine, and approach and pitfalls in neuroimaging.

With more than 1,000 high-quality black-and-white images and illustrations, this text serves as an atlas in addition to a very complete and authoritative reference in the field of neuroimaging.

**Pediatric Neuro-Ophthalmology, 2nd edition**
*Michael C. Brodsky, MD*
2010, 608 pp, Hard cover, 11 chapters
ISBN-10: 0387690662,
Price: $204.48

**Neurology Secrets**
*Loren A. Rotak, MD*
2010, 470 pp, Soft cover, 29 chapters
ISBN13: 9780323057127,
ISBN10: 0323057128
Price: $54.95

**Referenced**

**Intended audience:** Ophthalmologists, neurologists, neurosurgeons, pediatricians, pediatric neurologists and neurosurgeons, neuro-ophthalmologists, residents, and medical students.

*Neurology Secrets* is a multiauthored pocket-sized synopsis of neurologic disease including diagnosis and management. This book begins with 100 top “secrets” helpful in neurology certification examinations. Then, in question-and-answer format, the book addresses all major areas of neurology. Introductory chapters review clinical neuroscience and neuroanatomy, and latter chapters cover myopathies, seizures, peripheral neuropathies, motor neuron disease, brainstem disease, demyelinating disease, movement disorders, pediatric neurology, vascular disease, neuro-oncology, infectious disease, and sleep disorders. There is no specific chapter on neuro-ophthalmology, yet neuro-ophthalmology questions are interwoven throughout the book. With a 2-color page layout, multiple black-and-white line drawings, MRI scans, EEGs, a few clinical photographs, and the easy question-and-answer format, *Neurology Secrets* is an ideal review for neurology board examinations and recertification.
Neuro-Ophthalmology Virtual Education Library
(NOVEL: http://NOVEL.utah.edu/)

The Neuro-Ophthalmology Virtual Education Library (NOVEL) is an open-access, discipline-specific repository of multimedia (images, videos, lectures, and other digital content) to provide resources to neuro-ophthalmologists and other medical professionals in support of their clinical, research, and educational missions. Another NOVEL goal is to provide reliable and timely information to patients with neuro-ophthalmic illnesses. This collaboration between the North American Neuro-Ophthalmology Society (NANOS) and the Eccles Health Sciences Library of the University of Utah creates a unique model for digital collection development. NANOS members have committed a great deal of time and energy in providing content, metadata, and peer review.

**Collections in NOVEL.** NOVEL has expanded to consist of 15 collections of educational resources, all downloadable via a common search engine, and in process of being linked to a master neuro-ophthalmology curriculum. These collections include video clips of patients and examinations, full PowerPoint lectures, scholarly articles in PDF format, and selected animations. Shirley H. Wray, MD, PhD, has added her remarkable collection of instructional videos of 161 patients demonstrating neurovisual disorders this year. Each of her cases includes a patient history and video clip. Many have supplementary PowerPoint and provide additional information such as neuroimaging and pathology slides. The video clips have been converted to formats compatible with Flash and iPod/iPhone viewing. Soon, all video collections in NOVEL will offer these newer formats, making viewing the materials even more accessible for the practitioner needing easy access to this information.

Three important additions have been made to NOVEL this year. Robert B. Daroff, MD, has contributed his classic 1,991 teaching series of 56 videos, which present a variety of eye movement disorders. Helmut Wilhelm, MD, from Universitäts-Augenklinik, Tubingen, Germany, is the first international contributor. His set of 39 videos also covers common eye movement and pupillary disorders. David E. Newman-Toker, MD, PhD, has provided a series of clips describing various neuro-ophthalmic techniques, a lecture on skew deviation, and 2 clips on acute vestibular syndrome. Soon he will add a detailed animation of skew deviation.

*Journal of Neuro-Ophthalmology Archives.** The Journal of Neuro-Ophthalmology (JNO) archive collection is integrated into NOVEL searches, providing direct access to the literature when seeking educational materials. The library contains the JNO archive from 1994 to the present, with a 1-year embargo for current publications. NOVEL has obtained permission to add to its collection the Journal of Clinical Neuro-Ophthalmology, the predecessor to JNO. The articles are being harvested now and will be added to NOVEL to complete the literature archive (http://NOVEL.utah.edu/jno).

*NANOS Annual Meeting Syllabi.** To make the materials presented at the annual meeting more accessible, the syllabi are being added as a collection. The prototype, covering the 2009 meeting, is now available online. The NOVEL staff will work toward including every annual meeting syllabus since the inception of the society in 1975. All materials will be indexed and searchable through the NOVEL search function (http://NOVEL.utah.edu/nam).

*Patient Portal.** The NOVEL Patient Portal is growing. Patient brochures created by a NANOS committee (with peer review) and the translations of those brochures into several languages (French, German, Hebrew, and Spanish) are now available. In addition, links to literature, authoritative consumer health information, relevant societies, and support groups are included when available (http://NOVEL.utah.edu/portal/).

