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Satoshi Kashii
In 1945, Holmes found the search for anatomical substrates of visual behavior to be challenging work. The findings had to be “assembled” “with time and labor” from the “irregular rubble” of clinical material and were “rarely so simple or clean cut.” I was asked to review 3 articles that recapitulate Holmes’ experience: Visual involvement in corticobasal syndrome and Complex visual manifestations of posterior cortical atrophy that address insidious visual decline because of neurodegenerative disease, and Bálint syndrome and visual allostria in a patient with reversible cerebral vasoconstriction syndrome (4) that concerns sequelae of stroke. The profiles in these challenging cases may be compared to the century-old case report of Reszö Bálint (5).

Bálint found a remarkable triad of visual difficulties in a man with advanced cerebrovascular disease:

1. “Spatial disorder of attention,” the key component of Bálint syndrome, was described as an inability to perceive, at any one time, the several items of a visual scene. This has been compared to “visual disorientation” (6) and to “simultanagnosia,” an inability to interpret the totality of a scene, despite the preserved ability to apprehend individual portions of the whole—the misleading term that has stuck. Agnosia (Greek for “not knowing”), also known as “associative agnosia”, is the inability to recognize previously familiar objects, despite adequate perception wherein objects are effectively stripped of their meanings. It is a memory-related disorder, a “mnestic” defect. Simultanagnosia is a form of “apperceptive agnosia,” a failure to identify previously familiar objects as a result of impaired perception and is not memory related. (Practically speaking, patients with cerebral visual disturbances often have a mix of “mnestic” and apperceptive deficits, depending on the location and extent of lesions.)

2. “Psychic paralysis of gaze” is an inability to shift gaze voluntarily to objects of interest, despite unrestricted eye rotations. It resembles later descriptions of fixation spasm (8) and acquired ocular apraxia (apraxia, Greek for “not acting”) but differs from congenital ocular motor apraxia [in which children make head thrusts occur during voluntary refixation, despite a full range of reflexive saccades (9)].

3. Optic ataxia (OA) is the difficulty with the act of reaching under visual guidance, despite adequate limb strength and position sense. When Bálint positioned the patient’s left (more impaired) hand, the man could imitate the position with his right. Note that the terms “ocular apraxia” (from the Greek, apraxia, for “not acting”) and “optic ataxia” (Greek, ataktos, for “disorderly”) also are ineffective in conveying the underlying mechanisms in cases such as those of Bálint.

The term Bálint syndrome was coined approximately 50 years after the publication of Bálint’s original report (10). Key components of the syndrome can be dissociated and also show an important overlap with the left hemineglect syndrome (11). Importantly, Bálint’s patient showed prominent signs of left hemineglect syndrome with “constriction” of the “attentive field” and was unaware when approached from the left because his focus of attention was shifted 40° into the right hemifield. Postmortem examination showed a deformed, atrophic brain with bilateral lesions of the posterior parietal, upper temporal, and occipital lobes, marked damage in posterior superior and inferior parietal lobules, and changes around the left central gyrus and left internal capsule. Bálint emphasized the angular gyrus lesions, but there was damage in other vision-related structures including the posterior callosum, bilateral white matter, upper thalami, and pulvinar. The frontal lobes, and the afferent visual pathways, including optic nerve and tract, lateral geniculate body, and calcarine cortex, were largely spared. While Bálint’s patient had cerebrovascular lesions, different etiologies for the syndrome complex...
include neurodegenerative conditions (especially Alzheimer disease), tumor, trauma, spongiform encephalopathy, and viral infections, such as HIV, that produce differing profiles and trajectories of impairment.

The report of Rajagopal et al (2) on visual involvement in presumed cortical basal syndrome (also known as cortical basal [gangliocytic] degeneration [CBD]) in a 60-year-old woman with progressive vision and limb control difficulties had to be distinguished from Bálint syndrome. The CBD symptom complex includes “alien limb” (or hand), limb apraxia, cortical sensory loss, focal reflex myoclonus, rigidity, akinesia, postural action tremor, limb dystonia, hyperreflexia, and postural instability (12). Unlike OA, the alien limb phenomenon is not limited to reaching under visual guidance (11). The hand seems to move as if possessed by an outside agent and may show a grasp reflex and elements of “magnetic apraxia” (13) in association with frontal lobe lesions. Whereas OA may occur as part of Bálint syndrome in Alzheimer disease (with amyloid and tau pathology) (14), alien hand syndrome is more characteristic of CBD, a tauopathy (15).

The patient of Rajagopal et al (2) experienced frequent involuntary movements of the upper body and occasional tonic flexed posturing of the left arm (and had no resting tremor to suggest Parkinson disease). Yet, we cannot be sure of the underlying behavioral impairments of disease in this patient. She showed “marked ideomotor apraxia” (this generally manifests as an inability to imitate hand gestures or to pantomime use of tools [e.g., comb, toothbrush]); yet, it is not clear how this was defined or tested. She tended to use her left hand much less than the right, as can occur with motor neglect—which was apparently not considered. Could she imitate the position of one hand passively positioned by the examiner, with the other hand (see Bálint, above)? This would help exclude a role of cortical sensory loss or dorsal column disease in disordered limb control.

The patient also seemed to show “profound simultagnosia” based on her poor description of the “Cookie Thief” picture. (The Cookie Theft picture originated from the Boston Diagnostic Aphasia Examination (16) not from the National Institutes of Health as Rajagopal et al (2) and Walsh et al (4) indicate). Yet, “her cognitive impairment prevented prolonged coherent speech,” so her inability to describe the Cookie Theft could have been language related. The patient denied loss of vision, photopsia, scotoma, or diplopia but had severe communication problems and dementia. Yet, denial of defects because of the lack of self-awareness of impairment (known as “anosognosia”) is common in dementia. An earlier Mini Mental Status (dementia screening) score was 12/30 (very impaired), and dementia could have progressed even further by the time the authors saw the patient; yet, this was apparently not tested. She could not cooperate for visual field assessment, which means we cannot exclude visual field defects causing what might look like, it but is not simultanagnosia (e.g., objects “disappearing” into undetected scotomata). The authors do not state what medications the patient was taking or how they excluded posterior cortical atrophy (PCA), multisystem atrophy, B12 deficiency, syphilis, vasculitis, and other etiologies. Magnetic resonance imaging (MRI) showed “diffuse cortical atrophy, with some predominance in the posterior parietal regions,” which fits PCA (better than CBD), but we do not get to see the MRI for ourselves. Abnormal signal in basal ganglia could occur with metal deposition (copper in Wilson disease, iron in Hallervorden-Spatz), although these diagnoses seem unlikely. Functional brain imaging may have helped disentangle this case (see Rene et al (3)). Position emission tomography (PET) or single-photon emission computed tomography (SPECT) might show asymmetric activation in subcortical (basal ganglia) and cortical (frontal-parietal) regions in CBD (15).

Rene et al (3) report 5 cases of PCA, a visual variant of Alzheimer disease (17), in which visual difficulties are not explained by ocular pathology. Three patients had homonymous hemianopia, and 3 showed right posterior atrophy on MRI. Diagnosis was aided by observing clinical signs and PET in 2 patients with nonspecific MRI findings. Aspects of 1 case resembled the cases of both Rajagopal et al (parkinsonism or basal ganglionic features) and Walsh et al (right-left confusion). This patient had left homonymous hemianopia, left upper limb neglect and deafferentation, alexia, agraphia, right-left confusion, finger agnosia, bilateral stereognosia, sensory extinction, OA, and mild parkinsonism. SPECT showed severe right parietotemporooccipital hypoperfusion.

Walsh et al (4) reported “visual allochiria” in a 67-year-old woman with Bálint syndrome. MRI initially showed acute right parietal-occipital infarction and bilateral parietal-occipital infarctions days later. Impaired left arm movement under visual guidance was not explained to the degree of weakness. Allochiria (Greek for “other hand”) has been observed following right parietal lobe lesions (18). Patients mislocalize the side of the body that has been stimulated, despite adequate sensation. Walsh et al report allochiria in vision, but it is unclear how they measured this defect or distinguished it from (apperceptive) the effects of simultanagnosia (e.g., from irregular shifts of attention between hemifields), extinction to double simultaneous stimulation (generally on the left in patients with right parietal lesions), or akinetopsia—as in a patient reported by Zihl et al (19), who had bilateral parietal lesions and complained of objects appearing on one side or another without seeing them move in between (because of her profound motion apperception). The patient of Walsh et al may have had Gerstmann syndrome as a result of her left parietal lesion, which includes right-left confusion (20). Certain drugs that may have affected motor tone and cognition, such as promethazine, hydrocodone, alprazolam, and atenolol, further confound this case. Visual and neuropsychological assessments are lacking.
Visual disturbances caused by brain lesions, as above, offer a unique window on the psychoanatomical substrates of human behavior. The brain constructs a seamless, detailed picture from partial glimpses of the visual world. Brain lesions in Bálint syndrome destroy this illusion, producing a piecemeal visual experience (simultanagnosia/visual disorientation) and impaired visual control of eye and hand movements (ocular apraxia and optic ataxia). Evidence from these cases remains highly relevant to understanding the neural substrates of vision, motor control, memory, and even consciousness.

Because Bálint syndrome is not common and is difficult to assess with standard clinical tools, the literature is dominated by case reports. However, it is risky to generalize from these historical or modern single case reports, which are confounded by case selection bias, nonuniform application of operational definitions, inadequate study of basic vision, poor lesion localization, and failure to distinguish between deficits in the acute and chronic phases of recovery or duration or stage of neurodegeneration. There is variability of lesion effects, and the bilateral brain lesions in these cases cause extensive visual and cognitive impairments that hinder clinical testing. Interesting abnormalities are much more likely to be reported and less striking ones ignored, creating biased profiles. Lesion effects and recovery vary with patient age, time since lesion onset, and white matter involvement. Patients studied in the acute phase tend to show more profound deficits than those studied months or years later in the chronic phase of recovery. Methodological concerns include failure to adequately assess basic visual functions (other than acuity) and to consider confounding eye conditions (such as retinopathy, cataracts, or optic neuropathy). In addition, the abnormalities of eye or hand movements in the above cases were not quantified in any way. Cognitive and visual testing were sparse, neuroimaging data were limited, operational definitions were unclear, and theoretical interpretations are lacking. Future clinical research studies should address possible underlying psychoanatomical (“bottom up” and “top down”) mechanisms, with specific consideration to visual working memory and attention (including spatial and object attention) and to systems for the identification of object structure and depth from binocular stereopsis, kinetic depth, motion parallax, eye movement signals, and other cues (11). The successful approach to these cases requires clear operational definitions of behavioral impairments and sufficiently detailed assessments to classify patients who, as Holmes recognized, may be challenging to test because of their visual and cognitive difficulties.

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Bálint Syndrome and Visual Allochiria in a Patient With Reversible Cerebral Vasoconstriction Syndrome

Ryan D. Walsh, MD, Jessica P. Floyd, MD, Benjamin H. Eidelman, MD, PhD, Kevin M. Barrett, MD, MSc

Abstract: Bálint syndrome (simultagnosia, optic ataxia, and ocular apraxia) is typically caused by pathology affecting the parietal-occipital regions bilaterally. Visual allochiria is an uncommonly reported symptom associated with parietal-occipital pathology in which visual stimuli presented to one hemispace are transposed to the opposite side. We describe a patient with Bálint syndrome and visual allochiria whose initial brain MRI demonstrated acute infarction of the right parietal-occipital region. Repeat imaging 9 days later revealed bilateral parietal-occipital infarctions consistent with the observed clinical syndrome. Reversible cerebral vasoconstriction syndrome is introduced as a novel cerebrovascular etiology of Bálint syndrome.

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Bálint syndrome is a combination of simultagnosia, optic ataxia, and ocular apraxia (1). Simultagnosia is the inability to interpret a complex scene despite being able to perceive its individual elements (2). Optic ataxia describes misreaching under visual guidance despite normal limb strength and position sense resulting from dysfunction of visual connections to the motor cortex (1,2). Ocular apraxia manifests as difficulty with the initiation of voluntary saccades, while reflex saccades remain intact (2). Bálint syndrome typically results from pathology affecting bilateral parietal-occipital regions (3). Multiple etiologies have been described, including cerebrovascular disease, trauma, tumor, prion disease, HIV, leukoencephalopathies, and degenerative conditions, such as Alzheimer disease and posterior cortical atrophy (2,4). When the syndrome is a result of cerebrovascular disease, watershed infarction related to systemic hypotension is the usual cause (2). Vasculopathies, including central nervous system (CNS) vasculitis, have been implicated as well (1,5).

Reversible cerebral vasoconstriction syndrome (RCVS) describes a group of vasculopathic disorders characterized by reversible segmental vasoconstriction involving arteries of the circle of Willis and their branches (6). These disorders include thunderclap headache with vasoconstriction, benign angiopathy of the CNS, Call-Fleming syndrome, postpartum angiopathy, and drug-induced vasospasm. We describe a patient with RCVS who developed Bálint syndrome and visual allochiria, a unique symptom in which visual stimuli are transposed to the opposite side of visual space.

CASE REPORT

A 67-year-old right-handed woman presented to an outside facility complaining of severe right retro-orbital headache with abrupt onset while straining on the toilet. Medical history was significant for symptomatic hypertension requiring hospitalization, hyperlipidemia, diabetes, and renal artery stenosis with prior stent placement. Medications included aspirin, atenolol, and irbesartan. Family history included ischemic stroke in her father. She was employed as a nurse, consumed 2 alcoholic beverages daily, and had a remote smoking history. Blood pressure on presentation was 155/86 mm Hg. Neurologic examination revealed no abnormalities. Normal hematologic studies included angiotensin-converting enzyme, VDRL test, HIV, West Nile virus and Lyme antibodies, erythrocyte sedimentation rate, extractable nuclear antigens, and double-stranded-DNA. Cerebrospinal fluid (CSF) analysis was unremarkable, including cell count, glucose, protein, herpes simplex virus PCR, cryptococcal antigen, gram stain, bacterial culture, fungal stain/culture, and acid-fast culture.
While CT of the brain was normal, MRI reportedly showed abnormal punctate enhancing areas within the leptomeninges, involving frontal, parietal, and occipital lobes. The patient was treated symptomatically with promethazine, hydrocodone-ibuprofen, and alprazolam, and her atenolol dosage was increased prior to discharge.

Six days later, she was found to be confused with weakness in the left arm and was brought to our hospital. On examination, the patient was afebrile with blood pressure of 208/110 mm Hg. She was not oriented to place and time. Speech demonstrated mild dysarthria. There was neglect for visual and tactile stimuli on the left. She had a right-gaze preference overcome with oculocephalic maneuver. There was a left homonymous hemianopia on confrontation visual field testing. The patient demonstrated visual allochiria; when fingers were presented in her left visual field, she would report them in her right visual field. She had difficulty producing voluntary saccades to verbal command and voluntary saccades between targets and could not pursue beyond the midline to the left. When presented with a complex visual scene (the National Institutes of Health Stroke Scale “cookie theft” picture), she was able to identify individual items but could not describe the scene as a whole. Her visual acuity could not be accurately measured, but near vision was sufficient to identify elements of the cookie theft picture. There was a left lower facial droop. Strength was normal except for the left arm, judged to be 3/5 on the Medical Research Council scale. Arm reaching under visual guidance was abnormal; on the left, the abnormality was out of proportion to her degree of weakness.

Initial CT of the brain demonstrated a region of hypodensity in the right occipital lobe extending into the high right parietal lobe consistent with evolving acute infarction. Comprehensive laboratory evaluation was notable for elevated serum erythrocyte sedimentation rate and C-reactive protein and low serum sodium. Brain MRI performed 24 hours after the presentation was consistent with acute infarction in the distribution of the right middle and posterior cerebral arteries (Fig. 1). There was no evidence of cerebral venous thrombosis on CT venography. MRA of the head and neck showed 60% focal narrowing of the right internal carotid artery just proximal to the origin of the right posterior communicating artery. Nine days later, brain MRI showed areas of hyperintensity on diffusion-weighted imaging on both sides of the brain, consistent with the new regions of subacute infarction (Fig. 2). Repeat MRA revealed focal narrowing of multiple arteries in the region of the circle of Willis (Fig. 3). Conventional angiography exhibited beading of branches of the middle cerebral and anterior cerebral arteries bilaterally consistent with a vasculopathy and 75% stenosis of the paraclinoid segment of the distal right internal carotid artery.

Because of the possibility of CNS vasculitis, the patient was empirically treated with a short course of high-dose intravenous steroids. Minimal subjective improvement was noted. RCVS now was felt to be the most likely diagnosis prompting initiation of oral verapamil.

One month later, the patient was fully oriented, had improved left arm strength, and a left homonymous hemianopia. She was able to gaze to the left but still demonstrated

FIG. 1. Initial MRI. Top: Diffusion-weighted imaging showing an increased signal in the right parietal and occipital regions. Bottom: Apparent diffusion coefficient (ADC) maps reveal corresponding areas to be dark, consistent with restricted diffusion.
mild ocular apraxia with difficulty initiating voluntary saccades. Visually guided reaching was much improved, and visual allochiria was no longer present. Brain MRI and MRA showed evolutionary changes of previously noted infarcts. The area of stenosis in the supraclinoid portion of the right internal carotid artery was unchanged, but there was a near complete resolution of the multifocal segmental arterial stenoses (Fig. 4).

**DISCUSSION**

Our patient presented with the classic symptom triad of Bálint syndrome, although the initial CT and MRI revealed infarction limited to the right hemisphere. Several days later, repeat MRI demonstrated infarction involving the left parietal and occipital lobes. One possible explanation for this disconnection in clinical and neuroimaging findings is the occurrence of a functional cerebral diaschisis. Diaschisis refers to depressed metabolic function of cortex in a region anatomically distant from, but functionally connected to, a region of injury (7). Several types of diaschisis have been described: remote effects within the injured hemisphere (ipsilateral effects), remote effects in the uninjured hemisphere (contralateral effects), and effects on the cerebellum contralateral to the cerebral injury (crossed cerebellar diaschisis) (8). Diaschisis has been examined in preclinical and clinical studies including various measures of cortical function, such as metabolic factors, cerebral blood flow, and electrical activity (8–12). In our patient, right parietal-occipital ischemia may have caused

**FIG. 2.** MRI 9 days later. Top: Diffusion-weighted imaging demonstrating new hyperintensities (arrows) in the left parietal-occipital junction, left occipital pole, and right frontal region. Bottom: Apparent diffusion coefficient (ADC) maps are consistent with subacute infarction.

**FIG. 3.** MRA of circle of Willis. Stenotic lesions are indicated by arrows (clockwise from far left): right middle cerebral artery, A1 segment of right anterior cerebral artery, A2 segment of left anterior cerebral artery, left posterior cerebral artery, and right vertebral artery.
Alternative pathologies and lesion localizations may mimic the features of Bálint syndrome, and these features may be dissociable (4,17). Isolated ocular apraxia can occur with bilateral frontoparietal lesions (18,19). Optic ataxia has been associated with lesions of the parietal-occipital junction (20,21). Simultagnosia has been described with disorders of bilateral inferior parietal cortex, left extrastriate cortex, and bilateral superior visual association cortex (17,22). Severe restriction of visual fields can mimic simultagnosia as demonstrated by Dalrymple et al (5). The global impairment seen in patients with Bálint syndrome may be the result of a narrowed attentional window rather than an additional attentional deficit unique to the disorder (5). It is possible that simultagnosia or a limited visual attention (e.g., severely constricted visual fields) may cause difficulties with reaching in 3-dimensional space mimicking optic ataxia (5). However, such a deficit would not produce difficulty with voluntary saccades, impaired pursuit movements, or visual allochiria. In addition, optic ataxia and ocular apraxia are not typical features of severe visual field deficits. Patients with hemineglect may have impaired visual search (resembling ocular apraxia), impaired visually guided hand movements (resembling optic ataxia), and visuo-perceptual difficulties (mimicking simultagnosia) (4). Hemineglect could contribute or compound the difficulties with search and attention seen in patients with Bálint Syndrome.

Our patient initially presented with a thunderclap headache triggered by Valsalva maneuver and subsequently experienced ischemic strokes in multiple vascular territories. Neuroimaging demonstrated multifocal arterial stenoses consistent with the vasculopathy RCVS. Patients with RCVS typically present with thunderclap headache, often triggered by exertion or Valsalva maneuver, and can have any number of neurologic deficits (6,23). Following treatment with a calcium channel blocker, diminished cerebral vasospasm within 4 weeks is common (6). In our patient’s case, a negative vasculitis workup, normal CSF, and rapid clinical-neuroimaging improvement with verapamil are additional features supportive of the diagnosis of RCVS.

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Complex Visual Manifestations of Posterior Cortical Atrophy

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Abstract: We describe 5 patients with complex visual disturbances in the absence of ocular pathology who were ultimately diagnosed with posterior cortical atrophy (PCA). The presence of visual cortical symptoms, neuroimaging findings and clinical evolution led to the diagnosis 1-5 years after the onset of visual symptoms. Age of onset ranged from 50-66 years. In 3 cases, magnetic resonance imaging (MRI) of the brain demonstrated predominantly right posterior cortical atrophy. The other 2 patients had nonspecific MRI findings but the diagnosis was established given the findings on clinical examination and positron emission tomography (PET). All progressed to global dementia and an autopsy confirmed the diagnosis of Alzheimer disease in one patient. The possibility of PCA should be considered when a patient presents with complex visual symptoms in the absence of ocular pathology. Early neurological assessment may avoid diagnostic delay.

METHODS

Five patients were diagnosed with PCA in the Dementia Unit of the Hospital de Bellvitge in the past 10 years. A retrospective review was done of their medical records. Extensive neuropsychological examination, structural neuroimaging (magnetic resonance imaging and/or computed tomography [CT]), and functional neuroimaging ($^{99}$Tc-HMPAO single-photon emission computed tomography [SPECT] and/or $^{18}$FDG positron emission tomography [PET]) were performed in all patients, and, in 1 patient, neuropathological study was available.

RESULTS

Three men and 2 women aged 50–66 years were included. None of them had a family history of dementia. Clinical findings and examination results are summarized in Table 2. Detailed description of 3 cases is presented.

Case 1

A 65-year-old woman described problems with her vision over the previous 5 years. She reported difficulty threading a needle, thought there was not enough light in her home and wanted to use brighter light bulbs. Two years later, she began using her left hand less and gave up cooking because she dropped food out of the frying pan. She could not recognize people’s faces and identified her own children only by their voices. She could not find or organize her clothing. Two years ago, the patient decided to see an ophthalmologist. Visual acuity was normal, but a left homonymous hemianopia was found. Visual evoked potentials were normal. Brain CT revealed asymmetric enlargement of the lateral ventricles (Fig. 1). One year ago, she was unable to write, tell time on her watch,
On seeing a neurologist, she reported feeling depressed because she was aware of her deficits. Examination revealed a left homonymous hemianopia, left upper limb neglect and deafferentation, alexia, agraphia, right-left confusion, finger agnosia, bilateral stereoagnosia, sensory extinction, optic ataxia, and mild parkinsonism (Table 2). SPECT showed severe right parietotemoro-occipital hypoperfusion. PCA was diagnosed. She died in an institution 3 years later.

**Case 2**

A 56-year-old man with visual complaints that had started 1 year earlier was seen by his ophthalmologist. He had

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**TABLE 1. Diagnostic criteria of posterior cortical atrophy**

<table>
<thead>
<tr>
<th>Core features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual complaints in the absence of ocular or brain disease (stroke, tumor) explaining the symptoms</td>
</tr>
<tr>
<td>Absence of parkinsonism or hallucinations and relative preservation of anterograde memory and insight in early stages (to differentiate from Lewy body dementia or Alzheimer dementia)</td>
</tr>
<tr>
<td>Any of simultanagnosia, optic ataxia, ocular apraxia, constructional dyspraxia, visual field defects, spatial disorientation, and elements of Gerstmann syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supportive features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenile onset, alexia, apraxia (ideomotor, dressing), prosopagnosia</td>
</tr>
<tr>
<td>Parietal and/or occipital deficits on neuropsychological examination</td>
</tr>
<tr>
<td>Parietal and/or occipital (focal or asymmetric) deficits on structural or functional neuroimaging</td>
</tr>
</tbody>
</table>

Modified from Tang-Wai et al (4).

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**TABLE 2. Clinical findings and examination results of 5 patients with posterior cortical atrophy**

<table>
<thead>
<tr>
<th>Age of onset (yr)</th>
<th>59</th>
<th>54</th>
<th>57</th>
<th>50</th>
<th>66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to diagnosis (yr)</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Most affected side</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Visual field deficits</td>
<td>Yes (HH)</td>
<td>Yes (HH)</td>
<td>No</td>
<td>No</td>
<td>Yes (HH)</td>
</tr>
<tr>
<td>Focal atrophy CT/MRI</td>
<td>TPO</td>
<td>FP</td>
<td>PO</td>
<td>TPO</td>
<td>N</td>
</tr>
<tr>
<td>SPECT abnormality</td>
<td>TPO</td>
<td>TP</td>
<td>TP</td>
<td>TP</td>
<td>—</td>
</tr>
<tr>
<td>PET abnormality</td>
<td>—</td>
<td>—</td>
<td>TP</td>
<td>PO</td>
<td>PTO</td>
</tr>
<tr>
<td>Frontal dysfunction</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Verbal memory deficit</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression</td>
<td>AD like</td>
<td>AD like</td>
<td>Dementia</td>
<td>LBD like</td>
<td>AD like</td>
</tr>
<tr>
<td>Anosognosia</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Visual agnosia (94%–63%)</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Visuospatial deficits (88%–82%)</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Driving difficulty (82%)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>—</td>
<td>Yes</td>
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<tr>
<td>Ideomotor apraxia (76%–81%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Agraphia (70%–65%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
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<tr>
<td>Alexia (65%–91%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Spatial disorientation (65%–48%)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gerstmann syndrome (52%–60%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Anomia (52%–67%)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Acalculia (41%–46%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Dressing apraxia (35%–46%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Simultagnosia (29%–49%)</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
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<tr>
<td>Optic ataxia (29%–49%)</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Episodic memory loss (29%–45%)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Prosopagnosia (23%–24%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Achromatopsia (12%–9%)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Parkinsonism (12%–18%)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Visual hallucinations (6%–10%)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Cortical sensory loss</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>No</td>
</tr>
</tbody>
</table>

Frequency of abnormalities reported in the literature given in parentheses.

AD, Alzheimer disease; FP, fronto-parietal; HH, homonymous hemianopia; LBD: Lewy body dementia; N, normal; NA, not available; PET, positron emission tomography; PO, parieto-occipital; R, right; SPECT, single-photon emission computed tomography; TP, temporo-parietal; TPO, temporo-parieto-occipital.


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difficulties with reading and writing, laid the dishes upside down, could not tell the time, could drive and read road signs, but mounted the curb and entered the car through the wrong door. Visual acuity was 20/25 in both the eyes. The patient could not read any of the Ishihara color plates. Intraocular pressure and funduscopy were normal. Visual field testing demonstrated an incomplete left homonymous hemianopia (Fig. 2).

The patient was referred for neurological assessment. On examination, he had right hemineglect and apraxia, without language or memory alterations and a normal physical examination. While brain CT was normal, MRI revealed parieto-occipital atrophy bilaterally (Fig. 3). SPECT showed right parietotemporal hypoperfusion (Fig. 4). Neuropsychological examination 3 years later showed widespread deficits including complete Gerstmann syndrome and prosopagnosia (Table 2). In the following year, the patient was unable to read or write and had difficulty shaving, getting dressed, or going out alone. Visual acuity did not change, but visual field defects progressed in both left hemifields and reliability indices worsened. Brain MRI showed bilateral fronto-parietal atrophy. The patient also developed disinhibition and personality changes. As a result of the clinical suspicion of Alzheimer disease (AD), he received treatment with donepezil and memantine without improvement.
Case 4

A 56-year-old woman consulted an ophthalmologist because of progressive vision loss. Visual acuity, color vision, funduscopy, electroretinography, and visual evoked potentials were normal. There was a bilateral visual field constriction, but reliability indices were poor. No specific diagnosis was made, and nonorganic visual field loss was a diagnostic consideration. Two years later, she complained of memory loss and disorientation that was attributed to depression. Brain CT showed diffuse cortical atrophy.

The patient was referred to a neurologist, and neuropsychological evaluation detected frontal dysfunction, apraxia, and apperceptive agnosia. Throughout the following year, she developed memory loss, aphasia, severe depression, anxiety, irritability, and aggressiveness, and she received several antidepressants. SPECT revealed right hemisphere hypoperfusion with the absence of activity in the right parietotemporal region. The following year, she experienced visual hallucinations and cognitive fluctuations. She did not improve with donepezil, and in the last months of her life, there was progressive impairment of memory and orientation, apraxia, aphasia, agnosia, mood disorder, and clinophilia. Neurological examination revealed global rigidity, hypomimia, bradykinesia, and parkinsonian gait. The patient did not use her left hand and required nasoduodenal feeding due to severe dysphagia and buccolingual apraxia. PET showed bilateral parieto-occipital hypometabolism, while MRI revealed temporoparieto-occipital atrophy predominantly on the right. With the onset of cortical visual signs and progression to global dementia, she was diagnosed with PCA and progression to presenile AD. She died of respiratory infection, and neuropathology revealed AD (Braak stage VI) with numerous plaques and tangles predominantly in cortical areas, including primary visual cortex, with the absence of alpha-synuclein.

DISCUSSION

Our patients presented with complex visual symptoms in the absence of ocular pathology. The diagnosis of PCA was made 1–5 years after the onset of symptoms and established by the presence of visual cortical complaints, clinical evolution, and neuroimaging findings, fulfilling many of the clinical criteria proposed by Tang-Wai et al (4) (Table 1). The presenting visual complaints were nonspecific, and as in other case series (4,5), patients initially presented to an ophthalmologist. Unlike typical AD, memory, insight, and judgment were relatively preserved until late in the course, resulting in the failure to recognize PCA. This diagnostic delay has been reported to range between 1 and 9 years (4,5). The differential diagnosis includes Lewy body dementia (LBD), Creutzfeldt-Jakob disease (Heidenhain variant), cerebrovascular disease, and nonorganic visual loss.

The mean age of onset of PCA is earlier than in classical AD (4,5). Onset between 40 and 85 years has been reported, but most cases start between 50 and 60 years (4–7). Almost all cases are sporadic. Some have a familial history of late-onset dementia (5,7) but not of PCA, with the exception of 2 sisters reported by Otsuki et al (8). Our patients had onset ages between 50 and 66 years, and none had a family history of AD.

The spectrum of clinical signs of PCA reflects dysfunction of the dorsal (occipito-parietal) and/or the ventral (occipito-temporal) visual streams or primary visual cortical dysfunction (4,9). Almost a quarter of the patients with PCA develop visual hallucinations (4–6), and some have LBD at autopsy. In case

**FIG. 3.** Case 2. T1 axial (A) and sagittal (B) magnetic resonance imaging showing bilateral parieto-occipital atrophy.
4, despite the presence of hallucinations and spontaneous parkinsonism, the neuropathological diagnosis was AD.

Approximately half of the patients with PCA eventually complain of intermittent memory loss (6), but this is never a prominent initial feature. In most cases, memory loss develops later in the course of the disease. In neuropsychological studies, PCA patients are significantly more impaired in visual perception, spatial memory, visual attention, and


FIG. 5. Case 5. Positron emission tomography demonstrating severe, bilateral parieto-temporo-occipital hypometabolism.
visuospatial reasoning compared to AD patients, who are more impaired in episodic memory (9).

Hemianopic visual field loss is thought to be underdiagnosed (10), probably because visual fields are either tested only by confrontation techniques or perimetric examination is not fully reliable because of attention deficits and apraxia of PCA patients.

MRI typically shows bilateral PCA, predominantly affecting the occipital, parietal, and temporal lobes (11). If MRI appears normal or reveals nonspecific atrophy, voxel-based morphometry studies show a pattern of posterior lobe atrophy compared to controls (7). Cortical atrophy is bilateral but more severe on the right side. In studies comparing patients with PCA to those with typical AD, there is greater atrophy in the right visual association cortex and less in the left hippocampus (11). PET studies also show greater parieto-occipital impairment, also with right predominance (Fig. 5) (12). Frontal lobe involvement, although typical of AD, has been reported in PCA, clinically and with functional neuroimaging. This may be because of the degeneration of the afferent input from the parietal-occipital cortices contributing to ocular apraxia (11,12).

Autopsy findings of PCA patients usually show AD-type pathology but of posterior distribution and with hippocampal preservation (4). More rarely, some cases have shown LBD. PCA is a clinical syndrome and may be considered as a rare focal onset variant of AD or LBD, or alternatively regarded as a distinct entity.

No treatments for PCA have been evaluated in clinical trials. Cholinesterase inhibitors are sometimes used, but their effectiveness is unproven.

REFERENCES

Optic Nerve Biopsy in the Management of Progressive Optic Neuropathy

Marc H. Levin, MD, PhD, Joshua J. Ney, MD, Sriram Venneti, MD, PhD, Mark L. Moster, MD, Laura J. Balcer, MD, Nicholas J. Volpe, MD, Roberta E. Gausas, MD, Grant T. Liu, MD, M. Reza Vagafi, MD, Steven L. Galetta, MD

Background: In cases of progressive optic neuropathy, diagnostic uncertainty often persists despite extensive work-up. Optic nerve biopsy (ONB) can be considered, especially when visual decline of the affected or fellow eye ensues despite empiric therapy. We aimed to evaluate both diagnostic and therapeutic utilities of ONB based on the long-term experience at a tertiary care institution.

Methods: This was a retrospective chart review of biopsies over 20 years at a single institution involving intrinsic or adherent optic nerve masses. Main outcome measures included the impact of tissue sampling on reaching a diagnosis and on guiding treatment. Secondary measures included vision in the eye of the ONB and the fellow eye.

Results: Fifteen patients with a mean age of 51.7 ± 17.4 years underwent biopsies. At the time of biopsy, visual acuity was no light perception in 8 (53%) eyes, light perception to counting fingers in 5 (33%), and 20/400 or better in 2 (13%). The fellow eye of 7 patients (47%) experienced some degree of sequential vision loss before biopsy. Seven specimens included en bloc biopsy of the nerve, 7 contained the dural sheath (usually with a portion of the optic nerve), and 1 only of the compressive mass. Six patients (40%) had tumors. Six of 8 inflammatory lesions biopsied required further clinical data to arrive at specific diagnoses. In one case, a clinical diagnosis could not be made. No patients experienced further vision loss in the fellow eye at last follow-up (median, 8 months).

Conclusions: In diverse circumstances of progressive optic neuropathy, ONB can be beneficial in establishing the diagnosis. ONB can help direct specific local or systemic treatment, particularly when infectious or inflammatory etiologies are identified. ONB, if considered early in the disease course, can potentially halt or prevent vision loss when the fellow eye is threatened.

Evaluation of a progressive optic neuropathy can be challenging, at times yielding nonspecific laboratory results and equivocal neuroimaging findings in the setting of profound vision loss. Optic nerve biopsy (ONB) is considered a last resort when treatment risks outweigh benefits in progressive optic neuropathy of uncertain etiology. It is reserved for patients who have lost vision in one eye and are losing or may lose vision in the fellow eye. Once the nerve is severed, there is no hope for visual recovery, making the decision to proceed with such a diagnostic procedure particularly difficult. Even subtotal ONBs, which are occasionally done when vision is compromised but not completely lost, limit the potential for visual recovery. When possible, computed tomography (CT)–guided fine needle aspiration biopsy (FNAB) represents a minimally invasive alternate method for obtaining useful histopathology in cases of optic nerve tumors or inflammatory lesions (1).

To date, most reports of ONBs in the literature have been limited to single case reports and highlight the need to consider a broad differential diagnoses and to perform
extensive evaluations before biopsy (2–6). We performed a retrospective review at a tertiary care institute to identify patients who underwent ONB. We aimed to characterize the disease processes that required this highly invasive diagnostic surgery and evaluate the extent to which ONBs ultimately affected patient management and clinical outcome.

METHODS

This was a retrospective chart review of biopsies in a diverse set of clinical circumstances at the University of Pennsylvania from 1990 to 2010 involving intrinsic or adherent optic nerve masses. Cases were identified from digitized hospital pathology databases and from a survey of treating physicians in ophthalmology, neurology, neurosurgery, and otolaryngology departments.

Patients were included if surgical biopsy of intrinsic or adherent optic nerve lesions was undertaken to clarify an uncertain diagnosis in the setting of progressive visual decline. Cavernous hemangiomas were excluded from the analysis because they are orbital masses distinct from the optic nerve, which also carry no risk to the fellow eye. Data collected from inpatient and outpatient medical records included demographic information, ocular and systemic diagnoses, empiric treatments, differential diagnoses, and neuroimaging, surgical, and pathological characteristics of optic nerve lesions. Five of 15 cases were previously reported as case reports in the literature (7–11).

The Human Subjects Research Committee at the University of Pennsylvania provided the Institutional Review Board approval for this study. A waiver for patient consent was obtained based on the retrospective nature of this study.

RESULTS

Fifteen patients underwent biopsies (mean age of 51.7 ± 17.4 years) and were subsequently followed up for a median of 8 months after the procedure (range, 1 week to 15 years; mean, 2.5 ± 4.1 years) (Table 1). Surgical approaches depended on the location and extent of the tumors and included craniotomy (47%), orbitotomy (47%), and endonasal endoscopy (6%). The primary surgeons specialized in neurosurgery (47%), oculoplastics (47%), and otolaryngology (6%). Combined approaches were sometimes used (20%).

The amount of tissue obtained depended on the clinical findings, especially the pre-operative visual acuity, and goals of surgery, most notably the need to decompress the apical or intracanalicular optic nerve. Seven specimens (47%) included en bloc biopsy of the nerve, 7 contained the dural sheath (47%; usually with subtotal nerve), and one was limited to the compressive lesion (6%). In 3 cases, decompression was an additional goal of surgery.

At the time of biopsy, visual acuity was no light perception (NLP) in 8 (53%) eyes, light perception (LP) to counting fingers (CF) in 5 (33%), and 20/400 or better in 2 (13%). The fellow eye of 7 patients (47%) had experienced some degree of vision loss attributed to the optic pathway lesions before biopsy, which manifested as decreased visual acuity and/or visual field defects.

In 14 of 15 cases, a specific diagnosis was established at least in part based on information obtained from the ONB (Table 1). In 8 cases, the ONB established the diagnosis, whereas in 6 cases, a presumed diagnosis was made using additional clinical data combined with a negative or non-diagnostic ONB. Six patients (40%) had tumors, and these included metastatic carcinoma (Case 1), anaplastic astrocytoma (Cases 2 and 3), schwannoma (Case 4), and meningioma (Cases 5 and 6). Figure 1 demonstrates representative histopathology from this series.

Eight patients (53%) were found to have infectious or inflammatory disorders after ONB. In most of these cases, the leading diagnostic consideration was tumor (glioma, meningioma, or lymphoma). In 6 of these 8 Cases (11–16), including 2 of 3 cases of sarcoidosis, revised clinical diagnoses were made based on optic nerve biopsies that excluded neoplasm, combined with imaging, laboratory analyses, or biopsies at other sites. The diagnoses in this category were Aspergillus (Case 7), sarcoidosis (Cases 8–10), sclerosing orbital inflammation (Case 11), varicella zoster optic neuropathy (Case 12), rheumatoid pachymeningitis (Case 13), and tacrolimus toxicity (Case 14).

The final diagnoses in cases of bilateral vision loss varied and included neoplastic, inflammatory, and infectious etiologies. In 5 of the 7 cases with fellow eye involvement at the time of ONB, management was altered based on biopsy results. Although no patient in this series regained significant vision in the affected eye, none experienced significant vision loss in the fellow eye at the last follow-up. Of the 7 patients undergoing subtotal ONB, 3 (Cases 5, 7, and 13) experienced at least temporary ipsilateral improvement in vision after biopsy. However, vision remained at NLP in Cases 8 and 9 and deteriorated in Case 3 (HM to NLP) and Case 6 (20/30 to CF) after biopsy.

Two patients with ONB are described in detail to illustrate the diverse and unique circumstances that warrant this diagnostic procedure.

Case 1

A 65-year-old woman presented with several weeks of decreased vision in the right eye. She had a history of non–small cell lung cancer with metastasis to the humerus that had been treated with radiation and chemotherapy 8 years earlier. Four years before presentation, she had undergone enucleation of the left eye for intractable neovascular glaucoma after a retinal vein occlusion. The central acuity on the right was 20/20, with superotemporal visual field loss and optic disc pallor. Magnetic resonance imaging (MRI) revealed a large nonhomogeneous enhancing mass involving both the left optic nerve and the optic chiasm. The differential diagnosis included glioma, metastasis, and lymphoma. A metastatic
<table>
<thead>
<tr>
<th>Case</th>
<th>Age and Gender</th>
<th>Presenting Complaint</th>
<th>Clinical Evaluation</th>
<th>Differential Diagnosis</th>
<th>Surgical Approach</th>
<th>Specimen</th>
<th>Biopsy Pathology</th>
<th>Presumed Clinical Diagnosis</th>
<th>Revised Patient Management</th>
<th>Follow-up After Biopsy (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65 F</td>
<td>Decreased vision</td>
<td>MRI: heterogeneously enhancing nerve extending to chiasm</td>
<td>Glioma, metastasis, lymphoma</td>
<td>Craniotomy</td>
<td>FT</td>
<td>Metastatic carcinoma</td>
<td>Radiation; steroids</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>78 M</td>
<td>Ataxia, nausea, vomiting, decreased vision</td>
<td>MRI: enhancing hypothalamic mass</td>
<td>Glioma, metastasis, meningioma</td>
<td>Craniotomy</td>
<td>AM</td>
<td>Anaplastic astrocytoma</td>
<td>Radiation</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Perimetry suggesting chiasmal and right optic nerve involvement</td>
<td></td>
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<tr>
<td>3</td>
<td>63 M</td>
<td>Decreased vision</td>
<td>MRI: enhancing nerve mass spreading into sella/frontal lobe</td>
<td>Glioma, meningioma</td>
<td>Craniotomy</td>
<td>ST</td>
<td>Anaplastic astrocytoma (7)</td>
<td>Chemotherapy</td>
<td>84</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>Before ONB: nondiagnostic LP: nl</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>40 M</td>
<td>Proptosis, decreased vision</td>
<td>MRI: intrinsic optic nerve mass</td>
<td>Glioma, meningioma, hemangioma, schwannoma</td>
<td>Craniotomy</td>
<td>FT</td>
<td>Schwannoma</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>54 F</td>
<td>Headache, decreased vision</td>
<td>MRI: optic nerve mass</td>
<td>Meningioma, metastasis</td>
<td>Craniotomy</td>
<td>ST</td>
<td>Meningioma</td>
<td>Radiation, repeat resection</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>49 F</td>
<td>Proptosis, eye pain, decreased vision</td>
<td>MRI: homogeneous nerve mass compressing posterior globe</td>
<td>Meningioma schwannoma, fibrous tumor</td>
<td>Orbitotomy</td>
<td>ST</td>
<td>Meningioma</td>
<td>Radiation</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>74 F</td>
<td>Proptosis, ocular dysmotility, eye pain, decreased vision</td>
<td>CT: bony erosions</td>
<td>Aspergillus, metastasis, vasculitis, sarcoidosis</td>
<td>Endoscopic endonasal</td>
<td>ST</td>
<td>Aspergillus</td>
<td>Antifungals</td>
<td>5</td>
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</tr>
</tbody>
</table>

(Continued)
### TABLE 1. (Continued)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age and Gender</th>
<th>Presenting Complaint</th>
<th>Clinical Evaluation</th>
<th>Differential Diagnosis</th>
<th>Surgical Approach</th>
<th>Specimen</th>
<th>Biopsy Pathology</th>
<th>Presumed Clinical Diagnosis</th>
<th>Revised Patient Management</th>
<th>Follow-up After Biopsy (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>24 F</td>
<td>Decreased vision</td>
<td>MRI: heterogeneously enhancing compressive orbital mass; smooth bony remodeling</td>
<td>Glioma, sarcoidosis, fungal, tuberculosis, meningioma</td>
<td>Orbitotomy</td>
<td>ST</td>
<td>Sarcoïdosis</td>
<td>(8)</td>
<td>Second steroid trial; chemotherapy stopped</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>15 M</td>
<td>Headache, decreased vision</td>
<td>MRIs: resolving optic nerve enlargement/enhancement</td>
<td>Lymphoma, leukemia, glioma, sarcoidosis, optic neuritis</td>
<td>Orbitotomy</td>
<td>ST</td>
<td>Atrophy, inflammation</td>
<td>Sarcoïdosis</td>
<td>Second steroid trial; immunosuppression</td>
<td>16</td>
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<tr>
<td>10</td>
<td>42 M</td>
<td>Decreased vision</td>
<td>MRIs: optic nerve chiasmal enlargement; stable size, variable enhancement</td>
<td>Glioma, paraneoplastic radiation neuropathy, sarcoidosis</td>
<td>Orbitotomy</td>
<td>FT</td>
<td>Fibrosis, atrophy</td>
<td>Sarcoïdosis</td>
<td>Steroids; immunosuppression</td>
<td>9</td>
</tr>
<tr>
<td>11</td>
<td>42 F</td>
<td>Eyelid swelling, ocular dysmotility, decreased vision</td>
<td>MRI: enhancing, irregular mass surrounding nerve</td>
<td>Glioma, meningioma, lymphoma, orbital pseudotumor, sarcoidosis</td>
<td>Craniotomy</td>
<td>FT</td>
<td>Fibrosis, inflammation</td>
<td>Sclerosing orbital inflammation (10)</td>
<td>Gallium scan: neg ONB: probable glioma</td>
<td>8</td>
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<tr>
<td>Case</td>
<td>Age and Gender</td>
<td>Presenting Complaint</td>
<td>Clinical Evaluation</td>
<td>Differential Diagnosis</td>
<td>Surgical Approach</td>
<td>Specimen</td>
<td>Biopsy Pathology</td>
<td>Presumed Clinical Diagnosis</td>
<td>Revised Patient Management</td>
<td>Follow-up After Biopsy (mo)</td>
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<tr>
<td>12</td>
<td>55 M</td>
<td>Headache, decreased vision</td>
<td>MRI: white matter hyperintensity, perivascular enhancement</td>
<td>Lymphoma, syphilis, HIV invasion</td>
<td>Orbitotomy FT</td>
<td>Gliosis, atrophy</td>
<td>VZV optic neuropathy</td>
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<td></td>
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<td>LP: nl</td>
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<tr>
<td>13</td>
<td>47 F</td>
<td>Ocular dysmotility, diplopia, decreased vision</td>
<td>MRIs: homogeneously enhancing, hyperintense mass around nerve in apex/canal</td>
<td>Meningioma, sarcoidosis, lymphoma</td>
<td>Craniotomy ST</td>
<td>Inflammation</td>
<td>Rheumatoid pachymeningitis</td>
<td>Steroids; numerous immunosuppressants</td>
<td>75</td>
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<td>LP: nl</td>
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<tr>
<td>14</td>
<td>63 M</td>
<td>Headache, decreased vision</td>
<td>MRIs: stable nerve enhancement, occipital hyperintensities</td>
<td>Lymphoma, tacrolimus toxicity, infection, vasculitis</td>
<td>Orbitotomy FT</td>
<td>Gliosis, demyelination</td>
<td>Tacrolimus toxicity (11)</td>
<td>IVIg; tacrolimus stopped</td>
<td>7</td>
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<td></td>
<td></td>
<td></td>
<td>Temporal artery biopsies: neg</td>
<td>Occipital lobe biopsy: neg</td>
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<tr>
<td>15</td>
<td>63 F</td>
<td>Headaches, ataxia, eye pain, ocular dysmotility, decreased vision</td>
<td>Numerous imaging studies: unrevealing</td>
<td>Aspergillus, tuberculosis, metastasis</td>
<td>Orbitotomy FT</td>
<td>Gliosis, fibrosis</td>
<td>No diagnosis</td>
<td>Second steroid trial</td>
<td>2</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>LPs: nl</td>
<td>Bronchoscopy: nl</td>
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Differential diagnosis was based on laboratory data, radiographic findings, other diagnostic procedures, and/or response to empiric therapy. Fellow eye involvement was established by neuroimaging and examination findings consistent with a decrease in visual acuity and/or a loss of visual field.

AM, adjacent compressive mass; bk, normal; CT, computed tomography; F, female; FT, full thickness; IVIg, intravenous immunoglobulin; LP, lumbar puncture; M, male; MRI, magnetic resonance imaging; neg, negative; ONB, optic nerve biopsy; PET, positron emission tomography; ST, subtotal; VZV, varicella zoster virus.
survey was unrevealing. Meanwhile, vision in the right eye dropped to 20/70. The decision was made to seek a tissue diagnosis with the hope of salvaging vision in the remaining eye and guiding systemic therapy. Biopsy of the infiltrated left optic nerve on the enucleated left side, obtained via a frontotemporal craniotomy, revealed poorly differentiated metastatic adenocarcinoma, presumably from her primary lung tumor. She was treated with radiation and steroids, and she experienced initial improvement in her visual field deficit. Unfortunately, eventual tumor growth, including involvement of the left internal carotid artery, led to her death within 1 year of diagnosis.

Case 7
A 74-year-old woman with a medical history of lung and breast cancer and amblyopia of the right eye presented with 2 months of progressive vision associated with left peri orbital pain. She was started on prednisone for presumed giant cell arteritis at an outside hospital, and subsequent temporal artery biopsy was negative. On referral to our institution, visual acuity was CF, right eye, and LP, left eye. There was moderate left proptosis. The left pupil was miotic, and topical cocaine testing confirmed sympathetic denervation. Extraocular motility of the left eye was impaired except in abduction and the left optic disc was pale. MRI demonstrated an enhancing left orbital apical mass infiltrating the optic nerve, and CT revealed erosion of the roof of the sphenoid sinus.

Given concern for metastatic cancer, an endoscopic sinus biopsy was performed. The pathology showed acute and chronic osteomyelitis, with *Aspergillus* identified on culture. The patient was treated with systemic and topical antifungals and underwent several debridements of the sphenoid sinus. Because the suspicion for metastatic disease remained high, the patient underwent a subtotal left ONB and decompression via endoscopic sphenoidectomy. Culture from the biopsy confirmed the diagnosis of *Aspergillus* osteomyelitis, and the patient continued systemic antifungals. Vision improved from LP to 20/100 on the biopsied left eye and remained stable at CF on the right eye during the ensuing 5 months.

**DISCUSSION**

We reported the diagnostic and clinical outcome of a series of patients undergoing ONB over a 20-year time frame. These patients had experienced progressive visual loss in one or both eyes. Although the decision to proceed with ONB can be difficult and regarded as a test of last resort, we found that in 14 of 15 patients, we were able to establish a diagnosis, and in all 4 patients with useful visual acuity remaining in the unaffected fellow eye, prevent further vision loss. In all 6 patients with tumors (Cases 1–6), the final diagnosis confirmed what had been suspected clinically. However, among 8 patients found to have an infectious and inflammatory optic neuropathy, there was also a strong suspicion of optic nerve tumor in 6 patients (Cases 8–13). A number of these cases highlight unusual presentations of progressive optic neuropathy. Although optic nerve schwannoma (encountered in Case 4) is on the differential of well-circumscribed optic nerve lesions, it is rarely encountered. *Aspergillus*, diagnosed in Case 7, has been recognized as a rare cause of optic neuropathy and orbital apex syndrome (12). Rheumatoid pachymeningitis, encountered in Case 13, has also been described to affect the optic nerve (13,14). In our patient, visual acuity improved from CF to 20/40 after 2 years of treatment with cyclophosphamide and infliximab. Some of the other unique cases presented in this series have been previously reported including: radiation-induced chiasmal anaplastic astrocytoma (Case 3) (7); sarcoid optic neuropathies thought initially to be gliomas (Cases 8 and 10 (8,9); sclerosing orbital inflammation, also suspicious for glioma before biopsy (Case 11) (10); and tacrolimus optic nerve toxicity (Case 14) (11).

Only the 2 patients with optic nerve sheath meningiomas (ONSMs) (Cases 5 and 6) and optic nerve surgery experienced significant changes in their central vision at the last follow-up. Although partial tumor resection confirmed the presumed diagnosis in both ONSM cases, the main goal of surgery was optic nerve decompression to halt progressive visual field loss. These 2 patients illustrate the highly variable visual outcomes after surgical decompression of ONSMs (15–17). Over the past 3 decades, fractionated stereotactic radiotherapy of vision-threatening ONSMs has been shown to stabilize or even improve vision much more reliably and has become the therapeutic option of choice for patients with an ONSM and progressive visual loss (18–20). In our series, 1 patient (Case 5) with an ONSM experienced improvement in visual acuity on the affected side from 20/80 to 20/25 after surgery. Although this patient had subsequent radiation and a second orbital surgery for further nerve decompression, vision has remained stable for 12 years. Conversely, in the other patient with ONSM (Case 6), acuity dropped from 20/30 to CF shortly after surgery and remained poor despite a subsequent course of fractionated radiotherapy.

Of the 3 patients ultimately diagnosed with sarcoid optic neuropathy, only one of their biopsies demonstrated the characteristic noncaseating granulomas. One pediatric patient (Case 9) was presumed to have sarcoidosis based on concurrent idiopathic thrombocytopenia purpura, an elevated serum angiotensin-converting enzyme level, optic nerve enhancement, and a biopsy that was negative for malignancy. He has been treated with intravenous immunoglobulin and long-term systemic immunosuppression without involvement of the fellow optic nerve. Another patient (Case 10) was treated presumptively with both proton beam radiation and chemotherapy for a suspected optic nerve glioma, but vision declined to NLP. With clinical signs suggesting fellow eye involvement, left ONB was performed and the biopsy specimen showed scant nonspecific inflammation. The patient was soon diagnosed with sarcoidosis from a transbronchial biopsy that contained noncaseating granulomas (9). This patient has been...
FIG. 1. Optic nerve biopsy specimens. Case 1: A. Metastatic adenocarcinoma composed of pleomorphic cells (hematoxylin and eosin, ×20). B. Cells stain for cytokeratin AE 1/3 (×20). Case 2: C. Anaplastic astrocytoma with pleomorphic glial cells (arrows) (hematoxylin and eosin, ×20). Case 4: D. Schwannoma composed of spindle cells arranged in alternating cellular and hypocellular regions (arrows) resembling Antoni A and B patterns (hematoxylin and eosin, ×5). E. Although classic Verocay bodies are not seen, Verocay-like bodies (arrowheads) and hyalinized blood vessels (arrows) are present (hematoxylin and eosin, ×20). F. Tumor cells are strongly positive for protein S100 (×10). G. Reticulin stain shows pericellular basement membrane deposition (×20). Stains negative for epithelial membrane antigen, cytokeratin, neurofilament, glial fibrillary acidic protein, and Ki-67 (less than 1%) are not shown. Case 8: H. Sarcoidosis. Noncaseating and hyalinized granulomas (arrowheads) (hematoxylin and eosin, ×20). Stains were negative for acid-fast bacilli and fungal and bacterial organisms. Case 12: Presumed varicella zoster virus optic neuropathy. I. Optic nerve cross section with atrophied fascicles (hematoxylin and eosin, ×2). J. Loss of axons confirmed with neurofilament stain (×2). Case 13: Presumed rheumatoid pachymeningitis. K. Optic nerve meningeal biopsy with focal aggregates of chronic inflammatory cells, mainly lymphocytes (hematoxylin and eosin, ×20). Case 14: Presumed toxic optic neuropathy caused by tacrolimus. L. With routine staining, there is no apparent optic nerve abnormality (hematoxylin and eosin, ×20). M. Optic nerve axons show diffuse loss of myelin (luxol fast blue, ×20).
followed on mycophenolate mofetil for 4 years and has retailed 20/20 acuity in the right eye. The lack of sensitivity for sarcoidosis in this small series does not necessarily argue against the value of ONB. In both patients with nondiagnostic biopsies, the ONB was important in excluding a neoplasm. Although no patient in our series lost further vision in the fellow eye, it should be noted that 3 patients with fellow eye involvement (Cases 12, 14, and 15) already had CF or worse vision in both eyes at the time of biopsy. In these patients, establishing a diagnosis was deemed important in potentially saving their life. The extremely poor bilateral vision at the time of biopsy raises the question of whether clinicians hesitate too long before obtaining ONBs. In addition, some of our patients had disease processes with poor prognoses, suggesting that visual decline was unavoidable.