*Rare Disease Registry.** The Rare Disease Registry has 2 diseases posted with standardized data collection tools. The registry allows NANOS members and other interested physicians to contribute both past and current cases in standard format to the appropriate data steward who will analyze the data. The goal is to allow NOVEL to be a vehicle facilitating group definition of the natural history and best therapies of disorders too rare for any single institution to define (http://NOVEL.utah.edu/rare/).

*Illustrated Curriculum.** Based on the neuro-ophthalmology curriculum outline prepared by the NANOS Curriculum Committee, an illustrated curriculum outline is starting to take shape. Links to NOVEL materials have been added as
a prototype to the section covering Disorders of the Afferent and Efferent Visual Pathways. Demonstrations of a variety of examinations are also linked in the Ocular and Neurologic Evaluation section. The goal is to provide links from all sections, as the NOVEL grows to provide examples of all teaching areas of the curriculum (http://NOVEL.utah.edu/curriculum).

NOVEL Usage. All of these educational resources have brought much attention to NOVEL. In 2009, the Web site received 2,270,000 hits, 1,390,283 page views, and 199,974 visits from users in more than 100 countries. Approximately 440 video clips in the library were accessed.

We need your financial support to continue to build this valuable resource. Tax deductible contributions may be made at http://www.nanosweb.org/i4a/pages/index.cfm?pageID=3477.

Nancy Lombardo, MLS
Kathleen B. Digre, MD
Larry Frohman, MD


The 18th Meeting of the International Neuro-Ophthalmology Society returned to France, the country that hosted the first INOS meeting 34 years ago in La Napoule, a tiny resort at the French Riviera. While the first meeting was attended by only a handful neuro-ophthalmology enthusiasts, 350 participants from 30 countries and 5 continents gathered this year in Lyon, France. The meeting’s venue was in a beautiful congress center built in 1996 by Italian architect and Pritzker Prize awardee, Renzo Piano.

The meeting was superbly organized by Caroline Tilikete, MD and Alain Vighetto, MD, two neuro-ophthalmologists who work closely together at Université Claude Bernard in Lyon. They compiled a two and a half day program of intense teaching and scientific exchange in all important and up-to-date neuro-ophthalmic topics.

A variety of themes formed the centrepiece of the meeting. Each began with invited presentations followed by free papers of 10 minutes each grouped together to fit the session topic. Each afternoon was a poster seminar again organized to reflect the theme of the preceding sessions. On the last day a special lecture was given by Professor José Sahel from The Vision Institute in Paris on the latest advances in his “Artificial Retina Project.”

The sessions and invited lectures were:

1. Optic neuritis
   - Neuromyelitis optica—J. de Seze, Strasbourg, France

2. Optic neuropathies—genetic disorders
   - Dominant optic atrophy—C. Hamel, Montpellier, France
   - Leber’s hereditary optic neuropathy—N. Newman, Atlanta, USA

3. Central visual function—low vision
   - Vision, attention and eye movements—L. Pisella, Lyon, France
   - Future of perimetry—U. Schiefer, Tubingen, Germany

4. Degenerative brain diseases
   - Eye movements and degenerative cognitive disorders—C. Kennard, Oxford, England

5. Tumors
   - Radiotherapy for optic pathways meningioma—N. Miller, Baltimore, USA

6. Eye movements
   - Cerebellar control of saccades—D. Zee, Baltimore, USA
   - Ocular motility in brainstem stroke—J.S. Kim, Seoul, South Korea

7. Pupils, extraocular muscles, orbit
   - Thyroid orbitopathy—A. Boschi, Brussels, Belgium
   - Horner syndrome—A. Kawasaki, Lausanne, Switzerland

8. Intracranial hypertension
   - Treatment of IIH—N. Miller, Baltimore, USA
   - Endovascular therapy for IIH—A. Donnet, Marseille, France

9. Immune and inflammatory disorders
   - Tolosa-Hunt syndrome—K. Landau, Zurich, Switzerland
   - Antiganglioside antibody syndromes—J. Trobe, Ann Arbor, USA

10. Vascular diseases
    - Giant cell arteritis—V. Biousse, Atlanta, USA
    - Experimental ischemic optic neuropathy—N. Goldenberg-Cohen, Tel Aviv, Israel
    - Imaging of vascular malformations—M. Mazighi, Paris, France

Despite a full and exciting scientific program time was allotted for a Welcome Ceremony, City Tour and Congress Dinner. The last event was held in Chapelle de la Trinité during which the attendees were treated to a program of classical music performed by Orchestre de l’Opéra National de Paris and operatic performed by Mlle. Laurence Janot. The evening was capped off by a birthday celebration for William F. Hoyt.

INOS 2012 is planned for Singapore. See you there!

Klara Landau, MD

Conference organizers Caroline Tilikete, MD, and Alain Vighetto, MD.

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