In this clinical series, open biopsies of the optic nerve were performed in the majority of cases. Although CT-guided FNAB represents a minimally invasive alternative, the technique has not gained popularity partly because of limited tissue sampling, decreased utility in lesions with high fibrous content, and preference for en bloc removal of benign tumors (22). We were able to obtain adequate tissue sampling and/or tumor removal from an open approach and save for possible inadequate tissue sampling in the 2 non-diagnostic cases of sarcoidosis (Cases 9 and 10) and in the one case where no clinical diagnosis was reached (Case 15).

There are a number of limitations in this long-term retrospective chart review. These include subject or case selection bias in which severe visual loss prompted biopsy, small sample size, referral bias of difficult cases to a tertiary center, lack of a control group, and recall bias where cases seen many years ago were not as easily identified for inclusion. As a number of our patients were medically ill, the follow-up interval was limited. Soon after biopsy, several patients expired, while others were transferred to hospice or closer to their homes.

In conclusion, ONB should be strongly considered in patients with progressive optic neuropathy causing profound vision loss and when standard testing is unable to ascertain an etiology. ONB carries significant risk of morbidity in cases where the biopsied side retains vision. However, biopsy may be beneficial in substantiating the diagnosis and, if performed early in the clinical course, possibly lead to treatment that would halt or prevent vision loss in the fellow eye.

ACKNOWLEDGMENT

The authors thank Molly Nadelson, MD, for contributing to data collection.

REFERENCES


Novel Treatment for Radiation Optic Neuropathy With Intravenous Bevacizumab

Osman Farooq, MD, Norah S. Lincoff, MD, Nicolas Saikali, MD, Dheerendra Prasad, MD, MCh (Neurosurgery), Robert S. Miletich, MD, PhD, Laszlo L. Mechtler, MD

Abstract: Radiation optic neuropathy is a devastating form of vision loss that can occur months to years after radiation therapy for tumors and other lesions located in close proximity to the visual pathways. We present the case of a 24-year-old woman who underwent external beam radiation for treatment of a tectal pilocytic astrocytoma, and 5 years later she developed bilateral radiation optic neuropathy and radiation necrosis of the right temporal lobe. We opted to treat her with intravenous bevacizumab with 3 doses every 3 weeks, as well as dexamethasone and pentoxifylline. After the first infusion of bevacizumab, the patient noted improvement in vision and color vision, and a follow-up magnetic resonance imaging study showed that the previous enhancement of the optic nerves and chiasm was diminishing. Her vision improved dramatically and has remained stable over a 3-year period.


Radiation optic neuropathy (RON) typically leads to devastating vision loss in one or both eyes (1–3). Recently, there have been reports of anti–vascular endothelial growth factors used in the treatment of radiation damage, both in the eye (4–7) and the central nervous system (CNS) (8–11). We report the use of this therapeutic agent in a patient with RON.

CASE REPORT

A 26-year-old woman presented 10 years previously with headaches and somnolence. At that time, brain magnetic resonance imaging (MRI) revealed a tectal mass that was thought to be a pilocytic astrocytoma. Eight years ago, she developed obstructive hydrocephalus as a result of the growth of the tumor (Fig. 1). The patient underwent left ventriculostomy and resection of the tumor that confirmed the diagnosis. She received intensity-modulated radiation therapy of 54 Gy in 30 fractions at 1.8 Gy per fraction. Mean doses were as follows: right optic nerve 4.4 Gy (range: 1.2–10.3 Gy), left optic nerve 6.6 Gy (range: 2.8–10.4 Gy), and optic chiasm 24.8 Gy (range: 11.4–45.8 Gy). A Varian 21/CD linear accelerator using 6 MeV photons, with a 56 leaf (1-cm leaf width), multileaf collimator and sliding window technique was used (Fig. 2). Three months later, the patient underwent a second craniotomy for tumor resection.

FIG. 1. T1 sagittal magnetic resonance imaging (MRI) shows tectal tumor (asterisk).
recurrence, followed by treatment with carboplatin/vincristine chemotherapy for 15 months.

Five years and 3 months later, the patient reported headaches and vision loss in the right eye. She described her vision as “white.” Visual acuity was 20/80, right eye, and 20/40, left eye. Brain MRI showed a subcortical area of hyperintensity in the right temporal lobe (Fig. 3). This was thought to be consistent with radiation damage, and the
patient was started on intravenous methylprednisolone for 5 days, followed by 4 mg of dexamethasone daily.

Two weeks later, optic nerve enhancement was noted bilaterally (Fig. 4), which also was felt to be caused by radiation damage. The dose of dexamethasone was increased to 4 mg twice daily. Visual acuity was no light perception, right eye, and 20/100, left eye. Positron emission tomography (PET) was consistent with inflammatory changes of radiation injury (Fig. 5).

Four weeks after the onset of visual loss, the patient was given 675 mg of intravenous bevacizumab (7.5 mg/kg) with 3 doses every 3 weeks, as well as 8 mg of dexamethasone per day and 400 mg of pentoxifylline per day. MRI scanning 2 weeks after initiating treatment with bevacizumab showed decreasing enhancement of the optic nerves and chiasm.

During the second week of treatment, the patient noted improvement in her visual acuity and reported periods of extreme clarity for 5 to 10 minutes at a time. Visual acuity was 20/50, right eye, and 20/100, left eye. The patient identified the color plates slowly, but correctly, in each eye. Pupils reacted poorly to light, and automated visual fields revealed a bitemporal hemianopia (Fig. 6A). Bilateral optic atrophy was present. Over the next 4 weeks, her subjective episodes of clarity increased to hours at a time, and she regained acuity of 20/25, right eye, and 20/40, left eye, with further improvement in her visual fields (Fig. 6B).

Six weeks after initiation of bevacizumab, brain MRI revealed complete resolution of the areas of enhancement (Fig. 7). With 3 years of follow-up, the patient’s vision has stabilized at 20/20, right eye, and 20/25, left eye. Color vision is intact bilaterally. Subtle bitemporal visual field defects remain, and both optic discs are pale.

**DISCUSSION**

This report suggests that intravenous bevacizumab may be an effective treatment of RON. Our patient noted dramatic improvement in her vision within 4 weeks of initiation of therapy, and there was complete resolution of brain and optic nerve enhancement within 6 weeks. Over a 3-year period, her visual function has remained stable.

Bevacizumab has been reported to be effective in the treatment of radiation necrosis of the CNS. Gonzalez et al (8) demonstrated the benefit of using bevacizumab or...
bevacizumab with a chemotherapeutic agent (carboplatin, irinotecan, temozolomide) in 15 patients diagnosed with cerebral radiation necrosis. All patients showed improvement in both fluid-attenuated inversion recovery (FLAIR) and postcontrast T1 MRI abnormalities at an average of eight weeks after beginning bevacizumab. Torcuator et al (10) reported 6 patients with biopsy-proven cerebral radiation necrosis treated with bevacizumab between 2006 and 2008 and documented improvement in both FLAIR and contrast-enhanced T1 images. Levin et al (12) postulated that aberrant production of vascular endothelial growth factor is involved with radiation necrosis of the brain and that even short treatment (fewer than four doses) with bevacizumab seems to turn off the cycle of radiation damage. Levin et al (12) enrolled 14 patients into a placebo-controlled, randomized, double-blind study to evaluate the effect of bevacizumab in treating CNS radiation necrosis. In evaluating MRI findings, 0 of 7 patients receiving placebo responded, whereas all 5 of 5 randomized and 7 of 7 crossover patients showed regression of necrotic lesions. Only 2 patients had recurrence of MRI findings, and both were retreated with bevacizumab.

Adverse effects from systemic administration of bevacizumab include cardiovascular (hypertension, thromboembolism), CNS (headache, pain syndromes, tumor recurrence), gastrointestinal (abdominal pain, nausea, vomiting, anorexia), hematologic (hemorrhage, leukopenia, neutropenia), and musculoskeletal (weakness, myalgias) abnormalities (13–15). These adverse effects are fortunately rare, and none were observed in our patient.

Although pentoxifylline was part of our patient’s treatment protocol, its therapeutic efficacy is unproven. This hemorrhheologic methylxanthine derivative might increase tissue perfusion by reducing platelet aggregation and reduce cytokine-mediated inflammation by inhibiting tumor necrosis factor and fibroblast growth factor 2. Yet in a comprehensive review, Nieder et al (16) found “little evidence” that pentoxifylline has any significant effect on radiation therapy. We thus believe that it was the bevacizumab that was responsible for the patient’s visual improvement.

We acknowledge that our findings will need to be confirmed in a randomized trial to determine the optimal duration and effectiveness of treatment in a large study group. However, in the interim, we recommend that bevacizumab be considered in patients suffering acute visual loss from RON.

REFERENCES
Erythropoietin Treatment for Methanol Optic Neuropathy

Mohammad Pakravan, MD, Nasrin Sanjari, MD

Background: To present the effect of erythropoietin for the treatment of methanol optic neuropathy.

Methods: Two patients with methanol optic neuropathy were treated with 10,000 IU of intravenous erythropoietin twice a day for 3 days, 500 mg of methylprednisolone twice a day for 5 days (followed by 2 weeks of oral prednisolone [1 mg/kg per day]), and daily doses of vitamin B12, vitamin B6, and folic acid for 1 month.

Results: At presentation, the patients had no perception of light in both eyes, associated with mildly swollen optic discs. Both responded dramatically to the treatment regimen. In the first patient, visual acuity improved to 20/20 in both eyes within 3 days, whereas in the second patient, visual acuity returned to counting fingers at 6 feet, right eye, and 20/30, left eye, within 3 weeks.

Conclusion: Intravenous erythropoietin may be an effective adjuvant when combined with current treatment for patients with methanol optic neuropathy.

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Methanol is a clear, colorless, and flammable liquid produced by the reaction of hydrogen with carbon monoxide or carbon dioxide. Methanol is metabolized in the body to formaldehyde by alcohol dehydrogenase, following which formaldehyde is rapidly converted to formic acid, a metabolite that causes the majority of the toxicity associated with methanol (1). Methanol is highly toxic for humans if ingested. Ingestion of as little as 10 mL can result in complete and permanent visual loss from bilateral optic neuropathy, and 30 mL can be fatal, although the fatal dose is typically 100–125 mL. Toxicity usually occurs from accidental ingestion. For example, in some countries, alcoholic beverages are legally prohibited, and homemade alcoholic drinks containing methanol are a source of toxicity (2).

A variety of substances are used to treat methanol optic neuropathy. Fomepizole has been found to be safe and effective in the treatment of methanol poisoning, often resulting in both resolution of metabolic acidosis and complete restoration of vision. However, it is expensive and not readily available, particularly in developing countries (3).

Ethanol, B-group vitamins, and systemic steroids often are used, but with limited success. In such cases, the final visual acuity is in the range of counting fingers or worse (4).

Erythropoietin is a glycoprotein that stimulates red blood cell differentiation by preventing apoptosis of erythroid progenitors in the bone marrow. It has shown that erythropoietin also has neuroprotective and neuroregenerative properties in the central nervous system (5), and several small case series have documented improvement in vision when used in patients with nonarteritic anterior ischemic optic neuropathy and traumatic optic neuropathy (6,7).

We report 2 patients with methanol-induced toxic optic neuropathy who experienced dramatic visual improvement when they were treated with a combination of intravenous erythropoietin, systemic corticosteroids, vitamins, and folic acid.

CASE REPORTS

Case 1
A 30-year-old man was referred with a chief complaint of bilateral vision loss. He had no history of systemic disease and took no medications. He had drunk about 100 mL of a homemade alcoholic beverage 3 days previously. Subsequent analysis of the drink revealed that it contained methanol. We later found that 7 people had consumed the same drink, 3 of whom experienced vision loss, leading to complete blindness in 2, 1 of whom was our patient. A third patient died from severe metabolic acidosis despite
treatment with hemodialysis and other supportive measures. The other 3 individuals had no visual or systemic deficits.

This patient’s visual acuity had begun to decrease within 24 hours after ingestion. At presentation, his vital signs were normal, and he was alert and cooperative. Visual acuity was no light perception (NLP) in both eyes. Pupils were dilated and nonreactive to light. Slit-lamp biomicroscopy revealed no abnormality, and intraocular pressures were normal. Fundus examination revealed mild hyperemic disc swelling bilaterally. Systemic and neurological assessments were unremarkable. Optical coherence tomography (OCT) showed marked thickening of peripapillary retinal nerve fiber layer (RNFL), with average thicknesses of 160 and 171 μm in the right and left eye, respectively (Fig. 1).

The patient was admitted to hospital. Complete blood count, erythrocyte sedimentation rate, and C-reactive protein were within normal limits as was a metabolic panel. The patient’s blood methanol concentration was 5 mmol/L (normal, 5–15 mmol/L). Magnetic resonance imaging of the brain and orbits was unremarkable.

The patient was begun on intravenous methylprednisolone (500 mg twice a day) combined with vitamin B12 (100 mg/day), vitamin B6 (100 mg/day), and folic acid (10 mg/day). Because the patient’s serum methanol was within the normal range, we chose not to treat him with ethanol. After 2 days, the patient’s vision was unchanged. After approval from the ethics committee of the Ophthalmic Research Center and after obtaining written informed consent, the patient was given infusions of 10,000 IU of intravenous erythropoietin twice a day. After the first 2 infusions of erythropoietin, visual acuity improved to 20/200, right eye, and hand movements, left eye. Erythropoietin infusions along with methylprednisolone and vitamins were continued, and 3 days after initiation of erythropoietin, the patient’s visual acuity improved to 20/20 in both eyes, pupils were reactive to light, and visual fields were performed (Fig. 2). We continued erythropoietin for 3 days, and methylprednisolone for 5 days, followed by oral prednisolone (1 mg/kg per day) for 2 weeks. Vitamins were given for 1 month. After 3 weeks, the patient’s visual acuity remained 20/20 bilaterally, and the optic discs become mildly pale. OCT showed reduction in the peripapillary RNFL compared with pretreatment values, with average thicknesses of 102 and 114 μm in the right eye and left eye.
eye, respectively, and visual fields showed significant improvement.

Case 2
A 35-year-old man was referred 1 week after ingestion of a homemade alcoholic beverage containing methanol. He had experienced 24 hours of unconsciousness and severe acid–base imbalance and had been treated with systemic steroids, intravenous ethanol, hemodialysis, and supportive care. Despite improvement in his general condition, he was noted to have no perception of light in either eye. When he arrived at our hospital, his metabolic panel and blood methanol level were within normal limits. Visual acuity was NLP in both eyes, with moderately dilated pupils that were non-reactive to light stimulation. Slit-lamp biomicroscopy and intraocular pressures were normal, whereas fundus examination revealed mild swelling of both optic discs (Fig. 3).

After obtaining informed consent, the patient was treated with 10,000 IU of intravenous erythropoietin twice a day for 3 days, 500 mg of methylprednisolone twice a day for 5 days (followed by 2 weeks of oral prednisolone [1 mg/kg per day]), vitamin B12 (100 mg/day), vitamin B6 (100 mg/day), and folic acid (10 mg/day) for 1 month. There was no change in the patient’s vision over the next 5 days, but 2 weeks later, visual acuity was counting fingers at 6 feet, right eye, and 20/30, left eye. The pupils were sluggishly reactive to light, and the optic discs were pale.

DISCUSSION
Our 2 patients with methanol optic neuropathy responded dramatically to a combination of intravenous erythropoietin, methylprednisolone, vitamins, and folic acid. The effect of methanol poisoning on the optic nerve is complex. The only fundus lesion observed both ophthalmoscopically and angiographically is optic disc edema because of stasis of axoplasmic flow resulting from the inhibition of oxidative metabolism (8). This axoplasmic slowing appears to occur from swelling of the cytoplasm of the astrocytes and oligodendroglia in the retrolaminar space as well as from compressive obstruction of orthograde axoplasmic flow. The mechanism by which this swelling occurs appears to be a combination of metabolic acidosis and formic acid inhibition of cytochrome C oxidase, resulting in histotoxic hypoxia (9). In addition, methanol can cause central necrosis of the retrolaminar portion of the optic nerve, and necrosis of the basal ganglia, leading to both blindness and acute encephalopathy (10,11). Necrosis of the optic nerves may, in part, be due to alteration in blood flow (11,12).

Although methanol toxicity also leads to retrobulbar demyelination, it is unclear whether this is a primary effect or secondary to axonal damage. Sharpe et al (13) found that optic nerve axons were preserved, yet documented myelin degeneration behind the lamina cribrosa and in cerebral hemispheric white matter.

As in our patient, methanol optic neuropathy causes increased thickness of peripapillary RNFL in the acute phase and diffuse thinning chronically (14). Treatment strategies for methanol optic neuropathy are based on detoxification. Fomepizole, an inhibitor of alcohol dehydrogenase, is very beneficial in treating methanol toxicity, but is not readily available, particularly in developing countries (3). Other treatment protocols, including intravenous ethanol combined with vitamin B1, B6, and B12, have produced variable results (15). High-dose IV corticosteroids often are used, as it is believed that this treatment may inhibit demyelination. Abrishami et al (16) administered high doses of intravenous steroids for 3 days, followed by oral prednisolone (1 mg/kg) for 11 days in 6 patients with vision ranging from 0.93 to 0.86 logarithm of the minimum angle of resolution (logMAR) (equivalent to 20/150–20/160). Three months after treatment, mean visual acuity ranged from 0.33 to 0.2 logMAR (equivalent to 20/30–20/40). In contrast, Fujihara et al (14) found
that intravenous methylprednisolone given 6 days after ingestion of methanol was not effective in improving vision (14).

Group B vitamins are thought to decrease the toxic metabolites of methanol, particularly in the brain (17). In one series of 15 patients with methanol optic neuropathy, the combination of steroids, vitamin B12, and folate acid resulted in visual improvement (18).

The ability of erythropoietin to suppress neuronal apoptosis and decrease the inflammatory response has been demonstrated in different models of brain ischemia and inflammation (5). Erythropoietin also has been shown to have beneficial effects on retinal ganglion cells, including reduction in apoptosis and increased survival after experimental optic nerve transaction (19), and in the setting of experimental autoimmune encephalomyelitis, chronically elevated intraocular pressure, and diabetic retinopathy (20,21). This has led to reports of systemic and intravitreal injection of erythropoietin to treat patients with nonarteritic anterior ischemic optic neuropathy and traumatic optic neuropathy with beneficial effects (6,7) and without toxicity (6,22). Erythropoietin is readily available and inexpensive, making it a viable treatment option in developing countries.

We believe that significant vision improvement of our 2 patients is attributable to the additive effect of erythropoietin when combined standard treatments. However, additional studies are needed to determine whether erythropoietin alone or in combination with other therapeutic agents provide optimal visual recovery in patients with methanol optic neuropathy.

ACKNOWLEDGEMENT

The authors thank Neil Miller, MD, for his kind guidance and constant supervision and support in completing this study.

REFERENCES

Recurrent Third Nerve Palsy as the Presenting Feature of Neurofibromatosis 2

Victoria J. M. Barrett, MB ChB, FRCOphth, Mei H. Tan, MB BCh BAo, PhD, FRCOphth, John S. Elston, MD, FRCOphth

Abstract: Neurofibromatosis 2 (NF2) is a rare autosomal dominant disorder associated with the development of multiple central and peripheral nervous system tumors. Patients with NF2 are often diagnosed in adulthood, with symptoms of an isolated tumor or hearing loss associated with vestibular schwannomas. Diagnosing NF2 in children is complicated by the fact that the diagnostic criteria often are not met at presentation and there is usually no family history of the disease. The authors describe the diagnostic challenge posed by a pediatric patient who developed a relapsing and remitting third nerve paresis and was later diagnosed with NF2. A mechanism for the recurrent cranial mononeuropathy is proposed.

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Recurrent third nerve palsy in any age group is rare; in childhood, most cases are attributed to ophthalmoplegic migraine (OM). This entity is characterized by onset in the first decade of life with headache or periorbital pain, nausea, and the simultaneous or subsequent development of a unilateral third nerve palsy followed by recovery over several weeks. During the acute phase, thickening and enhancement of the cisternal segment of the involved third nerve may be seen on brain magnetic resonance imaging (MRI), which resolves with recovery of third nerve function. Ipsilateral recurrences are common. OM is no longer classified as a migraine variant but as an inflammatory neuralgia; resolution of the palsy is accelerated by systemic steroid treatment (1).

We present a case in which an ipsilateral isolated third nerve palsy occurred twice in the first 6 years of life of a healthy girl with complete spontaneous recovery. On both occasions, patient evaluation was unremarkable. Recurrence at the age of 9 years led to discovery of a schwannoma of the affected third nerve and bilateral vestibular schwannomas.

CASE REPORT

A healthy 2-year-old girl presented with complete right third nerve palsy with pupillary involvement that evolved over 1 week. There was no history of preceding illness or trauma. General physical and neurologic examinations were otherwise normal. The patient was born at term by Cesarean section and her medical history was unremarkable. Her visual development was normal. Her parents were both in good health, and there was no relevant family history.

Computed tomography (CT) and contrast-enhanced MRI of the brain were normal. Hematological and biochemical screening was negative for inflammatory markers and autoantibodies, including antiacetylcholine receptor and anti-GQ1b. Lumbar puncture showed normal opening pressure and cerebrospinal fluid.

The patient remained well, and her ptosis resolved within 3 weeks and pupillary and eye movement function were normal within 6 weeks. Because the right eye became amblyopic, a patching regimen was begun, and the patient regained visual acuity of 20/30.

At the age of 5 years, she again developed a painless isolated pupil involving right third nerve palsy over the course of a week. An unenhanced MRI of the brain was normal. Again, there was complete recovery of right third nerve function over a 6-week period.

At the age of 9 years, a partial right third nerve palsy with partial pupillary dilation developed slowly over 6 months. There was no sensory disturbance, and other cranial nerve function was normal. A focal posterior lens opacity in the right eye was noted for the first time. Contrasted MRI

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of the brain showed enhancement of the subarachnoid portion of the right third nerve consistent with a schwannoma (Fig. 1) and small bilateral vestibular schwannomas (Fig. 2).

The patient was thought to have NF2, and this was confirmed by genetic testing. A lymphocyte DNA sample revealed a single nucleotide substitution c.169C>T in exon 2 of the NF2 gene. This mutation results in a premature truncation of the polypeptide chain and, therefore, was a pathogenic mutation. Because there was no family history of neurofibromatosis and screening of other family members was unremarkable, this was presumed to be a de novo mutation.

Audiology testing showed no hearing loss. Spinal MRI revealed a small meningoïd at the T3 level 3 that was asymptomatic. The diagnosis and implications of NF2 were explained to the patient’s parents, and she was referred to the medical service dealing with NF2 patients. Her right third nerve paresis gradually worsened over the ensuing 2 years.

**DISCUSSION**

Isolated palsies of the third, fourth, and sixth nerves have been reported infrequently in NF2 patients (2). We are unaware of any other published cases of NF2 presenting with a relapsing-remitting third nerve palsy.

There are 2 previous reports describing recurrent third nerve palsy beginning in childhood in individuals who were subsequently shown to have the magnetic resonance changes compatible with ipsilateral oculomotor nerve schwannoma (3,4). There were no other stigmata of NF2. In both cases, the ophthalmoplegic attacks were associated with focal headache and systemic symptoms, including nausea, supporting the diagnosis of OM. Thickening and enhancement of the third nerve may persist after an attack of OM, and it may be that repeated episodes of inflammatory demyelination followed by remyelination led to focal schwann cell proliferation giving the appearance of schwannoma on MRI. In contrast, in our patient, there were no clinical features to suggest an inflammatory etiology for the initial 2 episodes of third nerve palsy, and neuroimaging was normal on both occasions.

We propose a different mechanism in our case. Schwannomas develop in NF2 as a result of a mutation, which inactivates the tumor suppressor gene located on chromosome 22q12 whose 17 exons encode a 69-kDa protein product called merlin found in schwann cells (5,6). Merlin is important in the control of schwann cell metabolism, including cell-to-cell interactions and both intracellular and intercellular signaling pathways. Schwannomas, consisting of abnormal mutated schwann cells in a collagen matrix, develop when the function of the normal NF2 allele is inactivated. The mechanism of inactivation is uncertain.

**FIG. 1.** Contrasted T1 coronal magnetic resonance imaging of the brain shows an area of abnormal enhancement in the subarachnoid portion of the right third nerve (arrow), consistent with a schwannoma.

**FIG. 2.** Contiguous contrast-enhanced T1 axial magnetic resonance images demonstrate bilateral vestibular schwannomas (arrows).
And in tumorigenesis, merlin dysfunction causes defects in the stability of the cell plasma membrane as it connects to the cytoskeleton, leading to cell deformation and instability (7). We speculate that merlin dysfunction in our patient compromised one or more schwann cells integral to right third nerve function before the development of a tumor detectable on MRI. This resulted in 2 episodes of acute conduction block causing a third nerve palsy, which spontaneously recovered. When NF2 presents in childhood with a mononeuropathy (e.g., facial palsy), spontaneous improvement may occur, possibly by the same phenomenon (8), with eventual progression of the cranial nerve palsy. We recognize that there are other possible explanations, including the presence of a microscopic schwanna not detectable by MRI at the time of the initial presentation or that the initial ophthalmoplegia was unrelated to the development of the schwanna and the diagnosis of NF2.

Our case highlights the difficulty in diagnosing NF2 in pediatric patients (9). NF2 has wide phenotypic variability, and only 18% of patients present in the first 15 years of life. Typically, adults initially develop hearing loss, tinnitus, and imbalance because of vestibular schwannomas; less than 30% of pediatric cases present this manner (9). Instead, children present with a mononeuropathy, most commonly affecting the seventh cranial nerve or rarely the peroneal nerve causing foot drop. The cranial nerve palsy may improve spontaneously and precede detection of a vestibular schwanna by many years (8–10).

Childhood NF2 is associated with more severe disease because of associated nonsense or frame-shift mutations that lead to truncation of a protein product. This was true in our patient, where the nucleotide substitution c.169C>T resulted in a nonsense mutation of the arginine residue at position 57 (p.Arg57X) and premature termination of the polypeptide chain. This also is true of mutations in exons 1 to 5 (9). In our patient, the mutation was detected on analysis of lymphocytes, eliminating mosaicism. Mosaicism occurs with high frequency in NF2, and patient with mosaicism have tumors confined to a specific level of the neuraxis or milder of asymmetric involvement.

Using the Manchester criteria (11), the presence of bilateral vestibular schwannomas coupled with the genetic findings enabled a diagnosis of NF2 to be made in our patient (Table 1). The characteristic focal lens opacity in the form of a posterior subcapsular cataract also was consistent with this diagnosis.

### REFERENCES


### TABLE 1. Diagnostic criteria for neurofibromatosis type 2

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<th>Major Criteria</th>
<th>Additional Criteria</th>
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<tr>
<td>Bilateral VS or family history of NF2 plus</td>
<td>Unilateral VS plus any 2 of: meningioma, glioma, neurofibroma, schwannaoma, and posterior capsular lens opacity</td>
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<tr>
<td>1) Unilateral VS or</td>
<td>or</td>
</tr>
<tr>
<td>2) Any 2 of: meningioma, glioma, neurofibroma, schwannaoma, and posterior subcapsular cataract</td>
<td>Multiple meningioma (2 or more) plus unilateral VS or any two of: glioma, neurofibroma, schwannaoma, and posterior subcapsular lens opacity</td>
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NF2, neurofibromatosis type 2; VS, vestibular schwannaoma.

Modified from the study by Evans et al. (11).
Vitreous Hemorrhage Secondary to Optociliary Shunt Vessels From Papilledema

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Abstract: A 15-year-old adolescent girl with idiopathic intracranial hypertension was noted to have papilledema and optociliary shunt vessels. Medical management was controlling her symptoms, but vision deteriorated rapidly in the left eye secondary to a vitreous hemorrhage. Given the lack of any other cause for vitreous hemorrhage, it most likely originated from the shunt vessels. Optic nerve sheath fenestration was performed in an effort to promote regression of the papilledema and the shunt vessels. Our case illustrates a rare complication of optociliary shunt vessels in the setting of papilledema.

CASE REPORT

A healthy 15-year-old adolescent girl, with normal visual function, was noted to have bilateral optic disc edema during a routine eye examination. One month later, she developed mild sporadic headaches. Magnetic resonance imaging (MRI) of the brain revealed an empty sella, flattening of the posterior globes, and chronic pansinusitis. She was treated with antibiotics, and her headaches resolved, but her optic disc edema persisted.

During neuro-ophthalmic evaluation 6 months later, the patient denied headaches, tinnitus, transient visual obscurations, or diplopia. She was not taking vitamin A or tetracycline derivatives. She had a body mass index of 20.1 kg/m² without a history of recent weight gain. Her blood pressure was 100/60 mm Hg. Visual acuity was 20/25 in each eye. Color vision, slit-lamp examination, pupils, and ocular motility were normal. She had bilateral disc edema with optociliary shunt vessels (Fig. 1). Disc drusen were not detected on B-scan ultrasonography.

Lumbar puncture demonstrated cerebrospinal fluid (CSF) opening pressure (OP) of 25 cm H₂O, but CSF analysis was not performed. Three weeks after lumbar puncture, the patient developed daily headaches requiring ibuprofen, but her examination was unchanged. One month later, she noted acute vision loss in the left eye. Visual acuity was 20/60 in the left eye with a vitreous hemorrhage.

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The authors report no conflicts of interest.

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Repeat lumbar puncture showed CSF OP of 28 cmH₂O and normal CSF constituents. MRI of the brain and orbits and magnetic resonance venography showed bilateral flattening of the posterior sclera, empty sella, a hypoplastic left transverse sinus, and distal right transverse sinus stenosis.

The patient was begun on oral acetazolamide 250 mg twice daily. At follow-up 10 days later, she complained of postural headaches and muscle cramps. Visual acuity was 20/25, right eye, and 20/40, left eye, with bilateral optic disc edema, shunt vessels, and vitreous hemorrhage in the left eye. A left optic nerve sheath fenestration was performed 10 months after the disc edema was first noted and 1 month after her vitreous hemorrhage. One week postoperatively, visual acuity was 20/25, right eye, and 20/30, left eye, with improvement of left optic disc edema and shunt vessels. Six weeks postoperatively, visual acuities were 20/20, right eye, and 20/25, left eye, with near-complete resolution of the vitreous hemorrhage. There was slight improvement of the disc edema with persistent shunt vessels in the right eye and substantial improvement of the disc edema with decreased prominence of the shunt vessels in the left eye (Fig. 3).

**DISCUSSION**

Optociliary shunt vessels may be congenital but are more frequently reported in association with ophthalmic conditions that produce impaired venous outflow, including central retinal vein occlusion (1), optic nerve sheath meningioma (2), optic nerve glioma, optic disc drusen (3), and chronic papilledema (4). Pre-existing anastamotic capillary collaterals between the retinal and choroidal circulations undergo compensatory dilation when central retinal venous pressure is elevated (4). Flow within these shunts has been documented on the optic disc during the venous phase of fluorescein angiography and from the disc margin to vortex veins using indocyanine green angiography (5).

Although vitreous hemorrhage with abnormal vessels on the optic disc is common with disc neovascularization, particularly in diabetic patients, to our knowledge, vitreous hemorrhage secondary to optociliary shunts has not been described. The combination of papilledema, disc swelling from raised intracranial pressure, and vitreous hemorrhage has been reported with Terson syndrome due to subarachnoid hemorrhage, cerebral venous sinus thrombosis, and leukemic infiltration of the optic nerve (6). Subretinal hemorrhages in the setting of chronic papilledema from idiopathic intracranial hypertension also has been reported (7). These cases include patients found to have underlying peripapillary choroidal neovascular membranes (8), but none, to our knowledge, have had subretinal or vitreous hemorrhage from optociliary shunt vessels. Additionally, although choroidal neovascularization, disc hemorrhage, and shunt vessels have been reported in patients with disc drusen (3), we could find no published cases of vitreous hemorrhage in that setting. In our patient, vitreous hemorrhage could have occurred secondary to an unrelated condition, such as a posterior vitreous detachment, trauma, or Valsalva retinopathy, but we found no evidence of this based on history or examination.
Case reports have demonstrated shunt vessel regression after treatments that reduce papilledema (9–13). There are documented cases of optociliary shunt vessels disappearing in children after CSF shunting procedures (11), and in adults when intracranial pressure is reduced medically combined with lumbar puncture (12), or after surgical removal of a brain tumor (13). Reduction in the caliber of the optociliary shunt vessels has been shown to occur within 3 days of normalization of central retinal venous pressure (9,10). The optociliary vessels in the unoperated eye of our patient did not regress, indicating that medical management alone was inadequate to control this complication. Given that optociliary shunts from raised intracranial pressure causing papilledema may be reversible, surgical intervention with optic nerve sheath fenestration to reduce the risk of further vitreous hemorrhage may be warranted. Because vitreous hemorrhage frequently will resolve spontaneously and further hemorrhage may not occur, the risk of permanent vision loss from optic nerve sheath fenestration must be balanced against the risk of vision impairment either from vitreous hemorrhage or from ongoing papilledema.

REFERENCES
Isolated Sixth Nerve Palsy From Hemorrhage of a Pontine Cavernous Malformation

Robert M. Mallery, MD, Joshua P. Klein, MD, PhD, Misha L. Pless, MD

Abstract: A 32-year-old woman who developed binocular horizontal diplopia was found to have an isolated fascicular sixth nerve palsy secondary to hemorrhage of a cavernous malformation within the left pontine tegmentum. There was sparing of the paramedian pontine reticular formation and absence of a horizontal gaze palsy. The natural history of cavernous malformations and a mechanism by which hemorrhage of these vascular lesions may produce minimal neurologic signs, including isolated ocular motor cranial nerve palsies, is discussed. Magnetic resonance imaging (MRI) that includes susceptibility-weighted sequences leads to their accurate diagnosis.

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A healthy 32-year-old woman awoke with binocular horizontal diplopia and a sensation of pressure in her head. On examination, there was a left esotropia measuring 20 prism diopters in primary gaze and limited abduction of the left eye. Ductions and torsional eye movements were otherwise intact, and the remainder of the neurologic examination was normal. Given her young age and lack of vascular risk factors, brain magnetic resonance imaging (MRI) was obtained that demonstrated a 5 × 5-mm² lesion within...
the left pontine tegmentum, consistent with a cavernous malformation (Fig. 1). The lesion was deemed inoperable, and her clinical deficit improved spontaneously over 6 months. Brain MRI at that time showed resolution of hemorrhage and edema (Fig. 2).

A lesion within the pontine tegmentum classically causes an ipsilateral, conjugate, horizontal gaze palsy because of either a failure of saccadic initiation by the excitatory burst neurons within the paramedian pontine reticular formation or loss of their axonal connections to the ipsilateral sixth nerve nucleus. In contrast, our patient presented with an isolated abduction deficit of the left eye, presumably from involvement of the left sixth nerve fasciculus. The remarkable absence of neighborhood signs in this case provides evidence that hemorrhage of cavernous malformations within eloquent areas of the brainstem may present with relatively minor neurologic deficits, including isolated ocular motor cranial nerve palsies.

Cavernous hemangiomas are vascular malformations that occur in approximately 0.4%–0.8% of the general population and typically cause initial symptoms in the third or fourth decade (1–4). They are well-circumscribed lesions that may reach several centimeters in diameter and consist of thin-walled, sinusoidal-like blood vessels. The risk of hemorrhage is estimated at 0.1%–3.1% per lesion per year, and the risk increases if there has been a previous hemorrhage (1). Their prevalence at various sites in the brain is proportional to brain volume, and the pons is thus a site of predilection in the brainstem accounting for approximately 62%–75% of brainstem cavernous malformations (2,4). The risk of hemorrhage from an infratentorial location has been reported to be 1.2–5.5 times greater than the risk from a cortical lesion (5).

The fact that cavernous malformations do not contain internal neural tissue may explain why hemorrhage of these lesions can be asymptomatic or result in only minor neurologic impairment. Although cavernous malformations distort surrounding neural tracts, there is no interruption of connectivity or function. When hemorrhage occurs primarily within the lesion itself and spares the surrounding brain parenchyma, there may be minimal effect on adjacent neural structures.

Detection of cavernous malformations has been facilitated by the use of MRI and protocols that include susceptibility-weighted sequences. In our patient, a cavernous malformation with subacute hemorrhage appeared hyperintense on T1 and T2 sequences (Fig. 1). Cavernous malformations are distinguished from other vascular malformations by lack of enhancement with administration of contrast (Fig. 1B). Subacute hemorrhage is often

FIG. 2. Brain magnetic resonance imaging performed 6 months after onset of symptoms. (A) T1 sagittal scan shows that most of the lesion appears isointense to brain. (B) T1 axial postgadolinium scan shows that the lesion is nonenhancing and contains an area of hypointensity (arrow). (C) Axial fluid-attenuated inversion recovery scan demonstrates resolution of abnormal T2 hyperintensity and a persistent rim of T2 hypointensity (arrow). (D) Susceptibility-weighted imaging reveals persistent hypointensity within the lesion, consistent with blood products.
accompanied by surrounding edema (Fig. 1C). Susceptibility-weighted sequences are highly sensitive for blood products, demonstrating hypointensity in the area of the lesion (Fig. 1D). Chronically, with resolved hemorrhage, the lesion may appear isointense or hypointense on T1 sequences (Fig. 2A, B) with a peripheral rim of T2 hypointensity, consistent with hemosiderin (Fig. 2C). With recurrent hemorrhage leading to accumulation of blood products of varying ages, the lesion takes on the typical “popcorn” appearance of mixed signal intensity on TI and T2 sequences. Hypointensity on susceptibility-weighted imaging persists in the chronic phase because of hemosiderin deposition (Fig. 2D) or dystrophic calcification.

Our case illustrates a good prognosis for neurologic recovery from a first-time hemorrhage. The patient’s symptoms resolved over a 6-month period, suggesting remyelination of the sixth nerve fasciculus as hemorrhage and edema resolved. However, cavernous malformations carry a high risk for recurrent hemorrhage and must be considered as a potential cause of an “idiopathic” ocular motor cranial nerve palsy.

REFERENCES
Visual Involvement in Corticobasal Syndrome

Rithwick Rajagopal, MD, PhD, Randall Bateman, MD, Gregory P. Van Stavern, MD

Abstract: Corticobasal syndrome (CBS) is the clinical presentation of corticobasal degeneration (CBD), a rare neurodegenerative disorder, with features of both cerebral and basal ganglia involvement. Visual disturbance is uncommonly a predominant symptom but when present can be markedly debilitating. Visual findings primarily manifest as oculomotor apraxia, but significant cognitive impairment may result in the inability to process visuospatial information and can result in simultagnosia and visuomotor ataxia. A 60-year-old woman with a history of CBS presented with progressive visual impairment. Her symptoms were primarily due to severe oculomotor apraxia, optic ataxia, and pronounced simultagnosia. We present the case and review the literature regarding visual dysfunction in CBS.

CASE REPORT

A 60-year-old woman noted progressive difficulty with vision over the past year, characterized by difficulty reading and performing everyday household tasks. Several years earlier, she experienced worsening memory and attention deficits, which initially were attributed to Alzheimer disease. She subsequently developed increasing gait and movement abnormalities. Cognitive and motor function testing revealed both extrapyramidal and cortical deficits, and she was given a diagnosis of CBS. The remainder of her medical and surgical history was noncontributory.

During her initial encounter in the neuro-ophthalmology clinic, much of her history had to be provided by her husband, as her cognitive impairment prevented prolonged coherent speech. Both her husband and her physical therapists had noted that she had difficulty with reaching for objects, and she often missed her targets. She had great difficulty in finding objects within visual space. She denied loss of vision, photopsia, scotoma, or diplopia. There was no family history of neurodegenerative or ophthalmologic disease. The patient was alert and responsive to commands. She had experienced frequent involuntary movements of her
upper body and head. Visual acuity was 20/40 in each eye. She had great difficulty in finding the Snellen chart optotypes and often made corrective head movements rather than ocular saccades. She was unable to perform color vision testing, as she was unable to locate the Ishara plates. Visual field assessment was difficult, but she appeared to have intact evoked saccades to hand motions in all fields. Pupils, external, slit-lamp, and fundus examinations were normal. While ductions and versions were intact, she had prolonged latency for saccadic movements in all directions, particularly upgaze. Her saccadic apraxia was also associated with mild saccadic dysmetria, but saccadic velocity appeared normal. Pursuit movements were also markedly and symmetrically impaired. There was no gaze preference. There was no nystagmus, but she had micro- and macro-square-wave jerks.

On neurologic examination, the patient demonstrated marked impairment with finger-to-nose tasks, felt to be secondary to optic ataxia. This deficit was more prominent with the use of her left hand or left-sided visual stimuli. The patient demonstrated profound simultagnosia in describing the Cookie-Thief drawing (used in the NIH Stroke Scale testing form). She displayed no resting tremor and had normal muscular tone. However, she had marked ideomotor apraxia. She tended to use her left hand much less than the right and was noted to exhibit an occasional tonic flexed posture of the left arm. The patient had an expressive aphasia and although her speech was intermittently fluent, she often displayed a hesitant cadence and had difficulty with certain words. She also demonstrated mild alexia, as she could only read the first sentence of the NIH Stroke Scale.

More detailed neuropsychometric testing performed earlier had revealed cognitive deficits consistent with moderate dementia, with a score of 12 (normal range: 23–30) on the mini–mental state examination and 5 (normal range: 7–10) on her word list memory tasks. Her testing was limited by expressive aphasia, and the level of her dementia may have been overestimated.

MRI of the brain revealed diffuse cortical atrophy, with some predominance in the posterior parietal regions. The patient was referred to low vision services and was advised to continue occupational and physical rehabilitation.

DISCUSSION

Our patient had clinical findings consistent with CBS and severe visuomotor dysfunction. Several features support the diagnosis of CBS, including focal ideomotor apraxia, a partial alien limb phenomenon involving the left upper extremity, and signs of moderate dementia (7–9). Consistent with her systemic manifestations, one of our patient’s primary visual deficits was oculomotor apraxia.

The clinical distinction between CBS and PSP or other tauopathies is difficult to define (Table 1). A review of patients with either clinical or histopathological diagnosis of CBS-CBD revealed that only 5 of 19 patients with pathologic confirmation of CBD were correctly diagnosed with CBS during life (10). Conversely, of 21 patients who were diagnosed with CBS during life, only 5 had pathology consistent with CBD. Some have suggested that the clinical presentation typically attributed to either CBS or PSP instead be grouped in a single entity (10,11).

Likewise, distinguishing visual involvement in CBS from that found in PSP may be challenging. The visual involvement in CBS overlaps to some degree with PSP, including an apparent supranuclear opthalmoplegia seen in both of these disease entities (12). However, in CBS, there is not a true paresis of saccades but rather prolonged saccadic latency. In PSP, saccades are slow, whereas in CBS, velocity and range of saccades remain intact (13). PSP typically affects vertical saccades, while in CBS, horizontal eye movements more often are affected. If the clinical examination is conducted hastily, prolonged saccadic latency may be mistaken for a gaze palsy and mislead the examiner to diagnose PSP.

Features of our case that are unusual for CBS include prolonged saccadic latency in upgaze and preserved horizontal saccades. There have been reports of pathologically confirmed CBD that have produced severe saccadic apraxia in upgaze (14).

Less commonly, visual involvement in CBS is due to disorders of higher processing functions of the cerebral cortex. Our patient demonstrated simultagnosia, optic ataxia, and oculomotor apraxia. These are features of Balint syndrome, which results from bilateral occipital-parietal dysfunction. Tang-Wai et al (16) reported a similar case of histopathologically confirmed CBD; the patient presented with visual processing dysfunction with features of both Balint and Gerstmann syndrome (16). The presence of higher-order visual processing dysfunction has been associated with the extent of cortical involvement in CBS. Neuroimaging and postmortem examination of patients presenting with visuospatial processing deficits in CBS has revealed diffuse or focal cerebral atrophy (16). A recent series of patients with atypical parkinsonian syndromes, looking specifically at visuospatial dysfunction, found that patients with CBS tended to show more deficits compared to those with PSP or MSA (6). In this study, many patients with CBS had normal mini–mental state examinations, suggesting that the visuospatial disorders observed could not solely be attributed to general cognitive decline.

While universally accepted diagnostic criteria for CBS are lacking, the neurologic evaluation findings should include unilateral or general apraxia and dystonia and focal or generalized cortical sensory loss. Neuropsychometric testing may demonstrate additional deficits of higher cognitive function, including memory and language. Neuroimaging, while not necessarily helpful for making a diagnosis of CBD, can exclude other more treatable conditions (2,17). Prognosis is poor, as most patients die within 10 years of the onset of
TABLE 1. Distinctive features of CBS, PSP, and FTD (7,15,19–21)

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<th>Higher Cognitive Functions</th>
<th>Oculomotor Signs</th>
<th>Motor Functions</th>
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<td></td>
<td>Global Dementia</td>
<td>Disinhibition</td>
<td>Cortical Sensory Loss</td>
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<td>CBS</td>
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<td>FTD</td>
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*FTD, frontotemporal dementia.*

the symptoms secondary to severe dysphagia or complications of being immobile (18). Although there is no treatment for CBS, low vision evaluation and physical therapy may improve patient functioning.

REFERENCES
Lemierre Syndrome Causing Bilateral Cavernous Sinus Thrombosis

Brooke Miller, MD, Yousuf Khalifa, MD, Steven E. Feldon, MD, MBA, Deborah I. Friedman, MD, MPH

Abstract: Lemierre syndrome is an uncommon septic thrombophlebitis of the veins of the head and the neck usually occurring after a severe oropharyngeal infection. Although subsequent septic emboli most commonly affect distant sites, such as the lungs and joints, the authors present a case of Lemierre syndrome causing bilateral cavernous sinus syndrome.

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In 1936, André-Alfred Lemierre, a French bacteriologist, described anaerobic septicemia following throat infections in 20 patients, 18 of whom died (1). Lemierre syndrome, an uncommon septic thrombophlebitis affecting the veins of the head and neck, generally follows a throat infection. It usually affects otherwise healthy individuals and is not contagious. Although it occurred more frequently and was often fatal before the antibiotic era, Lemierre syndrome still may be seen, often affecting otherwise healthy individuals. Our case demonstrates bilateral cavernous sinus involvement in Lemierre syndrome.

CASE REPORT

A previously healthy 35-year-old man presented to the emergency department with a 3-week history of sore throat, malaise, and fever. Outpatient treatment consisted of 3 days of 60 mg of prednisone for a positive monospot test. Several days before presentation, the patient developed acute binocular diplopia and right proptosis which, associated with progressive dyspnea, prompted initial evaluation in a local emergency room.

Ophthalmologic examination revealed a visual acuity of 20/30, right eye, and 20/25, left eye. The right eye was proptotic with chemosis and limited movements in all directions.

Magnetic resonance venography (MRV) revealed right transverse and sigmoid sinus thrombosis (Fig. 1), and computed tomography (CT) showed right internal jugular vein thrombosis (Fig. 2). Magnetic resonance imaging (MRI) of the brain was consistent with bilateral cavernous sinus thrombosis (Fig. 3). This was confirmed with diffusion-weighted imaging (Fig. 4A), which also demonstrated thrombosis of the right superior ophthalmic vein (Fig. 4B).

Laboratory testing was significant for leukocytosis of 24,600 cells per microliter and an elevated erythrocyte sedimentation rate of 65 mm/h. Blood cultures were negative, likely related to previous outpatient treatment with broad-spectrum antibiotics. Empiric treatment was initiated with vancomycin and meropenem, as well as intravenous heparin. The patient’s respiratory status deteriorated, presumably from septic emboli to the lungs causing acute respiratory distress syndrome, and he was intubated and transferred to our medical center.

The patient was intubated and sedated upon arrival, although he could follow commands. Visual acuity was 20/400, right eye, and 20/200, left eye. Pupils measured 3.5 mm, right eye, and 3.0 mm, left eye, and there was no relative afferent pupillary defect. Eye movements were limited in all directions (Fig. 5). There was bilateral proptosis, greater on the right, and increased resistance to retropropulsion was also greater on the right. External examination revealed bilateral periorbital edema with chemosis, with intraocular pressures of 24 mm Hg, right eye, and...
22 mg Hg, left eye. The only funduscopic abnormality was dilated retinal veins in the right eye.

The patient steadily improved during 2 weeks of hospitalization. He was discharged on anticoagulation and 4 more weeks of intravenous antibiotics. Six months later, he had 20/20 vision in both eyes with a residual mild right sixth nerve palsy.

**DISCUSSION**

Lemierre syndrome is a potentially fatal disorder that may complicate bacterial pharyngeal infection in an otherwise healthy individual and is characterized by thrombophlebitis of the veins of the head and the neck. Because of anatomic proximity, infection is thought to spread from peritonsillar tissues to the adjacent pharyngeal space, with subsequent thrombophlebitis of the internal jugular vein (2). Septic emboli arising from the internal jugular vein most commonly affect distant sites, such as the lungs and joints (2). Although the most commonly identified organism in infected patients is *Fusobacterium necrophorum*, other causative organisms include *Bacteroides* species, *Streptococcus* and *Enterococcus* species, and *Proteus mirabilis* (3). In the antibiotic era, Lemierre syndrome may be dismissed erroneously as a disease of the past (2). However, recent reports indicate that the incidence of Lemierre syndrome is increasing, possibly related to reduced use of antibiotic therapy for pharyngitis (4).

Ophthalmic involvement in Lemierre syndrome is rare with few reports of proptosis (5), endogenous endophthalmitis (6), vitreous hemorrhage (7), and orbitopathy (8,9). There are
reports of isolated fourth and sixth nerve palsies resulting from Lemierre syndrome (10,11).

Cavernous sinus syndrome has been associated with Lemierre syndrome, but, to our knowledge, there are no cases of severe bilateral ophthalmoplegia as an early manifestation. One report described a patient with MRI and MRA findings of cavernous sinus involvement but the patient did not have ophthalmoplegia (4). Another described a patient with extraocular muscle enlargement, chemosis, proptosis, and ophthalmoparesis (9). Neuroimaging demonstrated thrombosis of both superior ophthalmic veins and a left intracranial dural venous sinus, with thrombophlebitis of the left internal jugular vein and bilateral orbital abscesses. Despite anticoagulation and aggressive treatment with intravenous antibiotics, the patient's vision declined to bare light perception and he developed complete ophthalmoplegia with fixed and nonreactive pupils. MRI showed a right carotid-cavernous fistula, and the patient died less than 3 weeks after presentation.

Our report highlights an unusual cause of cavernous sinus syndrome, although the mechanism for cavernous sinus involvement remains speculative. It is possible that our patient had a heightened hypercoagulable state, related both to endothelial damage from microorganism invasion and a proinflammatory immune response to systemic infection. Supporting this notion, one study found that the surface of the \textit{F. necrophorum} bacterium activates branches of the contact system, the system that links inflammation and coagulation (12). In Lemierre syndrome, bacteria may migrate through the vessel wall of veins of the head and neck, causing platelet activation, inflammation, and activation of the extrinsic coagulation pathway, enhancing local coagulation (12).

**FIG. 4.** Diffusion-weighted imaging shows restricted diffusion in both cavernous sinuses (A) and the right superior ophthalmic vein (arrow) (B) consistent with thrombosis.

**FIG. 5.** Clinical examination findings include bilateral proptosis, conjunctival chemosis, and external ophthalmoplegia. The pupils have been dilated pharmacologically. Arrows represent the direction of attempted gaze.
REFERENCES

Optic Perineuritis as the Presenting Feature of Crohn Disease

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Abstract: Crohn disease (CD) is primarily considered an inflammatory condition of the small and large intestine although associated extraintestinal inflammation is relatively common. Ocular manifestations are generally localized to the anterior chamber and ocular surface but rarely can involve the posterior pole, orbit, and optic nerve. We report a case of an otherwise healthy 42-year-old man who was diagnosed with CD after presenting with acute vision loss from optic perineuritis.

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CASE REPORT

A previously healthy 42-year-old Caucasian man presented to the emergency room following acute, painless loss of the entire visual field in the left eye that morning. A review of systems revealed 10 days of abdominal cramping, low-grade fever, and diarrhea. Visual acuity was 20/20, right eye, and hand motions, left eye. Visual fields were full to confrontation technique in the right eye and showed a large central scotoma in the left eye. Pupils demonstrated a left relative afferent pupillary defect. Ocular motility and alignment were normal. Applanation tonometry revealed intraocular pressures of 6 mm Hg in both eyes. Slit-lamp examination was significant for mild conjunctival injection with 1+ anterior chamber cells in both eyes, and funduscop was normal bilaterally.

Patient evaluation included a complete blood count with an elevated white blood cell count of 19.5 cells per microliter and platelet count of 516 platelets per microliter. Infectious etiologies including syphilis, Lyme disease, tuberculosis, HIV, and bacterial causes of endogenous endophthalmitis were excluded with the following normal tests: blood cultures, urinalysis with urine culture, Lyme titers, reactive plasma reagin, HIV, and a purified protein derivative tuberculin skin test. Erythrocyte sedimentation rate, rheumatoid factor, angiotensin-converting enzyme, HLA-B27, antineutrophilic cytoplasmic antibody panel, and anti-nuclear antibody panel were also unremarkable. Cerebrospinal fluid analysis showed no cells with normal glucose and protein levels. Computed tomography (CT) of the chest and brain was normal. Magnetic resonance imaging (MRI) of the brain and orbits revealed thickening of the orbital portion of the left optic nerve with enhancement of the optic nerve sheath (Fig. 1).

CT of the abdomen showed wall thickening of the ascending, transverse, and descending colon indicative of colitis (Fig. 2). The workup for infectious etiologies of colitis was negative. A flexible sigmoidoscopy showed subtle patches of granular mucosa in the rectum and sigmoid colon along with discrete ulcerations of the colonic mucosa. Biopsies from the rectum demonstrated acute inflammation and noncaseating granulomas confirming the diagnosis of CD.
The patient was treated with intravenous methylprednisolone (1 g daily for 1 week) followed by an oral prednisone taper, as well as oral mesalamine and corticosteroid eye drops. Two weeks after presentation, funduscopy revealed multifocal choroidal infiltrates in the left eye and mild left optic disc swelling (Fig. 3). Eight weeks after steroid therapy, these fundus findings resolved, and 3 months later, vision was 20/25, left eye, with mild dyschromatopsia, a central scotoma, and mild optic disc pallor. The patient was maintained on 5 mg of prednisone daily and mesalamine to treat CD.

DISCUSSION

CD is named after gastroenterologist Burrill Bernard Crohn, who in 1932 published a seminal case series of 14 patients with “regional ileitis” (1). It is now clear that CD can affect the entire GI tract although it typically causes acute and chronic transmural inflammation of the distal small intestine and proximal colon (1). Although UC shares some features with CD and falls under the rubric of IBD, the 2 are distinct pathological entities and usually distinguishable clinically. Both UC and CD now are considered systemic inflammatory conditions and may involve skin, joints, liver, kidneys, coagulation pathways, central nervous system, lungs, and eyes (1–3).

CD and UC are associated with a broad spectrum of ophthalmic involvement, including the optic nerve (4–7).
This generally occurs in 4 clinical settings. First, CD-associated papillitis occurs with vitritis and/or anterior uveitis (8–10). Second, there are 5 documented cases of retrobulbar optic neuritis in patients with CD (10–13). In 2 cases, MRI findings were unremarkable with a favorable response to steroid therapy. Third, optic disc edema without clinical evidence of optic nerve dysfunction has been described with intermediate and posterior uveitis (14,15). Finally, patients with CD may develop idiopathic intracranial hypertension (15), in some possibly related to the use of systemic corticosteroids (16,17).

Our patient’s optic nerve involvement with CD seems unique. He experienced acute vision loss in the left eye, and MRI findings were consistent with OPN. OPN is characterized by inflammation of the meninges surrounding the optic nerve (18). The development of steroid-responsive choroidal lesions and anterior chamber cell in our patient supports the diagnosis of an inflammatory process involving the uveal tract as well.

OPN is usually idiopathic and considered within the spectrum of nonspecific orbital inflammation (pseudotumor). On occasion, OPN can be linked to a specific cause, including sarcoidosis, giant cell arteritis, Wegener granulomatosis, tuberculosis, and syphilis (18–20). There is usually retention of good central visual acuity, although Purvin et al (18) reported that 3 of 14 patients with OPN initially had visual acuity of 20/300 or worse. Enhancement of the optic nerve meninges is found on contrasted neuroimaging studies, and patients with OPN experience good recovery of visual functions with steroids, provided that they are treated early in the clinical course (18).

It is unknown whether systemic treatment with anti-inflammatory medications, such as 5-aminosalicylic acid and corticosteroids, to reduce IBD flares also prevents optic nerve inflammation. Many reports of IBD-associated optic nerve inflammation, including our case, occur concurrently with GI exacerbations. It is plausible that control of GI disease may help prevent extraintestinal inflammatory manifestations of IBD. One noteworthy exception may be the use of tumor necrosis factor-alpha inhibitors. These biologic agents (infliximab, adalimumab, and etanercept) have been implicated in causing inflammatory, demyelinating events within the central nervous system (21), including the optic nerve (22–24).

REFERENCES

Pourfour du Petit Syndrome Associated With a Cervical Vertebral Anomaly

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Abstract: Pourfour du Petit syndrome is a rare dysautonomic disorder characterized by mydriasis, eyelid retraction, and hyperhidrosis and is caused by irritative stimulation of the sympathetic cervical chain. The authors describe a 45-year-old woman with iris heterochromia, who presented with episodes of ipsilateral mydriasis and hyperhidrosis and was found to have a cervical vertebral anomaly, probably present since birth, as the cause of Pourfour du Petit syndrome.

CASE REPORT

A 45 year-old woman reported multiple episodes over 10 years of right pupillary mydriasis and blurred vision associated with ipsilateral hemifacial hyperhidrosis, triggered by exercise and stressful situations. There was no significant medical or surgical history nor a history of trauma.

On neuro-ophthalmic examination, pupils were 3.5 mm, right eye, and 2.5 mm, left eye, without ptosis or lid retraction. Direct and consensual pupillary light responses were normal, and eye movements were intact. Visual acuity, intraocular pressures, and funduscopes were normal, whereas slit-lamp examination showed iris heterochromia with the right iris being more pigmented than the left. The right pupil showed no supersensory to 0.125% pilocarpine drops, and the responses to 1% pilocarpine and 4% cocaine drops were normal and bilaterally symmetric. Within minutes of the patient starting physical exercise (the patient ascended and descended the stairs up to the sixth floor twice), we found that the right pupil dilated to 6.5 mm with ipsilateral hemifacial hyperhidrosis (Figs. 1, 2).

Laboratory data, including thyroid function tests, chest radiography, and brain computed tomography were within the normal limits. Magnetic resonance imaging (MRI) of the spine showed narrowing of both the C6–C7 disc space and the right C6–C7 neuroforamen (Fig 3). Because the patient’s clinical symptoms were not disabling and episodes were triggered only by exercise, no treatment was given. The patient remained stable over 6 months of follow-up.

DISCUSSION

At the beginning of the 18th century, François Pourfour du Petit, a French military surgeon, examined many soldiers with wartime neck injuries. He noted signs of increased facial sympathetic activity and related these to injuries of the cervical sympathetic chain (2).

The anatomy and physiology of the cervical sympathetic pathway is well known. It is important in the regulation of...
facial temperature and sweating and in the control of the pupil size. The most common disorder of the cervical sympathetics is HS, which is caused by sympathetic paralysis and resultant pupillary miosis, ptosis, and anhidrosis (10).

PdPS is an uncommon cause of unilateral mydriasis, lid retraction, and hyperhidrosis caused by hyperactivity of the ipsilateral oculosympathetic pathway. PdPS has been documented in association with intracranial aneurysms (11), nonpenetrating injuries of the cervical sympathetic chain and brachial plexus (3,12), severe craniocencephalic trauma (7), interrupted aortic arch (4), cervical and thoracic tumors (5,6), maxillofacial surgery (8,9), and regional anesthetic procedures (10). To our knowledge, the association of cervical disc abnormality and PdPS previously has not been reported.

In our patient, MRI showed disc space narrowing at the C6–C7 level with right lateroforaminal narrowing and compression of the C7 nerve root. We speculate that this injury to the cervical sympathetic chain produced an irritative stimulus that resulted in oculosympathetic hyperactivity.

Our patient had iris heterochromia. Congenital HS is classically associated with iris heterochromia with the ipsilateral iris being less pigmented. This is thought to be due to attenuated iris melanocyte development from reduced noradrenaline release. In contrast, in our case, the iris on the affected side was more pigmented than the fellow eye. Congenital PdPS could produce sympathetic overactivity from birth, leading to amplified noradrenaline release, with increased melanocyte development and iris hyperpigmentation.

REFERENCES
Intraorbital Ganglioglioma of Optic Nerve in a Patient With Neurofibromatosis Type 1

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Abstract: We report the case of an orbital optic nerve ganglioglioma in a 55-year-old woman with neurofibromatosis type 1 (NF1). Clinical course neuroimaging findings, pathology, and treatment options of ganglioglioma are discussed and contrasted with pilocytic astrocytomas of the optic nerve, a much more frequent visual pathway neoplasm in NF1 patients.

CASE REPORT

A 55-year-old woman reported a 1-year history of progressive and painless vision loss in her left eye. Neuroophthalmologic examination of the affected eye revealed visual acuity of counting fingers, uveal ectropion, Lisch nodules, 3 mm of proptosis, and optic disc pallor. Examination of the right eye was normal. Physical examination disclosed multiple café-au-lait spots and numerous cutaneous and mucosal neurofibromas. There were no abnormalities on neurologic testing. The patient’s medical history included a cyst of the upper pole of the right kidney, numerous cysts of the liver, hyperlipoproteinemia type IIb, and hypothyroidism after Hashimoto thyroiditis.

Magnetic resonance imaging (MRI) of the brain showed fusiform thickening of the entire orbital portion of the left optic nerve (Fig. 1). Because of poor vision in the left eye and uncertainty of the diagnosis, the patient consented to have the tumor removed. This was accomplished by a transcranial superior orbitotomy.

The tumor was solid, globoid in shape, 12 mm in diameter, with a smooth surface and whitish color on cross-section. Microscopically, the neoplasm was composed of well-differentiated glial and ganglion cell types (Fig. 2A). The glial component showed features of bipolar pilocytic astrocytes with Rosenthal fibers. Neuronal cells with abundant cytoplasm, round vesicular nuclei, conspicuous nucleoli, and marginated Nissl substance were dispersed among the glial elements or gathered in small groups in the central zone of the tumor. Some binuclear ganglion cells were found. There was no nuclear or cellular atypia in both tumor components, and there was no evidence of mitotic figures, necrosis, or perivascular lymphocytic cuffing. A few psammoma bodies were seen in the subcapsular region.

With immunohistochemistry, ganglion cells exposed synaptophysin, neuron-specific enolase, neurofilament, and chromogranin A in their cytoplasm (Fig. 2B, C). Some of these cells stained for membranous CD34.
(Fig. 2D). Pilocytic astrocytes demonstrated glial fibrillary acidic protein positivity.

During 6 years of follow-up, there has been no evidence of tumor recurrence with clinical and neuroimaging examinations, and the patient’s visual function remains normal in the right eye.

DISCUSSION

GG is a rare primary tumor of the optic nerve (7,8), and exceptional among orbital tumors (9). To the best of our knowledge, only 7 cases of GG involving intraorbital optic nerve have been reported in the literature (Table 1). Three
TABLE 1. Reported cases of ganglioglioma involving the intraorbital optic nerve

<table>
<thead>
<tr>
<th>Age (y), Sex, (Reference)</th>
<th>NF-1</th>
<th>Reduced VA</th>
<th>Optic Atrophy</th>
<th>Proptosis</th>
<th>Strabismus</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>15, M (4)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Removal of ON tumor</td>
</tr>
<tr>
<td>16, F (5)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Removal of ON tumor</td>
</tr>
<tr>
<td>71, M (6)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Incidental autopsy finding</td>
</tr>
<tr>
<td>2, M (10)</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Removal of ON tumor</td>
</tr>
<tr>
<td>38, M (11)</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Subtotal resection of tumor</td>
</tr>
<tr>
<td>10, F (12)</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Subtotal resection of tumor</td>
</tr>
<tr>
<td>18, F (13)</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Removal of ON tumor</td>
</tr>
</tbody>
</table>

F, female; M, male; NF-1, neurofibromatosis type 1; ON, optic nerve; VA, visual acuity.

were detected in NF1 patients (4–6), and the remaining 4 in patients without NF1 (10–13).

Pilocytic astrocytoma is the most common tumor of the optic nerve in patients with NF1, occurring in approximately 20% of affected individuals (14). While our patient met the diagnostic criteria for NF1, she had an unexpected optic nerve GG. Differentiation between optic nerve pilocytic astrocytoma and GG in NF1 patients can be challenging. Two-thirds of optic nerve gliomas in NF1 patients cause no symptoms and are detected only by neuroimaging (15). If they cause visual loss, this occurs gradually over many years. On occasions this optic nerve tumor may regress spontaneously (16). In contrast, GG of the optic nerve causes rapid, progressive visual failure. MRI findings also may distinguish GG from pilocytic astrocytoma. In our patient, GG appeared dark on T2 MRI probably because of tumoral calcification, while pilocytic astrocytoma is typically bright. Calcification of optic nerve tumor is highly suggestive of meningioma, yet meningioma is characterized by marked contrast enhancement. In our case, the tumor failed to enhance after intravenous contrast. The MRI findings in our patient raised suspicion that we were dealing with an unusual optic nerve tumor.

Histopathologic examination is definitive in distinguishing GG from pilocytic astrocytoma. The hallmark of GG is a mixture of neuronal and glial cell elements, both of which may display heterogeneity. The spectrum of GG ranges from a neuronal phenotype toward variants with a prominent glial population (1), as in our case. Findings of this neuronal component include abnormal localization, clustered appearance, perimembranous aggregate Nissl substance, and the presence of binucleated or multinucleated forms. The presence of the neuronal component is confirmed using synaptophysin and neurofilament stains. Interestingly, CD34 and chromogranin A are not present in neural cells of the adult brain but are identified in 70%–80% of cases of GG (17,18). The presence of immunohistochemical markers CD34 and chromogranin A in our patient’s GG confirms the neoplastic nature of neural cells and was a unique finding in our case. The glial component in GG shows substantial variability, comprising the proliferative cell population of the tumor. Cell types may resemble fibrillary astrocytoma, oligodendroglioma, or, as in our patient, pilocytic astrocytoma. Perivascular lymphocytic cuffing is often detected within the glial elements of GG (2) but was not found in our case.

The origin of optic nerve GG remains controversial. The predominant cell types in most cases are of monoclonal origin and develop from a common precursor cell that later differentiates to form neoplastic glial and neuronal components (19). GG may also arise from ectopic neural tissue in the orbit through neoplastic transformation (20,21).

Treatment of GG and pilocytic astrocytoma differs substantially. Seven of the 8 reported patients with optic nerve GG, including ours, underwent surgical removal of the tumor (Table 1). This management decision was made primarily on the basis of progressive visual loss and potential extension of the tumor. In contrast, because of the more favorable clinical course seen in patients with pilocytic astrocytoma, surgical removal is rarely necessary (7).

In conclusion, although rare, GG may present as a tumor of the optic nerve, including in patients with NF1. While pilocytic astrocytoma is the most likely optic nerve tumor, other neoplasms such as GG must be considered in the differential diagnosis. Clinical course, neuroimaging findings, and pathologic examination help to distinguish these two neoplasms of the optic nerve.

REFERENCES

Retinal Ganglion Cell Functional Plasticity and Optic Neuropathy: A Comprehensive Model

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Abstract: The clinical management of glaucoma and optic neuropathies has traditionally focused on stages of the diseases at which there are congruent losses of visual function and optic nerve tissue. Increasing clinical and experimental evidence suggests that the electrical activity of retinal ganglion cells, as measured by pattern electroretinogram (PERG), may be altered long before measurable changes in the thickness of the retinal nerve fiber layer. In addition, PERG alterations in early glaucoma may be either reversed by lowering the intraocular pressure or induced with head-down body posture. Here we apply the well-known concept of neural plasticity to model the reversible/inducible changes of retinal ganglion cell electrical activity during a critical period of dysfunction preceding death. Identification and characterization of this stage of modifiable retinal ganglion cell function represents both a rationale and a target for treatment to change the natural history of the disease.

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Retinal ganglion cell (RGC) death is the final common pathway that leads to loss of vision in glaucoma and most optic neuropathies. Lethal insult to RGCs and their axons originates from stressful changes of the cellular and molecular environment that exceed their survival capacity. The clinical management of glaucoma and optic neuropathies has traditionally focused on stages of the diseases at which losses of visual function of optic nerve tissue become manifest. Relatively less attention has been given to the fundamental issue of whether visual loss precedes, accompanies, or follows cell death. In the former case, visual dysfunction can be used as a marker to predict future nerve tissue loss and to initiate therapeutic strategies to prevent cell death and possibly reverse visual loss. In the latter cases, the only available therapeutic strategy is to slow down further cell death and visual loss. While this problem has been dealt with before (1), formal theoretical concepts leading to a testable model are lacking. In our view, this represents a limitation to progress in the field of degenerative diseases of the optic nerve. Here we provide a simple framework and a unified model to aid in understanding glaucoma and optic nerve diseases and for hypothesis testing. This model is supported by an increasing number of clinical and experimental results.

CENTRAL HYPOTHESIS

A reasonable hypothesis is that the early stages of optic neuropathies are characterized by failure of autoregulatory mechanisms to sustain normal RGC function under prolonged exposure to a stressful environment. Autoregulatory failure sets in motion adaptive mechanisms to prolong RGC survival. Surviving RGCs have altered function, which may be reversible under less stressful conditions. The duration of the stage of RGC dysfunction preceding death may be relatively long in glaucoma compared with Leber hereditary optic neuropathy (LHON). In these different diseases, however, RGC may share the same fundamental stress-dependent adaptive response to use fully the residual intracellular and extracellular resources and extend the time window during which RGC dysfunction preceding death may be still reversible under less stressful environmental conditions. Independent of the mechanisms or RGC/axon insult, an understanding of the time window of reversible RGC dysfunction would be applicable to most optic neuropathies and would represent key information to develop therapeutic approaches to prevent RGC death and restore RGC function.

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CONCEPTUAL MODEL

Here we apply the well-known concept of neural plasticity to describe the ability of RGCs to change their function over time in response to an environmental challenge that exceeds their autoregulatory capacity. If an intervention is applied during the plastic period, the natural history of the disease will be substantially modified. While neuroplasticity is known to be active in the early postnatal period, some degree of plasticity is retained in the adult. This is particularly evident in acquired brain injury, where plasticity represents the fundamental issue that supports a scientific basis for treatment (2,3). Synapse elimination is one of the earliest events in neurodegenerative diseases (4), and this also occurs in RGC dendrites in early stages of glaucoma in the DBA/2J mouse model through reactivation of developmental molecular mechanisms (5).

DEFINITIONS

We define RGC plasticity as the ability of RGCs to modify their electrical activity upon an environmental challenge that exceeds their autoregulatory capacity. We define critical period as the time during which changes in RGC electrical activity are possible. If RGC function is modifiable by specific stressors during the critical period of RGC plasticity, then this represents both a rationale for treatment and a target to change the natural history of the disease.

MODEL FOR SINGLE RGCS

The model is summarized in Figure 1. After a long period of a normal existence (Stage 1), the cumulative stress exposure becomes higher than the RGC can tolerate, thus setting the cell in survival mode (Stage 2). At Stage 2, the RGC is dysfunctional. However, RGC dysfunction is modifiable with stress modulation: it will worsen after a further increase in stress (e.g., by increasing intraocular pressure [IOP] in glaucoma) and will improve by reducing the level of stress. At a level of dysfunction incompatible with survival, the RGC will start the one-way process of apoptosis (Stage 3) and will be removed from the neuronal pool (Stage 4). No residual RGC function is expected at Stages 3 and 4, but the RGC body and axon would still be morphologically visible and quantifiable. This model predicts that there will be a time lag between loss of function and loss of structure, which represents the lifespan of a surviving RGC. The transition between Stage 1 and Stage 2 represents the onset of disease that is crucially important to start a timely treatment to prevent further dysfunction and neural loss.

MODEL FOR RGC POPULATIONS

In a large population of RGCs, it is expected that cells at different levels of dysfunction coexist with normal cells. During progression of disease, each RGC will follow structure–function time courses similar to those depicted in Figure 1 but shifted over time by different amounts. This will result in a family of functions whose average represents the time course of the functional–structural decay of the neuronal ensemble. The profiles of these time courses will be sigmoidal like those depicted in Figure 2. This figure shows 2 different conditions simulating different rates of progression of disease. One (Fig. 2A) is relatively fast as in LHON. The other (Fig. 2B) is relatively slow as in glaucoma. Except for the time scale, functions A and B are identical. The model is conceived on the assumption that RGC function/number can be specifically and quantitatively measured in vivo over time. These requirements are very difficult to achieve under ordinary circumstances. However, there are available noninvasive tools that have been shown to directly reflect RGC electrical activity, such as the pattern electroretinogram (PERG) (6–11) and RGC...
number, such as optical coherence tomography (OCT) (12). PERG and OCT have received extensive validation and can be used in both human patients and experimental models. The conceptual model depicted in Figure 2 is likely to apply using PERG and OCT as approximate measures of RGC function and number, respectively. Standard automated perimetry (SAP) seems less specific than PERG as a measure of RGC function, as it integrates functional changes occurring at RGC level and in the optic nerve, as well as secondary changes occurring in relay neurons of the lateral geniculate nucleus and primary visual cortex (13–15). Postretinal functional changes may either exacerbate those occurring at RGC level or even mitigate them as result of cortical compensatory mechanisms (16).

Predictions of the Model

Disease Onset

Given the sigmoidal nature of the curves, the model anticipates that the tipping point (disease onset) may be difficult to detect. The earliest discernable functional or structural loss must have a magnitude that exceeds the confidence intervals of the normal population (in a cross-sectional study) or the test-retest variability of individual subjects (in a longitudinal study).

Susceptibility to Provocation

A way to detect the tipping point is to use a provocative stressful event to exacerbate latent RGC dysfunction. Provocative conditions have successfully been used to disclose latent RGC dysfunction in glaucoma suspects by means of head-down (−10°) body posture. Postural change causes intraocular pressure (IOP) elevation in both normal subjects and patients with suspicion of glaucoma or early glaucoma. Head-down posture does not cause PERG alterations in normal subjects but reversibly alters the PERG of a subset of glaucoma patients (17), implying that RGC function is susceptible to IOP stress in these patients. A similar approach has been used in the DBA/2J mouse model of glaucoma. DBA/2J mice develop a pigment-liberating iris disease that causes elevated IOP and glaucoma (18). While RGC axon loss is first detectable at 8 months of age, the PERG signal can be altered approximately 3 months earlier (19,20). The time courses of RGC axon loss and PERG signal loss have profiles very similar to the theoretical model depicted in Figure 2B. In addition, the PERG signal is susceptible in an age-dependent manner to temporary IOP elevation induced by head-down (60°) body posture (21). That is, while preglaucomatous young (2- to 4-month-old) DBA/2J mice have normal PERG and are resistant to posture-induced IOP elevation, the PERG of older mice (5–6 months old) becomes abnormal during head-down body posture. At 7–8 months of age, the PERG is severely abnormal, and the loss of signal is exacerbated during head-down body posture (21).

Reversibility of RGC Dysfunction

The model (Fig. 2) predicts that there will be an excess of RGC dysfunction compared with that expected from loss of tissue. This has been shown by comparing PERG and OCT in human glaucoma (22) and LHON (23) and by comparing PERG and axon counts in DBA/2J glaucomatous mice (19,20). This excess dysfunction is potentially recoverable. A number of studies show that the losses of PERG signal in human and DBA/2J experimental glaucoma are, at least in part, recoverable (21,24–28).

Critical Period of RGC Plasticity

The model predicts that there will be a time lag between RGC dysfunction and death. A number of PERG studies in human and experimental models of glaucoma, multiple sclerosis, and LHON show that RGC dysfunction may be identifiable before structural loss within the optic nerve is evident with OCT, magnetic resonance imaging, or histology (19,20,22,23,29–32). This time lag represents the time window for therapeutic intervention to prevent cell death (33,34). Under ordinary circumstances, the time lag between dysfunction and death can only be established posteriorly by comparing the time courses of RGC dysfunction and death. Having an approximate prediction of the natural history of the disease with or without therapeutic intervention, one may study how to modify RGC electrical responsiveness under altered environmental conditions. High susceptibility of the PERG signal to provocative stress (e.g., IOP elevation (17,21), increased metabolic challenge (35,36)) would suggest a fast progressing disease. Reversibility of PERG signal after reduced stress (e.g., IOP lowering) or drug intake would suggest recovery of RGC function preceding death, and potentially that the disease can be prevented.

Structure–Function Correlations

The model (Fig. 2) predicts that structure–function correlations will be poor around the tipping point, whereas they will be relatively good at later stages, when both function and structure progressively deteriorate. Good correspondence between structural loss in the optic nerve head (as determined by either optic disc photos or OCT) and functional deficits in the visual field is a hallmark for establishing a clinical diagnosis of glaucoma and other optic nerve diseases. Some recent structure–function models based on the comparison between SAP and estimates of RGC number show that there is a precise causal relationship between loss of structure and loss of function in patients with glaucoma (37–41), ischemic optic neuropathy (42), and in nonhuman primates with experimental glaucoma (43). Other models would suggest that both RGC death and RGC dysfunction are necessary to account for empirical findings about relationships between perimetric and structural measures of glaucomatous damage (44). Our...
CONCLUSIONS

The concepts presented here provide a comprehensive unifying model of an identifiable stage of plasticity of RGC electrical responsiveness preceding death. Identification of this stage represents both a rationale and a target for treatment. The model does not make assumptions about mechanisms resulting in RGC dysfunction and death or does it make assumptions about genetic susceptibility to chronic stress exposure—and about the nature of stress—in different optic neuropathies. The model allows a set of testable predictions that are supported by an increasing number of clinical and experimental findings. It may be used as a framework for better understanding of how glaucoma and optic nerve disorders develop as well as the appropriate time window for treatment. The model has intrinsic limitations. First, both PERG and OCT have a limited dynamic range; the magnitudes of both PERG and OCT signals do not go to zero in advanced stages of optic neuropathy (floor effect) (22,40,45), limiting the use of the model to early-to-moderate stages of disease. Second, the OCT signal may spuriously increase as a result of either inflammation or gliosis of optic nerve axons (46). These factors need to be considered to reconcile the model with experimental findings.

REFERENCES


State-of-the-Art Review

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Progressive Diplopia and Facial Weakness in a 62-Year-Old Woman

Monika R. Kolloori, MD, Luis J. Mejico, MD, Joseph Corbo, MD, PhD, Aseem Sharma, MD, Melissa W. Ko, MD

Dr. Kolloori:
A 62-year-old woman presented to a local emergency department with horizontal diplopia that she first noted upon awakening the previous day. She had experienced a mild headache the prior evening but was otherwise well and denied any constitutional symptoms, concurrent or recent illnesses, jaw claudication, or eye pain. She had a history of hypercholesterolemia. Physical examination revealed normal vital signs. The patient’s visual acuity, intraocular pressures, and funduscopy were normal, and she had a mild abduction deficit of the left eye. Hematologic studies including complete blood count, metabolic panel, and sedimentation rate were normal. Noncontrast computed tomography (CT) of the head and magnetic resonance imaging (MRI) of the brain with and without contrast were performed.

Dr. Sharma:
Axial MRI with fluid-attenuated inversion recovery (FLAIR) technique demonstrates nonspecific hyperintense foci scattered in the white matter, without mass effect or loss of volume (Fig. 1). No enhancement or restricted diffusion was noted (scans not shown).

Dr. Kolloori:
The patient was diagnosed with left sixth nerve palsy, most likely ischemic in origin. Six days later, her diplopia worsened, and she was referred for neuro-ophthalmic evaluation. Visual acuity, color vision, pupillary reactions, and visual fields were normal. She had no ptosis, and extraocular movements revealed a complete left abduction defect. Corneal and facial sensations were equal and normal bilaterally. Further testing was done, including C-reactive protein, reactive plasma regain, and Lyme titers.

Four days later, the patient developed left facial weakness consistent with a left seventh nerve palsy, and she was admitted to the hospital. Lumbar puncture demonstrated a cerebrospinal fluid (CSF) lymphocytic pleocytosis with an elevated protein concentration (Table 1, sample 1). Cytologic assessment revealed abundant atypical lymphocytes with plasmacytoid characteristics and mitotic figures. CSF electrophoresis was suspicious for a faint monoclonal band, but the sample was not viable for flow cytometry. Autoimmune panel and serological testing for fluorescent treponemal antibody absorption, cryptoccum, and herpes simplex virus were negative or gave normal results. Blood cultures were negative. Repeat brain MRI was unchanged, and magnetic resonance angiography was normal. The patient was given 1 gm of intravenous (IV) methylprednisolone for a possible inflammatory disorder of the central nervous system (CNS). The following evening, the enzyme-linked immunosorbent assay and Western blot IgM for Borrelia burgdorferi returned positive (2.81 Lyme Index Value and 41 and 23 kDa bands, respectively), with a negative IgG pattern. The patient was treated with 2 g of IV ceftriaxone and discharged home on 21 days of IV antibiotic therapy.
Three days following discharge from hospital, she underwent repeat lumbar puncture that demonstrated further increase in the CSF pleocytosis (Table 1, sample 2). Flow cytometry showed 84% T cells with a normal CD4:CD8 ratio and 11% B cells with a decreased kappa:lambda ratio of 0.4. Cytologic assessment of the CSF again was performed.

**Dr. Corbo:**

As in the first CSF sample, numerous atypical lymphocytes are present. The cells have plasmacytoid features including prominent juxtanuclear areas of clearing that correspond to the Golgi apparatus (Fig. 2A).

**Dr. Kolloori:**

Immunoglobulin heavy chain polymerase chain reaction (PCR) of the CSF revealed a monoclonal band of approximately 240 base pairs using primers for the framework 2 region (Fig. 2B). Because these findings raised the concern of a B-cell lymphoma, the patient was referred to hematology-oncology, and a bone marrow biopsy was performed.

**Dr. Corbo:**

In contrast to the CSF samples, the bone marrow biopsy shows normal trilineage hematopoiesis without evidence of malignancy (Fig. 3).

**Dr. Kolloori:**

On serum protein electrophoresis, a vague clonal band of similar size to that found in the patient’s second CSF sample was detected (Fig. 4). CT of the neck, chest, abdomen, and pelvis revealed a thyroid nodule but were otherwise negative for malignancy. Ultrasound-guided biopsy of the thyroid nodule was not performed because of the nodule’s close proximity to the patient’s internal carotid artery.

With completion of a 3-week course of antibiotics, the patient’s diplopia and left peripheral seventh nerve palsy improved, such that the treatment for a possible lymphoproliferative disorder was withheld. A third spinal tap performed 10 days following the completion of therapy revealed a reduced lymphocytic pleocytosis, small lymphocytes, and monocytes of normal appearance, with no evidence of malignancy (Table 1, sample 3).

Two months following the patient’s initial presentation, the Western blot IgG returned positive (58, 45, 41, 39, and 23 kDa) for *B. burgdorferi*.

**Final Diagnosis**

Neuroborreliosis associated with a reactive lymphocytosis mimicking CNS lymphoma.

**Dr. Kolloori:**

Five months after presentation, the patient had complete clinical resolution of her left sixth and seventh nerve palsies. CSF analysis at this time was entirely normal (Table 1, sample 4).

**DISCUSSION**

Lyme disease is the most common tick-borne illness in Europe and North America (1). In North America, only 1 strain, *B. burgdorferi sensu stricto*, is recognized as pathogenic (2). Approximately 10%–15% of all *B. burgdorferi* infections progress to neuroborreliosis (3). Symptoms may include radiculopathy, cranial neuropathies, with the seventh cranial nerve most often affected, and mononeuropathy multiplex (3). Involvement of the nervous system may occur anywhere from 3 to 12 weeks following infection, often in the presence of the classic
erythema migrans (EM). Additional findings including peripheral neuropathy, encephalopathy, or encephalomyelitis may develop later (4). The patient’s MRI findings of nonspecific white matter FLAIR hyperintensity have been described in Lyme disease. Prior case reports have documented nonspecific demyelinating lesions with brain, nerve root, and spinal cord imaging that may be clinically asymptomatic (3,5 7).

The possibility of coexisting lymphoma with positive B. burgdorferi serology is an important diagnostic consideration. Of particular interest in our case was the possibility of malignancy versus infection raised by the patient’s initial CSF and PCR findings. There are reports of neuroborreliosis mimicking lymphoma, but flow cytometric analyses were not performed in those cases (5,8). In neuroborreliosis, alteration of the blood-brain barrier allows for intrathecal antibody formation, which may appear as oligoclonal bands on PCR.

Typical CSF findings in neuroborreliosis include elevated protein, normal glucose, and a lymphocytic pleocytosis (9). Cellular atypia suggestive of non-Hodgkin lymphoma may simply represent a lymphocytic response to antigenic stimulation by B. burgdorferi (5). In rare cases, B. burgdorferi causes a persistent antigenic stimulation that leads to malignant transformation of cells (10), although in our patient, the monoclonal B-cell expansion was self-limited. An association between Lyme disease and B-cell lymphoma may result from specific B-cell lymphocyte chemoattractants released in Borrelia infections. CXCL13, a B-cell chemoattractant, has been found to be increased in the CSF of neuroborreliosis patients (11). Upon exposure to Borrelia garinii antigen (a pathogenic European strain causing Lyme disease), monocytes release...
CXCL13, which may be a significant chemoattractant for B-cell migration to the CSF (12,13).

In distinguishing between neuroborreliosis and lymphoma, high-grade cellular atypia, monomorphism, and large numbers of lymphoid cells are characteristics of lymphoma, whereas polyclonality and elevated protein fractions are more likely because of infection (5). Utilizing these criteria, our patient’s initial cytology and CSF analysis had components consistent with either diagnosis. A further confounding factor in our case was the use of methylprednisolone, leading to potential steroid suppression of lymphoma.

Our patient exhibited signs of monoclonality on PCR analysis of serum and CSF. Although the B-cell kappa:lambda ratio was abnormal, consistent with monoclonal expansion, the absolute number of B cells was small compared with the number of T lymphocytes. This monoclonality diminished in the patient’s bone marrow 10 days following antibiotic administration. As a result, the final pathologic interpretation of these findings was one of the infections causing a reactive CSF lymphocytosis with transient monoclonal B-cells production. B-cell lymphocytosis with monoclonal or oligoclonal expansion in blood and bone marrow occurs in approximately 3.5% of individuals older than 40 years (14). There are no known clinical consequences if the following criteria are met: lack of cytopenias, lymphocytosis with monoclonal B cells of chronic lymphocytic leukemia phenotype (CD5+) numbering less than 5,000 per microliter, or lymphocytosis lasting less than a 3-month duration. However, it remains unclear if this lymphocytosis is a precursor to lymphoma (14).

Although our patient clearly had neuroborreliosis, initially she denied a history of EM or tick exposure. Although EM is the most common symptom reported in B. burgdorferi infection, it is found in only 60%–80% of all infections (6). Despite absent history of EM on initial visit, the patient’s transient headache the night before symptom onset may have been significant. In 1 clinical trial, patients with sixth or seventh nerve palsies and neuroborreliosis reported pain including headache more often than patients with cranial neuropathies of other etiologies (15). Possible tick exposure in our patient became apparent when her husband recalled that she frequently cleared brush in a local state park, known to be endemic for Lyme disease. Her husband remembered that the patient had complained of a red rash 3 months before the initial presentation, but his description was not typical EM. During the year of the patient’s illness, 50% of Lyme disease cases reported in her county of residence were within the patient’s home ZIP code. The greatest number occurred during the month of the patient’s presentation (Morrow C, personal communication, November 2010). In summary, Lyme neuroborreliosis can simulate CNS lymphoma. Despite concern for neoplastic process, clinical and diagnostic abnormalities can completely resolve with appropriate antibiotic treatment for neuroborreliosis. The reasons for overlap between Lyme infection and CNS lymphoma may be purely coincidental or because of a common etiology. In clinical practice, given the distinctive treatment for each condition, thoroughly pursuing evaluation for both etiologies would be our recommended diagnostic approach.

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REFERENCES

Should Optical Coherence Tomography Be Used to Manage Patients With Multiple Sclerosis?

Fiona Costello, MD, FRCP, Gregory P. Van Stavern, MD

Over the past decade, optical coherence tomography (OCT) has become widely used in neuro-ophtalmology, mostly to assess the thickness of the peripapillary retinal nerve fiber layer (RNFL) and macular volume (1,2). OCT allows for objective and quantitative assessment of structural damage in the visual pathways, with a multitude of clinical and research applications. Thinning of RNFL and loss of macular volume have been found in multiple sclerosis (MS) patients, both with and without distinct episodes of optic neuritis (ON) suggesting ongoing loss of axons and neurons within the anterior visual system (1–3). There is strong evidence that accrual of neurologic dysfunction in MS correlates best with axonal and neuronal loss (rather than demyelination), but the magnetic resonance imaging (MRI) techniques available to measure such loss are cumbersome, expensive, and time consuming. OCT has emerged as a noninvasive and relatively inexpensive technique for capturing what we infer to be loss of central nervous system (CNS) axons and neurons. Whether OCT should be used mostly as an outcome measure in clinical trials or routinely to evaluate and follow patients with optic neuropathies, particularly those with ON and demyelinating disease, remains debated, as illustrated by the case below.

A 31-year-old Caucasian woman was evaluated in the neuro-ophtalmology clinic for subacute painful visual loss in the right eye. Her examination was consistent with an isolated right retrobulbar optic neuropathy. She was diagnosed with right optic neuritis, likely secondary to demyelinating disease. She reported episodes of tingling over her left arm, and her brain MRI demonstrated multiple white matter lesions, some of which enhance. The diagnosis of clinically definite MS was made. She received intravenous methylprednisolone and was started on immunomodulating treatment for MS. Her visual function recovered over a few weeks, and she developed mild right optic nerve pallor. The treating neurologist requests a baseline OCT of the peripapillary RNFL.

In my opinion, a baseline OCT should be obtained to better understand what the diagnoses of ON and MS may mean for this patient.

In the case provided, the patient has experienced a clinical episode of ON in the right eye, whereas the left eye is presumed to be normal. Previous OCT studies have demonstrated that RNFL measurements and macular volumes are lower in both the ON eyes and presumed unaffected eyes of MS patients relative to healthy controls (Fig. 1) (3–6). A recent systematic review and meta-analysis of time-domain OCT (TD-OCT) studies showed an estimated RNFL loss of −20.38 μm (95% confidence interval, −22.86 to −17.91) in the ON eyes of MS patients as compared to control eyes (6). In eyes with no evidence of ON, TD-OCT measured RNFL values were reduced by −7.08 μm relative to the eyes of healthy controls, and the estimated RNFL loss in ON eyes vs unaffected eyes of MS patients was −14.57 μm (95% confidence interval, −16.50 to −12.63) (6). One advantage to obtaining a baseline OCT scan would be to better define the extent of anterior visual pathway damage and CNS involvement in this patient.

While the diagnoses of ON and MS seem quite straightforward in the case provided, distinguishing ON in MS patients from ON associated with neuromyelitis optica (NMO) can at times be challenging. This has important clinical implications because early initiation of immunosuppressive therapy can prevent vision loss and reduce neurological disability in NMO patients. In patients with prior unilateral ON, an intereye difference in RNFL thickness exceeding 15 μm is more commonly seen in
NMO patients (75%) compared to patients with relapsing-remitting MS (24%) (Fig. 2). It has been suggested that NMO-IgG antibody testing not only be considered for patients with a history of bilateral ON, poor visual recovery, but also when there is an intereye asymmetry in RNFL thickness exceeding 15 μm 3 or more months after an ON event (7).

In the case provided by Drs Lee and Biousse, quantifying the intereye asymmetry in RNFL thickness with a baseline OCT will likely lend further support for the diagnosis of relapsing-remitting MS. Furthermore, for patients who experience incomplete recovery from ON and/or lack classical MRI evidence of MS, a baseline OCT could aid in the early diagnosis of NMO.

From the Optic Neuritis Treatment Trial (ONTT), we have learned that most ON patients recover normal high-contrast visual function (mean visual acuity at 1 year after entry into the ONTT was better than 6/5 [Snellen equivalent], with less than 10% of patients having a visual acuity worse than 6/12) (8,9). High-contrast visual acuity testing is known to be a relatively insensitive means of capturing visual dysfunction in MS patients (1,5). Vision after ON can be highly variable, with patients frequently reporting symptoms of heat-associated vision loss (Uhthoff symptom), problems with motion perception, and fatigue-related visual dysfunction. Previous OCT studies have shown robust correlations between lower RNFL values and reduced visual function scores after ON (1,3–6,10), providing a structural basis for the functional deficits frequently reported by MS patients. Below a threshold RNFL thickness of approximately 75 μm, there is a corresponding decrease in visual recovery after ON (1,10). Therefore, obtaining an OCT in this case could be helpful in establishing the relation between structural integrity and functional recovery in the anterior visual pathway for this patient, using ON as a single-lesion relapse model of MS.

There is some debate about whether RNFL loss in the absence of ON occurs in an insidious progressive manner or arises as a consequence of episodic inflammatory insults to the anterior visual pathways in MS patients (10–12). In a prior prospective case series, serial OCT measurements were used to detect subclinical ON in previously unaffected eyes of ON patients (10). In these cases, the patients did not report a history of pain or vision loss, but ophthalmic...
testing showed a new visual field deficit, an abnormal visual evoked potential, and newly detected thinning of the RNFL to support the diagnosis of subclinical ON (10). More recently (12), OCT testing performed in 299 patients (593 eyes) with at least 6 months of follow-up showed that RNFL thinning increased over time, with average losses of 2.9 μm at 2–3 years and 6.1 μm at 3–4.5 years. The pooled analysis (MS and ON affected and unaffected eyes) in this study showed that each year of follow-up was associated with an average 2-μm increase in RNFL thinning (P < 0.001, generalized estimating equation models) (12). From their findings, the authors concluded that progressive RNFL thinning occurs over time in MS, even in the absence of ON (12). Obtaining a baseline OCT in concert with ophthalmic testing could potentially provide the means to monitor RNFL thinning over time; and in turn, provide insights into mechanisms of brain injury and neurological disability in this patient, by distinguishing episodic inflammatory events from insidious disease progression.

MS traditionally has been viewed as an inflammatory demyelinating disorder of the CNS. Recently, the contributions of early axonal damage and neuronal loss toward neurological disability in MS patients have gained greater recognition. A recent study suggested that OCT testing may have identified a unique subset of MS patients, referred to as the macular thinning predominant phenotype. These patients manifested disproportionate thinning of the inner and outer nuclear layers, secondary to a presumed primary retinal pathology. Patients with the macular thinning predominant phenotype had worse overall neurological disability, with primary neuronal loss as a possible underlying disease mechanism. The findings from this study may indicate a potential role for OCT as a method of distinguishing different disease mechanisms in MS patients. As our knowledge regarding the interpretation of OCT findings in MS continues to evolve, we may gain insights that challenge conventional wisdom and advance our current

FIG. 2. A 30-year-old man with NMO and prior left optic neuritis manifests significant optic disc pallor in the left eye and marked intereye asymmetry (43 μm) of the mean retinal nerve fiber layer thickness, reflecting significant optic nerve damage in the left eye. His visual acuity was 20/20, right eye, and 20/100, left eye, with a left relative afferent pupillary defect, a dense central scotoma in the left visual field, and absent color vision in the left eye with Hardy-Rand-Rittler pseudoisochromatic plate testing (20/20 plates in the right eye).
understanding disease mechanisms and potential treatments for MS. For this reason, I would obtain a baseline OCT in this patient so that I may learn more about the potential factors that contribute to neurological disability in MS, which could enhance my ability to care for these patients in the future.

CON—OCT Is Not Necessary in This Patient: Gregory P. Van Stavern, MD

Although there is considerable evidence that OCT-measured RNFL values correlate (to some degree) with impaired visual and neurologic function, the degree to which this information can impact the day-to-day clinical management of ON and MS remains uncertain. I do not believe that we currently have enough evidence to justify the routine use of OCT and OCT-measured RNFL thickness in the management of ON and MS.

The utility of any clinical diagnostic test ultimately rests upon the degree to which it influences clinical decision making. In this context, we can envision several potential uses for OCT in daily practice, including to 1) establish a diagnosis in symptomatic patients, 2) screen for disease in asymptomatic patients, 3) provide prognostic information in patients with established disease, and 4) monitor efficacy of therapy, or progression of disease with or without therapy.

As the acute and chronic changes in RNFL and macular volume are nonspecific and can occur in a wide variety of ophthalmic diseases (14), OCT plays no major role in the clinical diagnosis of either typical ON or MS aside from screening for other conditions that can mimic ON (Fig. 3).

**FIG. 3.** A 38-year-old woman was referred to the neuro-ophthalmology clinic with probable left optic neuritis. Ten days earlier, she had developed a central scotoma in the left eye. Visual acuity was 20/20, right eye, and 20/30, left eye. The lack of relative afferent pupillary defect and lack of pain suggested an alternate diagnosis. There was a suggestion of macular thickening in the left eye, but this was subtle. Spectral-domain optical coherence tomography macular cube of the left eye demonstrated submacular fluid, establishing the diagnosis of central serous maculopathy, rather than optic neuritis.
Early loss of RNFL after acute ON has been shown to predict incomplete recovery. A 2010 study (11), building on previous work by Dr Costello et al (10) described 23 patients with acute, clinically isolated ON, who had an OCT performed at baseline followed at 6, 12, and 18 months. Measurements included RNFL and macular volume. The mean time to loss of 90% of initial RNFL was 2.38 months. Baseline RNFL thickness did not differentiate patients destined for poor visual recovery from those with good visual outcome. Those subjects with poor final visual outcome showed a significantly greater decrease from baseline RNFL to 3-month value, but only 5 subjects had poor recovery. At 12 months, RNFL thickness significantly correlated with logarithm of the minimum angle of deviation visual acuity, visual field mean deviation, and impaired color perception. Although these and other studies (10,15) have suggested a potential “window of opportunity” for intervention with a neuroprotective agent, sample sizes have been relatively small, and only 1 group (11) studied patients using a prospective rather than cross-sectional design. The fact remains that to date, no such neuroprotective agent exists, and even if one emerges, it will need to pass multiple hurdles before becoming widely available for clinical practice.

Few studies have explored the potential role of OCT in predicting conversion to MS in patients presenting with ON as a clinically isolated syndrome (CIS). Dr. Costello et al (16) retrospectively compared RNFL thickness in ON eyes vs non-ON eyes between groups of patients who developed MS and those who did not 2 years after an ON CIS. Temporal quadrant RNFL values were lower in the non-ON eyes of MS patients, but this difference was not statistically significant. These investigators concluded that RNFL thickness did not reliably identify patients at a higher risk for developing MS. Another group (17) studied 56 consecutive patients with CIS (18 with ON, 38 with non-ON CIS) and 32 controls subjects. Global and quadrantary RNFL values, as well as macular volume measurements, were obtained in all subjects. Their results showed that patients who developed clinically definite MS (n = 13) or those meeting the McDonald criteria (n = 23) did not have more severe RNFL atrophy or more macular volume loss. They also found no association between RNFL thickness and dissemination in space by Barkhof criteria or revised McDonald criteria at initial MRI, gadolinium enhancement at initial MRI, or development of MS at 6 months. They concluded that OCT measurements (both RNFL and macular volume) did not predict conversion to MS at 6 months.

NMO is an immune-mediated inflammatory disorder associated with preferential involvement of the optic nerve and spinal cord, and can present as demyelinating ON. There is good evidence that NMO is a distinct disease from MS, with poorer visual and neurologic outcomes and lack of response to conventional MS therapy (18). The ON associated with NMO is typically bilateral rather than unilateral, but is in many ways indistinguishable from MS-related ON. RNFL measurements could potentially serve as a biomarker to distinguish between NMO and MS, perhaps early enough to influence therapy. Several studies have found lower RNFL and macular volume measurements in patients with NMO vs MS. In a study of 47 patients with MS and 22 subjects with NMO, NMO-related ON eyes had lower RNFL values compared with MS (19). However, there was considerable overlap of OCT measures at each level of visual function, limiting the diagnostic utility of the test in an individual patient. In addition, subjects were not screened for other ophthalmic conditions known to alter RNFL, such as glaucoma and high myopia. Finally, the authors did not report what they considered an acceptable level for signal strength on OCT. Ratchford et al (7) measured RNFL thickness in 26 patients with NMO, 378 patients with transverse myelitis, 378 patients with relapsing-remitting MS, and 77 controls. The authors found significant thinning of RNFL in NMO-ON eyes relative to the other groups, and there was no significant difference among groups in RNFL thickness in non-ON eyes. A recent study (20) compared the results of automated perimetry in patients with NMO-related ON and MS-related ON and found that visual field mean deviation was significantly greater in the NMO-ON eyes than in the MS-ON eyes. Therefore, OCT in this setting may simply be another marker of incomplete visual recovery after ON, and it is unclear whether OCT measurements add any further prognostic information regarding the future development of NMO.

Finally, the changes in RNFL are not tissue specific. The thinning reflects loss of axons (and ganglion cell neurons) secondary to acquired, pregeniculate lesions in the visual pathway, although recently a purely pregeniculate origin has been challenged (21). Patients with lesions in the optic radiations had reduced overall RNFL compared with controls, indicating that decreased RNFL in some MS patients may reflect transsynaptic degeneration from post-geniculate axonal loss, accentuated, in some, by episodes of ON causing anterior visual pathway damage (22).

Although most of the thickness of RNFL using OCT is presumed to be from axons, other components, including blood vessels and glial elements, influence the measured thickness (23). A study of 4 eyes with no light perception vision (from different causes of optic neuropathy) and severe optic atrophy showed persistent RNFL thickness of approximately 40–45 μm, illustrating the contribution of other retinal elements (24). Chauhan and Marshall (25) performed progressive ablation of inner retinal tissue in cadaver eyes using excimer laser, with sequential
measurement of RNFL thickness using OCT. They found a persistent signal of approximately 36 μm even after destruction of the entire RNFL. These studies suggest that there may be a “floor effect,” in which clinically meaningful data cannot be obtained at RNFL thickness measurements of <40 μm (Fig. 4).

Studies documenting changes in OCT measurements over time suggest that there is considerable variability in measurements among (and within) patients, making it difficult to apply population statistics in cross-sectional studies to the individual patient. Similarly, since progression of disease (optic neuropathy and MS) is highly variable, it can be challenging to detect clinically meaningful (as opposed to statistically significant) change in RNFL thickness with longitudinal monitoring of disease activity. For example, what change in RNFL would be enough to warrant a change in therapy in a patient with MS?

RNFL thickness and macular volume measurements are currently used as a secondary outcome in many ongoing and planned future MS clinical treatment trials. This should provide higher quality longitudinal data about the utility of OCT in monitoring disease. Even so, the issues with test-retest reliability, heterogeneity, and variability in the clinical course of MS among patients and inherent limitations in the technology (floor effect, effect of other ocular disease on measurements) will remain. Further innovations in OCT technology may offer higher levels of resolution and better test-retest variability, but various OCT technologies are not quantitatively comparable to one another. Each new iteration disrupts previous collections of the longitudinal data, which might best inform daily practice. The effect of postgeniculate lesions on RNFL thickness and macular volume might indicate that the measurements obtained with OCT are a mixture of anterior and posterior visual pathway disease, and it may be difficult or impossible to dissect out the “pure” anterior visual pathway axons and ganglion cell neurons. OCT remains a powerful tool, which can complement or augment the metrics currently used to

![Image](image_url)

**FIG. 4.** A 46-year-old woman with neuromyelitis optica experienced several episodes of optic neuritis in each eye for more than 3 years. For the past year, visual acuity was 20/100, right eye, and no light perception, left eye. Fundus photographs demonstrate bilateral optic disc pallor. Stratus OCT measurements show residual retinal nerve fiber layer thickness of approximately 45–48 μm bilaterally with excellent signal strength. This likely represents “floor effects” of the residual retinal nerve fiber layer values, indicating either nonneuronal elements in the nerve fiber layer or an artifact inherent in the method of measurement.
monitor the progression in MS, such as neuroimaging, tests of visual function, and electrophysiologic studies, and will likely be included as an outcome measure in all future clinical trials. Future large-scale, longitudinal studies may provide data, which can more easily be transferred into clinical practice and patient care. More detailed analytic techniques, such as segmentation of the ganglion cell layer within the central macula, may provide more precise and meaningful structure-function relationships (2). However, I suspect that the use of OCT measurements in MS (and NMO) will remain limited to large-scale clinical trials and clinical research for the foreseeable future.

**Rebuttal: Fiona Costello, MD, FRCP**

I agree with many of the excellent points made by my colleague, Dr Van Stavern regarding the limitations of OCT in the routine management of ON and MS patients. Most OCT publications in MS patients have reported the findings from small, observational studies; and there is a paucity of long-term data. Caution must be exercised in interpreting what incremental changes in retinal architecture may mean in terms of global brain injury in MS. The severity of anterior visual pathway involvement may vary with the age, stage, and subtype of MS; and the extent of RNFL thinning may not be commensurate with other metrics of disease activity for this reason (26). As Dr Van Stavern has indicated, statistical significance is not synonymous with clinical relevance when it comes to determining the amount of RNFL thinning that is meaningful in the management of any given patient. Suffice to say, like any technology, OCT has inherent limitations. These limitations need to be fully understood, lest OCT become an imaging tool that is initially oversold, only to ultimately underdeliver in the area of patient care.

I would also echo the concerns raised by Dr Van Stavern regarding our ability to accurately track MS-related disease activity with OCT in “all comers” because the estimated yearly thinning of the overall RNFL (2 μm) has been below the detection limit of time-domain OCT technologies. This challenge will remain in the Fourier or spectral-domain OCT (SD-OCT) era because the longitudinal monitoring of RNFL is technically challenging (6). While promising methods are on the horizon, there remains uncertainty regarding the optimal approach to obtain and analyze longitudinal OCT data in MS (6). Going forward, the goal will be to define the amount of RNFL change measured by SD-OCT that represents pathology related to MS and to distinguish this “signal” from the “noise” of the technology (27).

I believe the most robust evidence for the use of OCT is in the ON “relapse” model of MS in which there is a clear time of onset, and potential interventions can be tested within a defined time “window” with objectively measurable end points. Even in this context, the effects of potential biases including age of onset of ON, disease duration, history of disease-modifying therapy use, acute management with high-dose corticosteroids (or lack thereof), gender, and MS subtype on RNFL thickness and macular measurements remain unknown. As OCT is implemented in ongoing randomized controlled trials of MS patients, many of the issues that have hampered previous observational studies will be addressed because the randomization process will help equalize the effects of potential confounders.

Returning to the original question and with due respect to the valid concerns raised by my colleague, I would argue that the question could be rephrased as follows: “Should OCT be used to complement our existing arsenal of tools in the management of patients with multiple sclerosis?” I believe that OCT findings should not be interpreted in the absence of validated opthalmic and/or neurological end points and should not be viewed as a putative “stand-alone” marker of disease activity in MS. As anyone who has ever depended upon GPS (Global Positioning System) can attest, there are obvious pitfalls to reliance on a tool without knowledge of its potential shortcomings. This is equally true for OCT as it is for the MRI. The latter is largely held as the gold-standard surrogate marker of disease activity in MS but is at best, “gold plated.” There is an established dissociation between MRI-measured lesion burden and corresponding deficits on the neurologic examination in MS patients, which is commonly referred to as the “clinical-radiological paradox” (28). While more than 95% of MS patients have MRI manifestations of focal or confluent abnormalities in the white matter of the CNS, the presence of such MRI lesions does not alone confirm the diagnosis of MS (29). Similar neuroimaging lesions can appear in people without clinical signs of disease, and many individuals older than 50 years have nonspecific white matter cerebral lesions, which need to be interpreted with caution (26). Despite these issues, few would suggest that the MRI does not have a role in the management of MS patients. Its utility comes from understanding the context of its use, and balancing the information it provides against its inherent limitations.

To answer Dr Van Stavern’s salient question of “What change in RNFL would be enough to warrant a change in therapy in a patient with MS?” my response would be that this decision should be based not upon a single OCT measurement but rather a careful consideration of several factors, including the patient’s clinical course, existing comorbidities, knowledge of his/her disease and indications for therapy, recent MRI findings, history and tolerance of
disease-modifying therapies, previous response to high-dose corticosteroids, potential contraindications to disease-modifying therapies, lifestyle factors, and, if appropriate, RNFL measurements. While it is true that we do not have established neuroprotective agents in MS, we must avoid the tendency to become somewhat nihilistic in our approach to the long-term management of MS. Instead, we must explore new technologies that might help us better understand the mechanisms and manifestations of disease activity. By doing so, we may be in a more proactive position to objectively measure the purported benefits of current, emerging, and future therapies for our patients.

Finally, OCT is not an esoteric, inaccessible ocular imaging device utilized only in obscure research laboratories, but rather a tool commonly used in clinical ophthalmic practice. Neuro-ophthalmologists need to understand it. I would recommend that our colleagues approach the question posed with a balanced attitude of skeptical curiosity and open-mindedness and determine for themselves how OCT may aid them in the care of their patients.

Rebuttal: Gregory P. Van Stavern, MD

Dr Costello presents a cogent argument for the routine use of OCT in ON and MS. I agree that OCT has enormous potential as a noninvasive method of analyzing and tracking axonal and neuronal loss in MS. However, there remain limits to our ability to infer clinically meaningful information from OCT in a way that informs daily clinical decision making. This test, as with all other testing techniques, must be integrated into the entire clinical picture and combined with other data to make the best decision for a particular patient on a particular day. This actually touches on an important point regarding the use of any paraclinical test, that of clinical expertise and interpretation. The utility of any diagnostic test relies not just on issues such as test–retest reliability, sensitivity, and specificity but on the skill and expertise of the clinician interpreting the test and placing the result into the entire clinical framework (26). Clinicians who utilize a diagnostic procedure frequently and have a high level of expertise in performing and interpreting the test may be better able to integrate the results of that test into patient care. Dr Costello is one of the foremost authorities on the use of OCT in clinical practice and MS, and she is also an expert neuro-ophthalmologist. She also practices in a large, well-respected MS center. Possibly, this combination of factors provides a more favorable environment for using OCT in daily practice.

I also agree that newer OCT modalities, such as high-resolution macular OCT and segmentation analysis, might provide the clinicians better data regarding disease status in their MS patients. However, issues regarding heterogeneity of disease and reproducibility may still hinder routine use, and these newer techniques have yet to be validated. At this time, I do not believe that OCT has a role in the day-to-day management of ON or MS.

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

We have witnessed multiple applications of OCT over the past decade. High-quality studies have demonstrated that OCT has enormous potential as a noninvasive method of analyzing and tracking axonal and neuronal loss in ON and even in MS patients without a history of ON. In the right hands, OCT measurements are reliable and reproducible; for the right patient, OCT provides valuable information. Each new study is a step toward a better understanding of how to use this technology to guide us in managing our patients efficiently and better outcome for clinical trials. As emphasized in this debate, it is certainly a mistake to think that OCT can replace measurement of visual function or other clinical markers of disease activity or could be a “stand-alone” test. However, it is probably equally invalid to reject OCT as an ancillary test in patients with ON and MS at this time. We predict that the incorporation of OCT findings into validated ophthalmic and neurological evaluations will likely become routine for neuro-ophthalmologists much in the same way that this has already occurred for automated visual field testing and for MRI in patients with ON and MS.

REFERENCES


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

The Scholarly Contributions of Daniel M. Jacobson, MD

Jonathan D. Trobe, MD

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The North American Neuro-Ophthalmology Society (NANOS) has but one named lectureship. Established in 2007, the Daniel M. Jacobson Memorial Lecture honors a man who accomplished a rare trifecta of scholarship: 1) the selection of topics of clinical importance; 2) the use of impeccable research methods; and 3) the production of superbly written publications.

In a 15-year period that extended from the beginning of his neuro-ophthalmology fellowship at the University of Iowa in 1985 to the onset of a terminal illness in 2000, he authored 75 articles or letters in respected peer-reviewed journals (Archives of Ophthalmology, American Journal of Ophthalmology, Ophthalmology, Journal of Neuro-Ophthalmology, Neurology, Annals of Neurology) (see Appendix, Supplemental Digital Content, http://links.lww.com/WNO/A58) In 48 of those 75 publications, he was either the first or the second author. During the decade before he became ill, he authored 44 papers at a rate of more than 4 publications per year. His publications included not only case reports but also pharmacologic experiments, case-control studies, case series, surveys, and topic reviews covering every aspect of neuro-ophthalmology. These works have had an enduring effect on patient management. In 2001, The Marshfield Clinic, where he conducted most of his work, recognized his achievements by bestowing on him its Gwen D. Sebold Research Fellowship Award.

In his scholarly endeavors, he was guided by three criteria. 1) Is this an important and unsettled issue? 2) Would addressing it make a difference in patient management? 3) Are the available means sufficient to permit meaningful research?

He was enormously successful. Here is a sample of the issues he addressed and the impact of his findings.

DOES PUPIL SPHINCTER SUPERSENSITIVITY TO DILUTE CHOLINERGIC EYEDROPS REALLY SIGNIFY A POSTGANGLIONIC DISORDER?

Background
Cholinergic supersensitivity of the iris sphincter is said to be a hallmark of a postganglionic lesion of the pupillomotor pathway. Investigators have questioned this idea, but with little rigor.

 Approach
In a prospective trial (1), he instilled pilocarpine 0.1% into the eyes of 3 groups of subjects: 1) 13 patients with
compressive or ischemic third nerve palsies; 2) 16 control subjects; and 3) 10 control subjects in whom one pupil had been previously dilated with hydroxyamphetamine.

Findings
The pupils of the 16 control subjects constricted minimally to dilute pilocarpine, allowing him to establish a cutoff for pathologic pupil constriction. Based on that cut-off, 9 of 13 patients with preganglionic third nerve palsies displayed cholinergic supersensitivity, a finding that was unrelated to the duration or cause of the palsy but was proportional to the degree of anisocoria. Among the control subjects with hydroxyamphetamine-induced anisocoria, the degree of constriction was correlated with the degree of anisocoria.

Conclusions
He concluded that cholinergic supersensitivity likely did not reflect trans-synaptic degeneration because it occurred in acute palsies. Because large pupils constricted more than small pupils to dilute pilocarpine, even in those without palsies, he postulated that pupil size may be a confounder.

Contribution
The meticulous and laborious design and execution of this study make it especially notable. It formed the basis of a later study (2) in which he showed that there was no difference in the amount of pupil constriction produced by dilute pilocarpine in the affected pupils of 11 patients with Adie syndrome and 11 patients with preganglionic compressive, traumatic, or congenital third cranial nerve palsy. The upshot of this pair of studies was to dismiss pupil pharmacologic finding that was unrelated to any other feature and which these features were not the main interest. In previous reports, the frequency of reported anisocoria ranged from 14% to 32%. To decide how far to push intracranial imaging in patients with acute palsies, it would be important to know if there is an upper limit to the degree of anisocoria in diabetic patients with ischemic third nerve palsies.

Approach
This study (4) used extremely rigorous criteria for patient selection and documentation of clinical features. There were

WHAT IS THE NATURE OF EPISODIC UNILATERAL MYDRIASIS?

Background
Episodic mydriasis raises fear on the part of the patient and triggers imaging studies on the part of concerned physicians. But this phenomenon is rarely observed by physicians, so its mechanism has been a matter of conjecture. Are the features suggestive of a parasympathetic or a sympathetic disturbance? Who is at risk? Is it a manifestation of migraine? Does anything precipitate the attacks?

Findings
The 24 patients included 19 women (80%), mostly between the ages of 20 and 50 years. Eleven patients were examined during an attack, 7 by the author and 4 by other neuro-ophtalmologists. Many patients had a history of migraine (58%), but most mydriatic episodes did not occur during typical migraine attacks. Events appeared to be unprecipitated, but there were usually other symptoms, such as blurred vision in the affected eye (62%), headache (37%), and discomfort around the affected eye (21%). The attacks occurred with a broad frequency (median: 2.5 attacks per month), and a duration ranging from 10 minutes to 7 days (median: 12 hours). Near vision and accommodation were impaired in 4 patients. Anisocoria ranged from 1 to 3 mm, increasing in light in 6, remaining unchanged with different levels in 1, and increasing in darkness in 1. There was no toxicity or distortion of the pupils and there were no other neuro-ophtalmic abnormalities. Dilute pilocarpine testing was normal in 6 of the 7 patients who were tested, showing supersensitivity in only 1 patient. Among 24 patients examined in between attacks, no notable findings were discovered.

Conclusions
Episodic mydriasis probably represents a temporary and isolated disorder of parasympathetic iris innervation in some patients and sympathetic overactivity or underactivity in others. Migraine is often a background condition, but these episodes are usually not coincident with a migraine attack.

Contribution
This publication expanded the profile of a common and important clinical phenomenon. For the first time, it gathered a reasonably large number of patients who were examined during an attack and tested for signs of pupillomotor denervation. It showed that useful information can be gathered on such a clinical disorder with a valid survey instrument sent to reliable observers.

HOW MUCH ANISOCORIA OCCURS IN PATIENTS WITH THIRD NERVE PALSY CAUSED BY DIABETES?

Background
Classic teaching has been that anisocoria and impaired pupil constriction to light are features more characteristic of compressive than ischemic lesions of the third nerve. But documentation has been based on retrospective studies in which these features were not the main interest. In previous reports, the frequency of reported anisocoria ranged from 14% to 32%. To decide how far to push intracranial imaging in patients with acute palsies, it would be important to know if there is an upper limit to the degree of anisocoria in diabetic patients with ischemic third nerve palsies.

Approach
This study (4) used extremely rigorous criteria for patient selection and documentation of clinical features. There were
26 patients with diabetes and isolated third nerve palsy, all examined by the author and defined by appropriate duc-
tional deficits, the absence of other pertinent clinical find-
ings or imaging evidence for an alternative cause, and full
recovery of the palsy within 6 months. The subjects had
a firm biochemical diagnosis of diabetes. Pupil size was
measured under controlled lighting and fixation conditions
with a standard pupil gauge.

Findings
Fourteen patients (54%) were found to have anisocoria,
mostly 1 mm or less (80%), and not more than 2.5 mm. In
some of the patients, the anisocoria did not resolve,
suggesting that it might have been at least partially caused
by diabetic dysautonomia.

Conclusions
Anisocoria is common in diabetic third cranial nerve palsy
but rarely exceeds 1 mm.

Contribution
This publication suggested that anisocoria of greater than 1
mm should not be attributed to diabetes. Moreover,
because the mechanism of third nerve palsy in patients
with hypertension and other risk factors for arteriosclerosis
may be similar to that in diabetes, one could reasonably
assert that anisocoria of greater than 1 mm is strong
evidence of a nonischemic cause of isolated third nerve
palsy. In a later study of 24 consecutive cases of third cranial
palsy with anisocoria of 0.5 to 2 mm (5), the author showed
that compressive lesions (including aneurysms) were as
commonly the cause as microvascular ischemia. The upshot
of these 2 studies is that a small amount of anisocoria is
common in ischemic third nerve palsies (“relative pupil
sparing”), but it can also occur in nonischemic palsies for
which urgent imaging is necessary.

WHAT ARE THE RISK FACTORS FOR
ISCHEMIC OCULAR MOTOR PALSY?

Background
Diabetes has been a well-established risk factor for ischemic
(“microvascular” and “vasculopathic”) ocular motor cranial
nerve palsies. However, it is also widely known that patients
without diabetes are prone to such palsies. What are the risk
factors in those patients? No study had applied adequate
epidemiologic methods to answering this question.

Approach
In this case–control study (6), strict inclusion and exclusion
criteria provided assurance that the diagnosis of an ischemic,
extra-axial cause for the palsy was firm. For the 65 patients
who met entry criteria, examination included a thorough
history probing standard arteriosclerotic risk factors, height,
weight, blood pressure, cervicothoracic auscultation, hemo-
gram, random glucose, cholesterol, and electrocardiography.
Most patients who did not have diabetes underwent brain
imaging, acetylcholine receptor antibody testing, chest
x-ray, sedimentation rate, and protein electrophoresis, as
well as tests for antinuclear antibody, syphilis, and Lyme
disease. Each patient was matched for age and gender with
a patient attending The Marshfield Clinic who did not have
an ocular motor palsy. The control patients had undergone
virtually the same battery of medical assessments as the palsy
patients. The three ocular motor cranial nerve palsies were
almost equally represented.

Findings
The 2 risk factors that emerged as significant for ischemic
ocular motor palsy were diabetes and left ventricular
hypertrophy. Hemoglobin A1C was higher among diabetics
with palsies than in those without them, suggesting that
poorly controlled diabetes may be an important risk factor.
Because hypertension was so common among control
subjects, it was not significantly associated with a palsy.
However, a marker of poorly controlled hypertension, left
ventricular hypertrophy, was implicated.

Conclusions
The principal risk factor for ischemic ocular motor cranial
nerve palsy is poorly controlled diabetes. Chronic hyper-
tension, as evidenced by left ventricular hypertrophy, is
probably an additional risk factor, although it could not be
established by blood pressure measurements in this study.

Contribution
This was the first of 2 elegant in-house case–control studies
of risk factors for a common disorder. In establishing with
proper methods that poorly controlled diabetes and chronic
hypertension are likely the chief causes of ischemic ocular
motor cranial nerve palsies, it signaled the need to modify
these risk factors.

OVER WHAT PERIOD OF TIME DO
ISCHEMIC THIRD AND SIXTH NERVE
PALSY PROGRESS?

Background
Conventional wisdom has been that ocular motor cranial
nerve palsies caused by extra-axial nerve ischemia reach
a maximal deficit within days of onset. Therefore, pro-
gression of deficit beyond a few days would suggest an
alternative cause such as a compressive lesion.

Approach
From the author’s Marshfield Clinic patient files extending
over the previous 8 years, he reviewed clinical data using the
rigorous inclusion criteria established for his earlier study of risk factors for ischemic ocular motor cranial nerve palsies.

**Findings**

Among 16 patients with third nerve palsy (7), 11 (69%) showed progressive ductional deficits over a period of 3 to 23 days (median: 10 days). Those who had progression took a mean of 11.2 weeks to resolve, whereas those who had no progression took a mean of 7.2 weeks to resolve. The progressive and nonprogressive groups could not be distinguished by risk factor profile. Similar findings were noted in a later study of 35 patients with ischemic sixth nerve palsy (8).

**Conclusions**

Progression of ductional deficits over a period extending up to 3 weeks occurs in ischemic ocular motor cranial nerve palsies.

**Contribution**

These studies firmly established that, even though the mechanism of these ocular motor cranial nerve palsies is believed to be ischemia, ductional deficits may continue to worsen over a week or more. Such progression should not cause the clinician to reject an ischemic cause unless there are other persuasive features. The author acknowledged that patients were not examined daily, so he might have overestimated the duration of progression.

**HOW DO YOU DISTINGUISH IDIOPATHIC FROM NON-IDIOPATHIC DIVERGENCE INSUFFICIENCY?**

**Background**

Adult-onset divergence insufficiency, defined as comitant esodeviation present only with distance viewing and with full ocular ductions, is a perplexing entity. It is known to occur in otherwise neurologically intact individuals (“primary” type) but also in those with a variety of neurologic conditions, including brainstem lesions and increased intracranial pressure (ICP) (“secondary” type). The natural history of the primary type had been unknown.

**Approach**

In a retrospective study (9) of patients examined at The Marshfield Clinic over the previous 12 years, the author identified 20 patients who had no other neurologic manifestations (primary type) and 15 patients who had other pertinent neurologic manifestations (secondary type). The clinical features of the 2 groups were described on initial evaluation and on follow-up.

**Findings**

There were 5 important findings: 1) the ocular motility and alignment measurements at the time of initial evaluation did not distinguish the 2 groups; 2) in the primary group, there were no pertinent clinical or imaging abnormalities on follow-up; 3) in the primary group, the diplopia resolved in nearly half of the patients over a maximum period of 26 months; 4) in the secondary group, the underlying neurologic condition had already been diagnosed at the time of initial evaluation or evident on that examination; 5) in the secondary group, increased ICP was the most common underlying condition, followed by cerebellar degeneration, temporal arteritis, progressive supranuclear palsy, and brainstem stroke.

**Conclusions**

Although the ocular motor features did not distinguish the primary (idiopathic) and secondary groups, they could be separated by the fact that an underlying neurologic condition was evident in all patients in the secondary group at the time of initial evaluation.

**Contribution**

Although retrospective and small, this study was suitably designed to tell clinicians that there will be clinical clues at outset as to whether the patient with divergence insufficiency has an idiopathic condition that requires no further workup or a nonidiopathic condition that does. It also suggested that spontaneous improvement occurred often enough to warrant postponement of realignment surgery. An open question is whether the neurologic abnormalities would be obvious to a non-neurologist! The finding of spontaneous improvement in the idiopathic group is at variance with my observations, so I wonder if the author inadvertently included some patients with spasm of the near reflex or subtle ischemic sixth nerve palsy.

**IS THE OPTIC NEURITIS THAT BEGINS AT OR AFTER AGE 50 SIMILAR TO THE OPTIC NEURITIS OF YOUNGER INDIVIDUALS?**

**Background**

The clinical profile of typical optic neuritis, which affects individuals under age 50, has been well established by the Optic Neuritis Treatment Trial and other large studies. Excluded from those studies were older patients because the diagnosis of optic neuritis would have been uncertain at study entry. Could the results from the studies of younger people be generalized to older people?

**Approach**

This retrospective study (10) involved 14 patients ranging in age from 50 to 72 years (average: 58 years) after exclusion of more than half of a pool of 31 patients because of confounding features. All patients had undergone appropriate studies to exclude alternative diagnoses.
Findings
The optic neuritis in these older individuals had clinical features identical to the optic neuritis in younger patients.

Conclusion
The optic neuritis of late onset is probably the same disorder as that of earlier onset.

Contribution
This study provided important information about optic neuritis, a diagnosis often dismissed if it develops for the first time after age 50. The author cautioned that in this cohort, one can be sure only in retrospect that the diagnosis is typical optic neuritis, so that a wider evaluation should be done at the time of initial evaluation to exclude other optic neuropathies.

WHAT ARE THE RISK FACTORS FOR NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY?

Background
Hypertension and diabetes had been assumed to be important risk factors for this condition, but the information came largely from uncontrolled descriptive studies.

Approach
The author received strong support from The Marshfield Clinic biostatisticians in designing this elaborate population-based case–control study (11). Patients met strict criteria for the diagnosis of nonarteritic anterior ischemic optic neuropathy (NAION). To reduce biases as completely as possible, the author chose not one but 2 control groups, one from a health database established for the surrounding community and the other from patients examined by internists or family physicians at The Marshfield Clinic. Standard arteriosclerotic risk factors were selected for study.

Findings
Diabetes was the most robust risk factor, but it accounted for only a small proportion of cases. Hypertension did not meet the standard of a risk factor, perhaps because it was common in the control groups.

Conclusions
Diabetes, but not hypertension, is a risk factor for nonarteritic ischemic optic neuropathy.

Contribution
This study established a new model for examining risk factors in neuro-ophthalmic disorders. The failure to show hypertension as a risk factor differs from other studies with less rigorous design and is intriguing. Other factors must be at play, such as cupless optic discs (“disc at risk”) or sudden drops in blood pressure.

DOES A RELATIVE AFFERENT PUPIL DEFECT OCCUR IN PATIENTS WITH UNILATERAL OPTIC NERVE DYSFUNCTION IN LEBER HEREDITARY OPTIC NEUROPATHY?

Background
Several investigators have reported that there was no relative afferent pupil defect (RAPD) in patients with Leber hereditary optic neuropathy (LHON) who have clinically apparent optic neuropathy in only one eye. The absence of a RAPD is meaningful because it would lead clinicians away from a diagnosis of optic neuropathy.

Approach
In this study (12), entry criteria included patients with proven LHON mutations, normal visual acuity and visual field in the unaffected eye, no confounding medical conditions, and an RAPD measured with neutral density filters. To the author’s single case were added 4 from the University of Iowa, 2 from neuro-ophthalmologists trained at the University of Iowa, and 3 from NANOSNET. To show whether the RAPD in LHON obeyed the principles identified for RAPDs in other optic neuropathies, the author correlated the size of the RAPDs in the LHON patients with their visual field loss using a template designed by Stanley Thompson, MD.

Findings
All 10 patients had RAPDs. They ranged from 0.3 to 1.8 log units, with all but 1 patient having 0.6 log units or higher, identifying a defect easily observable with the swinging light test. The RAPDs were of a size expected on the basis of the extent of visual field loss.

Conclusion
Easily discernable RAPDs are always present in patients with apparently uniocular LHON.

Contribution
This first rigorous study of RAPD in LHON was limited by the small patient cohort. Contrary to the findings in this study, observers have continued to note the absence of a RAPD in this setting, and the subsequent discovery of melanopsin-containing ganglion cells has provided a rationale for this phenomenon.

DOES COMPRESSION OF THE OPTIC NERVE BY AN ENLARGED SUPRACLINOID CAROTID ARTERY CAUSE VISUAL LOSS?

Background
Compression of the intracranial optic nerve by an enlarged supraclinoid carotid artery was a postulate for optic nerve
damage before the advent of advanced imaging. But neurosurgical decompression was unhelpful and sometimes caused worsening of the optic neuropathy. Because enlarged carotid arteries are associated with arteriosclerosis, optic neuropathy in these patients was alternatively attributed to NAION. The author had accumulated a roster of patients who lacked the clinical features of NAION and appeared to have progressive optic neuropathy without explanation other than clearly visible displacement of the intracranial optic nerve by an enlarged supraclinoid carotid artery.

Approach
The patients were drawn from the author’s files at The Marshfield Clinic.

Findings
In the first of 2 publications (13), the author reported the frequency of imaging evidence of compression in 100 consecutive patients without evidence of optic neuropathy who had undergone T1 coronal magnetic resonance imaging for conditions unrelated to loss of vision. He found that compression occurred on at least one side in 17% of patients. In the second publication (14), he described the results in 18 patients with progressive optic neuropathy and compression of the affected optic nerve. Many had been followed for glaucoma but had been referred for neuro-ophthalmological evaluation because they had visual field loss considered atypical for that diagnosis. Some patients had diabetes or hypertension, but none reported acute visual loss. The progression of visual loss extended from 3 weeks to 21 years, with a median of 4 years, but this information was largely gleaned from the records of referring ophthalmologists. Most patients had progressive visual acuity loss but in only 4 patients was there solid documentation of progressive visual field loss. Most patients had nerve fiber bundle visual field defects; only one patient had a chiasmal pattern. Optic disc pallor was present in most affected eyes, cupping consistent with glaucoma was present in only 2 eyes.

Conclusions
There are patients who have progressive optic neuropathy and imaging evidence of ipsilateral carotid artery compression of the optic nerve. Given the lack of evidence for an alternative cause, compression is the likely mechanism.

Contribution
This is the author’s most controversial work. The data were acquired and displayed scrupulously. But documentation of progression was often based on the documentation of referring physicians. Acknowledging that carotid compression of the optic nerve is often noted incidentally in patients without optic neuropathy, the author advised long-term observation to document progressive damage. In the years since these publications, no one has followed through on his idea.

WHAT ARE THE APPROPRIATE DIAGNOSTIC CRITERIA FOR THE DIAGNOSIS OF IDIOPATHIC INTRACRANIAL HYPERTENSION?

Background
The criteria for diagnosing idiopathic intracranial hypertension (IIH; previously called “pseudotumor cerebri”) were first elaborated in 1937 by Walter Dandy, MD, a neurosurgeon at Johns Hopkins University and the inventor of pneumoencephalography. The criteria included clinical manifestations of increased ICP with normal cerebrospinal constituents, normal or small ventricles ascertained by air ventriculography, and no evidence of a brain mass. Acknowledging advances in neuroimaging, Lawton Smith, MD substituted computed tomography for ventriculography in 1985.

Approach
This review article, authored in collaboration with Friedman (15) was prompted by the recognition that the diagnostic criteria for IIH needed updating to encompass new evidence.

Findings
There were 4 principal modifications. First, the symptoms and signs should include the visual manifestations of papilledema. Second, the lumbar puncture opening pressure should be more than 250 mm H₂O as recorded in the lateral decubitus position because research had established that opening pressures between 200 and 250 mm H₂O are within the normal range. Third, brain vascular imaging should exclude occlusive disease of the dural venous sinuses as the cause of high ICP. Fourth, there should be no contributory systemic illness or medication use.

Contribution
Although the disease had not changed since Dandy’s time, more mimickers had been recognized and imaging methods had evolved. The timely modifications wisely expanded the definition of IIH to take account of these facts.

These excerpts from the author’s extensive scholarly work (see Appendix, Supplemental Digital Content) show how one well-liked, respected, and talented individual, backed by a medically sophisticated institution with good recordkeeping and a relatively captive population, can generate a body of clinical research without extensive financial support or collaboration. It does not convey how honestly and graciously he conducted his research and how beautifully he phrased his submissions.


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Each publication begins with a succinct recapitulation of the issue. That is followed by a review of the contributions others have made, generously acknowledging the good work and gently stating the flaws. With a clear framing of what is left to be done, the reader can appreciate the need for the methodology, which is thoughtfully designed and clearly explained. Biostatisticians play a critical role in study design. Patients who do not fit are summarily excluded. The results are compactly displayed in text, figures, and tables that are easy to read. In discussing the results, the author adheres to the narrowest of implications, always providing a reasonable explanation and admitting the limitations of the studies.

The scholarly contributions of Daniel M. Jacobson, MD have set a high investigative bar for us, his colleagues, and established clinical guidelines that vastly improve the care of patients with neuro-ophthalmic disorders.

REFERENCES

Literature Commentary


Background: Clustered acetylcholine receptor antibodies (clustered AchR-Abs) have been detected in a proportion of patients with previously "seronegative" (SN) generalized myasthenia gravis (GMG), but their presence in patients with ocular MG (OMG) and their pathogenicity in vivo are unknown.

Objective: To test the presence of clustered AchR-Abs and their pathophysiologic properties in patients with SNMG.

Design: Screening and diagnostic tests.

Setting: Regional specialist myasthenia center and clinical laboratory.

Patients: Serum samples from 16 patients with SN and OMG were tested for binding to clustered AchRs. Results from 28 further SN patients (14 OMG) were correlated with their single fiber electromyography values.

Main outcome measures: Presence, complement-fixation capacity, correlation with neurophysiologic changes, and in vivo pathogenicity of clustered AchR-Abs.

Results: Up to 50% of patients with previous SN-OMG had complement-fixing IgG1 clustered AchR-Abs. IgG binding (n = 28) and complement deposition (n = 21) each correlated with the mean consecutive difference (jitter) on single-fiber electromyography. Injection of purified IgG from 2 patients with clustered AchR-Abs into wild-type or complement regulator-deficient mice reduced miniature end plate potential amplitudes to an extent similar to that found with AchR-Abs, and complement was deposited at the end plates. A trend was noted toward an increase in the number of packets of acetylcholine released (quantal content).

Conclusions: A proportion of patients with SN-GMG or OMG have clustered AchR-Abs that correlate with their electrophysiologic features. Clustered AchR-Abs can passively transfer disease to mice, demonstrating their pathogenicity, and the mechanisms seem similar to those of patients with typical AchR-Abs.

Approximately 50% of patients with ocular myasthenia gravis (OMG) are seronegative (SN) for the 3 most common acetylcholine receptor antibodies (AchRab): binding, blocking, and modulating. Of these, very few demonstrate antibodies to muscle-specific kinase (MuSK), which makes a serologic diagnosis more challenging. Jacob et al describe a new assay, clustered AchRAb, which potentially could improve detection. They call it clustered because they transfect human embryonic kidney cells with AchR's and then add a protein, rapsyn, which causes these AchR to cluster densely together on the cell surface. The authors incubate these cells with the patient sera, wash, and fix them, and then add monochlonal Ab for detection of human immunoglobulin G (IgG) and IgM Ab. Eight of 16 patients with SN-OMG showed clustered AchRAbs. Because MG results in complement-mediated damage to neuromuscular junctions, the authors also assessed complement activation by detecting membrane attack complexes. Ten of 16 SN-OMG patients were positive for complement activation. Finally, the authors injected purified IgG from patient sera into complement regulator deficient mice and found electrophysiologic and histopathologic changes consistent with MG.

There is no obvious difference in disease activity or response to treatment among patients with Ab-positive or Ab-negative OMG. This paper suggests that the current commercially available assays are incapable of detecting the Ab to the AchR among those SN patients rather than true absence of these Abs. Indeed, the techniques described here were able to detect clustered AchRab in only 50% of the OMG patients. Further room for improvement may be possible, but the current data are encouraging.

—Michael S. Lee, MD

In contrast to anti-MuSK antibodies, which are rarely positive in the 50% of OMG patients "seronegative" by the conventional AchRab patients, it is helpful to have a test that is positive in 50% of those patients. If used clinically, this leaves only 25% requiring further diagnostic testing (i.e., single fiber electromyography). What remains to be seen is the sensitivity and specificity in larger populations and whether this test becomes commercially available.

—Mark L. Moster, MD


Purpose: To assess quantitatively the efficacy of monovision correction in the treatment of acquired small-angle binocular diplopia in adult patients.

Design: Prospective, interventional case series.

Methods: Twenty patients with symptomatic diplopia were enrolled in a prospective treatment trial at a tertiary university neuro-ophthalmology practice. All had stable deviations of 10 prism diopters or less for more than 3 months. Each received monovision spectacles, contact lenses, or both with distance correction in the dominant eye. The authors performed refraction using the spherical equivalent and compared the results with an objective method using a modified optotype chart. The patients then wore monovision spectacles for 3 months. The authors assessed visual acuity and discomfort using a visual analog scale. The monovision spectacles were worn for 3 months, and the patients were then assessed for visual acuity and discomfort.

Results: The authors found that monovision spectacles improved visual acuity and reduced binocular disparity. The patients reported less discomfort with monovision spectacles than with traditional lenses. The authors concluded that monovision spectacles are a viable option for the treatment of small-angle diplopia.

—Mark L. Moster, MD


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eye. Half received a +3.00-diopter add and the others received +2.50 dipters. The validated and standardized Diplopia Questionnaire and Amblyopia and Strabismus Questionnaire were used to quantify the efficacy of monovision correction for diplopia by measuring the functional impact on vision-specific quality of life.

**Results:** primary outcome: Based on the results of the Diplopia Questionnaire, 85% of patients experienced significant improvement in diplopia symptoms after monovision correction. There was a statistically significant 58.6% improvement in the Diplopia Questionnaire score in our patients (P < .0001), secondary outcome: The Amblyopia and Strabismus Questionnaire scores demonstrated improved quality of life and daily function after monovision correction (P = .03), especially in the areas of double vision (P = .0003) and social contact and appearance (P = .0002).

**Conclusions:** Monovision decreased the frequency of diplopia and improved subjects’ quality of life. Monovision may be a feasible alternative for presbyopic diplopic patients who are dissatisfied with other conservative treatment options.

The treatment of patients with diplopia is a challenge, with many having persistent symptoms despite prescription of prisms, botulinum toxin injections, and strabismus surgery. This prospective study of monovision to treat small-angle diplopia enrolled presbyopic patients older than 45 years with symptomatic diplopia greater than 50% of the time who were not considered surgical candidates because of the small angle of deviation. Some patients had difficulty with adapting to monovision or reported worsened stereovisual acuity. Nonetheless, at least half the patients had significant improvement. Monovision is a welcome additional therapeutic option in patients with diplopia.

—Mark L. Moster, MD

This is not something that I would have considered, but it certainly makes sense. Sometimes I will prescribe a high plus lens in one eye to adequately blur out the second image. But as this article points out, why not make use of the “blurred” image! I cannot help but think this could also apply to patients with deviations greater than 10 prism dipters who cannot fuse with prisms or following eye muscle surgery.

—Michael S. Lee, MD


**Purpose:** Evaluation of the effect of angle of incidence on macular thickness and volume measurements obtained by spectral-domain optical coherence tomography (OCT).

**Methods:** A total of 30 eyes from 15 healthy young subjects underwent macular cube volume scans (512 × 128 protocol) following dilation using the Cirrus spectral domain OCT. For each eye, scans were obtained by positioning the scanning beam in the center of the dilated pupil, as well as in four eccentric positions (approximately 3 mm from the center), superior, inferior, nasal, and temporal to the pupillary center, to create oblique angles of incidence between the light beam and retina. In all cases, the region scanned by the volume cube was centered on the fovea. Macular thickness and volume measurements were computed for volume scan acquisitions, and differences in values between eccentric scans and the central scan were analyzed.

**Results:** Retinal thickness and volume values were observed to increase significantly in all subfields for all eccentrically-obtained scans compared to scans obtained through the center of the pupil. The mean increase in thickness for the various scan positions and subfields ranged from 3.76 to 11.38. Scans that were displaced temporally consistently showed the greatest increase in thickness and volume, whereas nasally positioned scans showed the least increase. The increase in retinal thickness for all subfields correlated significantly with angle of inclination or tilting of the retina.

**Conclusions:** Macular thickness and volume measurement results may be affected significantly by positioning of the scanning beam in the pupil and resultant angle of incidence on the retina. These findings suggest that care should be taken to position the scanning beam consistently in the center of the pupil to achieve reliable measurements.

Nearly all (note that I said “nearly all,” not “all”) neuro-ophthalmologists use optical coherence tomography (OCT) to some extent, whether it is to measure retinal nerve fiber layer (RNFL) or to look for macular edema. In some cases, we follow serial measurements to determine progression or stability. The OCT machines typically are equipped with automated algorithms to calculate measurements, and these measurements are predicated upon b-scans taken through the center of the pupil and centered on the fovea or the optic disc. The authors compared the OCT retinal thickness of normal volunteers aimed eccentrically through the pupil vs centrally through the pupil with both centered on the fovea. The eccentric entry generates a tilted b-scan meaning either the left or right side of the scan is higher than the opposite side. They found that eccentric OCT scans showed thicker maculae than centered ones. The maximal difference was 30 μm or 10% of retinal thickness.

Before you say, “this is so unlikely to happen,” I spoke with my photography team and they mentioned they sometimes shoot eccentrically through the pupil if some central lens or corneal opacity precludes a high-quality image. Intuitively, this would be the same for the RNFL, where the tilted image would show a “thicker” RNFL compared with the en face one. This may be an issue to discuss with whoever does OCT scanning in the office. Also, we should proceed with caution when interpreting an OCT that shows a tilted b-scan.

—Michael S. Lee, MD

This article points out one important technical factor affecting thickness measurements in macular OCT. For an individual patient in a single study, the amount of change...
noted would not likely alter a clinical diagnosis (e.g., a 5 μm centered subfield difference when normal is close to 300 μm). However, in following changes in a patient’s clinical course or in clinical trials monitoring change over time, it would be important to keep the angle of incidence similar each time.

—Mark L. Moster, MD


Objective: Neuroimaging studies frequently are ordered to investigate neuro-ophthalmic symptoms. When misused, these studies are expensive and time consuming. This study describes the type and frequency of neuroimaging errors in patients referred to an academic neuro-ophthalmology service and measures how frequently these neuroimaging studies were reinterpreted.

Design: Prospective cohort study.

Participants: Eighty-four consecutive patients referred to an academic neuro-ophthalmology practice.

Methods: From November 2009 through July 2010, 84 consecutive new patients who had undergone a neuroimaging study in the last 12 months specifically to evaluate their presenting neuro-ophthalmic symptoms were enrolled prospectively. Participants then underwent a complete neuro-ophthalmic evaluation, followed by a review of prior neuroimaging. Questions regarding appropriateness of the most recent imaging, concordance of radiologic interpretation, and re-evaluation of referring diagnoses were answered by the attending physician.

Main outcome measures: The frequency and types of errors committed in the use of neuroimaging and the frequency of reinterpretation of prerereferal neuroimaging studies after neuro-ophthalmic history and examination.

Results: Most study participants (84.5%; 71/84) underwent magnetic resonance imaging before referral; 15.5% (13/84) underwent only computed tomography. The rate of suboptimal neuroimaging studies was 38.1% (32/84). The 3 most common reasons for suboptimal studies were incomplete area of imaging (34.4%; 11/32), wrong study type (28.1%; 9/32), and poor image quality (21.9%; 7/32). Twenty-four of 84 subjects (28.6%) required additional neuroimaging. The authors agreed with the radiology interpretation of the prior neuroimaging studies in most patients (77.4%; 65/84). The most common anatomic locations for discordance in interpretation were the intraorbital optic nerve (35%; 7/20) and the brainstem (20%; 4/20).

Conclusions: There was a high rate of suboptimal neuroimaging studies performed in patients referred for neuro-ophthalmologic examination. These findings have significant implications given the increasing attention to resource use currently and in the near future.

Early in my career, when magnetic resonance imaging (MRI) emerged, there were predictions that the field of neuro-ophthalmology would become obsolete and replaced by neuroimaging ordered by referring clinicians. A few years later, we were receiving many consultations of asymptomatic patients based on abnormalities found on neuroimaging that needed clinical correlation.

As the authors point out, their study is limited by small sample size, inherent subjectivity in defining appropriateness, and inherent bias in reinterpretation of imaging. Nonetheless, the findings are similar to previous reports and collective clinical experience that neuroimaging performed before neuro-ophthalmic consultation is often suboptimal in numerous ways. My own sense is that when patients come in with a neuroimaging diagnosis, the diagnosis is changed approximately 20% of the time after reviewing the studies in the context of the clinical findings.

In addition to the neuroimaging issue, the authors found that when patients arrived with a referring diagnosis, the diagnosis was changed 69% of the time following neuro-ophthalmic consultation.

The training and ongoing experience of neuro-ophtalmologists and other subspecialists add value to patient care and is crucial for appropriate allocation of resources. A combination of diagnostic modalities with a skilled clinician guiding the testing yields the best results.

—Mark L. Moster, MD

This comes as no surprise to the neuro-ophthalmologist. As Mark alludes to, this study tells us what we already know. I think the big question is why? The current paper references the study of Elmalem et al (1), which focused on imaging of aneurysmal third nerve palsies. If an aneurysm was not diagnosed, the authors assumed this would be due to suboptimal scans. Rather, they found contributing factors included that the wrong diagnosis was given to the radiologist and the radiologist lacked neuroradiology training. In the current paper by McClelland et al, the authors acknowledge the inability to gather this information.

So what are the causes of suboptimal neuroimaging in patients that we see in consultation? Is most of the problem ignorance on the part of the referring clinician? Or is it because the support staff (secretary, nurse, or ophthalmic technician) fills out the imaging request? Is it because the radiology protocols for an orbital MRI do not have fat suppressed images or the clinician did not order an orbital MRI? Did the radiologist have too many films to read that day or lack of information or proper training? If we could dig deep and determine the answer(s), then perhaps we, as a neuro-ophthalmic community, could help improve the cost-effectiveness of imaging studies for our patients.

—Michael S. Lee, MD


Aim: To investigate the accuracy of individual and combinations of signs on brain magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) in the diagnosis of idiopathic intracranial hypertension (IIH).

Materials and methods: This study was approved by the institutional research ethics board without informed consent. Forty-three patients and 43 control subjects were retrospectively identified. Each patient and control had undergone brain MRI and MRV. Images were anonymized and reviewed by three neuroradiologists, blinded to clinical data, for the presence or absence of findings associated with IIH. The severity of stenosis in each transverse sinus was graded and summed to generate a combined stenosis score (CSS). The sensitivity, specificity, and likelihood ratios (LR) were calculated for individual and combinations of signs.

Results: Partially empty sella (specificity 95.3%, P < 0.0001), flattening of the posterior globes (specificity 100%, P < 0.0001), and CSS < 4 (specificity 100%, P < 0.0001) were highly specific for IIH. The presence of one sign, or any combination, significantly increased the odds of a diagnosis of IIH (LR+ 18.5 to 46, P < 0.0001). Their absence, however, did not rule out IIH.

Conclusions: Brain MRI with venography significantly increased the diagnostic certainty for IIH if there was no evidence of a mass, hydrocephalus, or sinus thrombosis and one of the following signs was present: flattening of the posterior globes, partially empty sella, CSS < 4. However, absence of these signs did not exclude a diagnosis of IIH.

I know this has come up before and may seem like old news, but I was at a meeting where I presented a complicated case of idiopathic intracranial hypertension (IIH). A senior neuroophthalmologist commented that the diagnosis was a bit questionable because the patient did not have a partially empty sella. I did not know the pertinent data and could not definitively say how right or wrong he/she was. Additionally, most papers on this subject determine the sensitivity and specificity of either magnetic resonance imaging (MRI) or magnetic resonance venography (MRV) findings in IIH, whereas the current study looks at both studies together.

Maralani et al retrospectively identified patients with IIH and a control group without IIH who underwent brain MRI and MRV. They assessed the studies in a masked fashion for 10 different features. There were significantly more women in the IIH group, but otherwise the groups were similar. The sensitivity of having any one of the 3 most specific findings (empty sella, flattened globe, narrow transverse sinus) was 86%. The sensitivity of an empty sella alone was 65%. If any 2 of the 3 features were present, the specificity was 100%.

So, I think my colleague at that meeting might have had the numbers crossed. If you see an empty sella, the specificity approaches 95%. In patients with IIH, only about two-thirds have an empty sella. In either case, I just kept my mouth shut!

—Michael S. Lee, MD

This is another paper which confirms that patients with IIH have the findings of empty sella, flattening of the posterior globe and compression of the venous sinuses. Over the past few years, with numerous reports of neuroimaging testing in IIH in the literature, I have seen a large increase in MRI (and CT) reports that comment “findings consistent with elevated intracranial pressure (ICP) as seen in IIH.” These radiology reports result in referrals and phone consults which often are in patients without symptoms or examination findings of elevated ICP. A study that can truly tell us the specificity of these findings in the broader population would be helpful.

—Mark L. Moster MD


Objective: To present the results of the nonrandomized arm of the Cervical Artery Dissection in Stroke Study (CADISS-NR) trial, comparing anticoagulation and antiplatelets for prevention of recurrent stroke after carotid and vertebral dissection, and perform a meta-analysis of these results with previously published studies comparing the 2 therapeutic strategies.

Methods: A total of 88 patients from 22 centers with extracranial carotid and vertebral dissection were recruited within 1 month of symptom onset. The primary endpoint was recurrent stroke at 3 months. A systematic review was performed, and results of published studies included in a metaanalysis with the CADISS-NR results.

Results: In CADISS-NR, one patient in each group had recurrent ischemic stroke (antiplatelet 1/59 [1.69%], anticoagulant 1/28 [3.57%]). At the primary endpoint of 3 months, 3 (5.08%) antiplatelet patients had recurrent TIA, compared with none in the anticoagulation group. For metaanalysis, there were data from 40 nonrandomized studies including 1,636 patients. There was no significant difference between the 2 treatments in recurrent stroke risk (antiplatelet 13/499 [2.6%], anticoagulant 20/1,137 [1.8%], odds ratio [OR] 1.49) or risk of death (antiplatelet 5/499 [1.00%], anticoagulant 9/1,137 [0.80%], OR 1.27).

Conclusion: There is no evidence for superiority of antiplatelet therapy over anticoagulation in prevention of stroke after carotid and vertebral artery dissection; however, all data are from nonrandomized studies and randomized studies are required. The nonrandomized CADISS data show a lower rate of recurrent stroke than reported in some previous studies.

Traditional teaching in neuro-ophthalmology has been to treat all suspected cervical dissections with anticoagulation,
based on a high risk of impending stroke. However, there has been a move toward antiplatelet agents, particularly in patients seen following some time delay after initial symptom onset.

The Cervical Artery Dissection in Stroke Study (CADISS) is an ongoing randomized trial comparing antiplatelet therapy with anticoagulation for cervical artery dissection. Inclusion criteria are imaging evidence of extracranial carotid or vertebral dissection presenting with ipsilateral TIA or stroke (including retinal ischemia), ipsilateral Horner syndrome, headache or neck pain, with known date of onset. Evidence of dissection must be on magnetic resonance imaging/magnetic resonance angiography, computed tomographic angiography or catheter angiography.

The current study reviews the nonrandomized arm of patients not selected based on exclusion criteria, mainly a delay of >7 days (CADISS-NR). It compares treatment with antiplatelet agents vs warfarin, which was chosen at the discretion of the treating neurologist. The study found no difference in stroke between antiplatelet agents and anticoagulation (1.69% and 3.57%, respectively). However TIA was more frequent in the antiplatelet group (5.08% vs 0%). The authors also report a meta-analysis of the literature and found no difference in outcomes of antiplatelet vs anticoagulation treatment.

Although this study supports the use of antiplatelet agents for cervical dissections, the limitations include its nonrandomized nature, the low recurrence rate compared with other studies (attributed partly to the delayed recruitment of 10.8 days on average), and the lack of a standardized treatment regimen for both antiplatelet agents and anticoagulation. The CADISS is ongoing with 250 patients randomized and treated within 7 days of onset and should provide more valuable data in the near future.

—Mark L. Moster, MD

I think it is important to note that CADISS and CADISS-NR are open label, so there are inherent biases on the part of the investigators and patients when it comes to symptoms of TIA. The primary objectives of CADISS, which the authors describe as a feasibility study include “(a) There are sufficient clinical endpoints to provide the power to determine treatment effect. (b) Adequate numbers of patients can be recruited.” The authors are attempting to generate data to determine their power calculations and it is uncertain if they can recruit enough patients. This helps explain why the patients receive varying antiplatelet agents and doses at the discretion of the physician in both CADISS and CADISS-NR. So, while I agree that CADISS will provide further information on this issue of antiplatelets vs anticoagulants in dissection, it would not supply the final conclusion until a double-masked trial with standardized dosing takes place.

—Michael S. Lee, MD
Throat Pain as a Presenting Symptom of Giant Cell Arteritis

We read with great interest the state-of-the-art review on giant cell arteritis (GCA) by Weyand (1). We recently saw a 76-year-old man who presented with severe throat pain to the point where he had difficulty swallowing. He was treated with doxycycline for “strept throat”, although swabs and culture were not performed. He failed to improve and developed hoarseness and unintentional weight loss of 10–15 pounds. Three months after developing a sore throat, the patient experienced jaw claudication without headache, scalp tenderness, or night sweats. Two months later, he had several episodes of transient monocular vision loss in the left eye, reporting “snowflakes” in the superior left visual field. Five days later, he experienced abrupt vision loss in the left eye. His medical and surgical histories, medication use, and review of systems otherwise were negative.

Neuro-ophthalmic examination revealed visual acuity of 20/40, right eye, because of a cataract, and hand motions, left eye. There was a left relative afferent pupillary defect, ocular motility was normal, and fundoscopy showed right optic disc hyperemia and the left disc had pallid edema. Fluorescein angiography confirmed bilateral optic disc leakage while choroidal and retinal filling times were normal.

Erythrocyte sedimentation rate (ESR) was 84 mm/h. The patient was treated with intravenous methylprednisolone (1,000 mg) and then switched to 80 mg of oral prednisone per day. A temporal artery biopsy revealed chronic inflammation, histiocytes, and giant cells within the vessel wall with destruction of the internal elastic lamina.

Over the next 2 weeks, the patient’s sore throat, hoarseness, and jaw claudication resolved. His visual acuity remained unchanged and after 6 weeks of treatment, his ESR was 5 mm/h, and he was clinically stable.

Our patient presented with respiratory tract symptoms that, we believe, were due to inflammation of branches of external carotid arteries (ascending pharyngeal arteries) causing reversible ischemic injury to pharyngeal tissue. Larson et al (2) reported that 9% of GCA patients present with prominent respiratory symptoms, such as cough, sore throat, and hoarseness, whereas respiratory tract symptoms are the initial complaints among 4% of the patients with GCA (3). These symptoms usually resolve quickly with steroid treatment. Other respiratory symptoms of GCA include nonproductive cough, changes in voice, fatigue and pain in the tongue, and dyspnea with orthopnea (3–6). Arthritis might also produce hoarseness in GCA from involvement of the recurrent laryngeal nerve (7).

Our patient’s initial presentation of isolated throat pain resulting from GCA is unusual (8,9). Subsequently, he developed more classic manifestations of the disorder, including jaw claudication and arteritic anterior ischemic optic neuropathy. Our case serves as a reminder to the clinician of the diverse clinical presentations of GCA.

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Corneal Endothelial Decompensation and Ocular Hypotony in a Case With Temporal Arteritis

In patients with giant cell arteritis (GCA), anterior segment ischemia can cause anterior uveitis, corneal edema, corneal ulceration, and ocular hypotony (1–3). We present a patient who developed severe anterior segment ischemia because of GCA, despite the use of high-dose intravenous corticosteroid therapy.

A 71-year-old man, with a 15-day history of right-sided headaches, experienced sudden complete loss of vision in his right eye. He had a history of hypertension, which had been well controlled with medication. Visual acuity was no light perception, right eye, and 20/70, left eye. The right pupil was amaurotic. Anterior segment examination of the right eye revealed folds in Descemet membrane and marked corneal edema (Fig. 1A) with a dense cataract. Intraocular pressures were 4 mm Hg, right eye and 12 mm Hg, left eye. The right fundus could not be visualized. There was a cataract present on examination of the left anterior segment while the left fundus was normal including fluorescein angiography. Confocal microscopy of the right cornea showed irregularities in endothelial cell size and morphology with loss and shift in cell nuclei (Fig. 1B). The patient was hospitalized and treated immediately with intravenous pulse methylprednisolone at a dose of 1,000 mg/day for 3 days.

Erythrocyte sedimentation rate was 97 mm per hour, and temporal artery biopsy showed chronic inflammation with giant cells. Carotid doppler revealed moderate stenosis of the right internal carotid artery and mild stenosis of the left internal carotid artery with normal flow. The patient was given a 6-week course of systemic corticosteroids, but at 3-month follow up, there was no recovery of vision in the right eye.

There are several reports of corneal involvement in GCA (3–5). However, hypotony occurs infrequently, and it is thought to be caused by a reduction in aqueous production as a result of inflammation of the ciliary body (2–4,6–8). Hypotony was detected in one third of patients without other signs of anterior segment ischemia. We present a case of severe anterior ischemia in GCA. They suggested that low intraocular pressure may help distinguish arteritic from nonarteritic anterior ischemic optic neuropathy.

Mild corneal edema and Descemet folds have been reported in GCA (3–5) in several cases, but severe corneal edema and corneal decompensation is unusual. Our patient had a 15-day history of visual loss prior to beginning corticosteroids, and this delay possibly contributed to the poor visual outcome. Our report is similar to that of Hwang et al (6) documenting that severe corneal edema and hypotony in patients with GCA may be refractory to even high-dose corticosteroid therapy.

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**FIG. 1.** A. Severe right corneal edema. B. Confocal microscopy of the right eye showing irregularities of endothelial cell size and morphology.
Visual Improvement With the Use of Idebenone in the Treatment of Wolfram Syndrome

Recently in the Journal of Neuro-Ophthalmology, we discussed the potential efficacy of idebenone, a coenzyme Q derivative that acts as a carrier in the mitochondrial electron transport chain, in treating patients with Leber hereditary optic neuropathy (LHON) (1). Within the past 2 decades, Wolfram syndrome (WS) has been mapped to chromosome 4p16.1 (2) and is thought to harbor a mitochondrial genome deletion (3,4) or complex III deficiency (5). The only current treatment for this devastating disease is limited to blood sugar control with lower doses of insulin compared with patients with diabetes mellitus (DM). We had the opportunity to treat a patient with WS with idebenone, hoping for improvement in visual function.

A 21-year-old Romanian man was initially evaluated 5 years previously with progressive bilateral visual and hearing loss and a neurogenic bladder. Surgical history was significant for bilateral cataract extractions with intraocular lens implants at 11 years of age. Medications included insulin and effexor. Family history was significant for DM in both parents, without a history of hearing or visual loss. Genetic testing confirmed the diagnosis of WS with the mutation of the WFS1 Wolframin gene.

The patient was overweight but appeared younger than his stated age. Visual acuity was light perception to bare hand motion bilaterally. Pupils were sluggishly reactive without a relative afferent pupillary defect. Intraocular pressures were normal and funduscopy revealed bilateral optic disc pallor (Fig. 1). Spectral domain optical coherence tomography (OCT) showed marked thinning of the retinal nerve fiber layer in each eye (Fig. 2). The patient had bilateral sensorineural hearing loss of higher frequency sounds with preservation of hearing lower frequencies. He was prescribed idebenone that was gradually increased from 150 mg daily to 150 mg twice a day at 2 months, and then to 150 mg 3 times a day at 4 months.

At 3 months, the patient’s vision improved to hand motions at 1 foot bilaterally. At 6 months, visual acuity was hand motions at 2 feet, right eye, and hand motions at 4 feet, left eye. Ophthalmoscopic and OCT findings remained unchanged. Our patient had difficulty with standard kinetic visual field testing given his poor vision (Fig. 3). To enhance light intensity of the stimulus, we used green and red laser stimuli rather than white. We were able to quantitate the visual field using a kinetic technique with these colored stimuli (Fig. 2). The patient could see the brighter more intense green stimulus, with some false positives with the red stimulus, whereas he previously was unable to detect any such stimulus on visual field testing.

Recent publications describe the use of idebenone, a coenzyme Q10 derivative, in the treatment of LHON (1,7,8). Given that WS has features of mitochondrial dysfunction, we decided to initiate idebenone treatment.

In our patient, idebenone resulted in progressive but subjective visual recovery at 6 months. Similarly, in reports of response to idebenone in LHON, the effects usually do not begin until after 6 months (1,7). This long-term
recovery may relate to potentiation of axonal action potentials (9). Carelli et al (10) demonstrated histologically that intact axons with poor myelination showed occasional remyelination, which may occur during the course of idebenone treatment. This finding suggests that there may be a subset of axons that, with remodeling of myelin, acquire a functionally useful firing pattern, and potential for visual improvement with time.

Our patient with WS seems to have experienced some visual recovery with idebenone treatment. A prospective study

**FIG. 2.** Spectral domain optical coherence tomography demonstrates severe thinning of retinal nerve fiber layer in each eye, most prominently in the superior and inferior quadrants.
using idebenone in patients with WS will be necessary to define the efficacy of this therapy.

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FIG. 3. Kinetic visual field testing demonstrates the patient’s ability to detect high-intensity green stimulus (A) and less intense red stimulus (B). The dots in the visual field (B) represent areas that the patient initially recognized but failed to do so when re-tested.


The First Chinese Neuro-Ophthalmology Society Conference in Beijing, the People’s Republic of China, June 8–10, 2012

The First Chinese Neuro-Ophthalmology Society (CNOS) Conference was held at the international conference meeting center of Beijing People’s Liberation Army (PLA) General Hospital in Beijing, People’s Republic of China, from June 8 through June 10, 2012, in conjunction with the second National Neuro-ophthalmology Key Doctor Training Course. Having been organized by the Chinese Ophthalmological Society and approved by the Chinese Medical Association, the Neuro-Ophthalmology Academic Conference came into being in China. Prof Shihui Wei, the President of the CNOS, Department of Ophthalmology, General Hospital PLA and Prof Xiaojun Zhang, the Vice President of the CNOS, Department of Neurology, Beijing Tongren Hospital, Capital Medical University, in Beijing, served as cochairs (Fig. 1). More than 400 participants were in attendance, reflecting the rapidly growing number of ophthalmologists and neurologists in China with an interest in neuro-ophthalmology.

There were 17 invited lectures covering a wide variety of topics. These included “Visual field maps: how are they formed in the brain?” by Satoshi Kashii, MD, PhD (Aichi, Japan), “Work-up for the swollen optic disc” by An-Guo Wang, MD (Taipei, Taiwan), “Leber Hereditary Optic Neuropathy: from disease mechanisms to therapeutic strategies” by Patrick Yu-Wai-Man, BMedSci, MBBS, PhD (Newcastle Upon Tyne, United Kingdom), “Natural history of refractive development in children” by Ian Morgan, PhD (Canberra, Australia), “Integrated imaging: MRI + MEG + eye movements” by David Crewther, PhD (Melbourne, Australia), and “A role for the visual system in recovery and rehabilitation from stroke” by Sheila Crewther, PhD (Melbourne, Australia).

Scientific sessions were composed of 114 platform and poster presentations. Twelve clinical cases in neuro-ophthalmology were presented and discussed on the morning of the second day. Thereafter, the conference was followed by the second National Neuro-Ophthalmology Key Doctor Training Courses, featuring lectures on vision loss, diplopia, and pupillary disorders.

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FIG. 1. Shihui Wei, President of the CNOS (left) and Xiaojun Zhang Vice President of the CNOS (right) organized the first meeting of the Chinese Neuro-Ophthalmology Society.