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Retinal Ganglion Cell Thickness to Assess the Optic Nerve

Byron L. Lam, MD

Assessment of the retinal ganglion cell layer (GCL) using automated quantitation of retinal ganglion cell–inner plexiform layer (IPL) thickness has become increasingly available with spectral domain optical coherence tomography (SD-OCT). Given the clinical benefits of using GCL thickness as an objective anatomic measure, there are now many reasons to incorporate GCL thickness into clinical practice. This is exemplified by 3 articles in this issue of Journal of Neuro-Ophthalmology (1–3).

Available SD-OCT algorithms provide GCL thickness measures in the macular region where the retinal ganglion cells are most numerous. Retinal ganglion cells are absent in the center of the fovea and increase dramatically to a peak of >10,000 cells per square degree at 0.6° eccentrically, followed by a decrease to <100 cells per square degree at 10° eccentricity (4). Meaningful measures of GCL thickness beyond the macular region are not available due to the resolution of the SD-OCT. Nevertheless, when permanent anatomic damage occurs as the result of optic neuropathy, reduction in GCL thickness is expected in the macula where the most of retinal ganglion cells reside.

There are several advantages of using SD-OCT macular GCL thickness as an objective measure of optic nerve injury compared with SD-OCT peripapillary retinal nerve fiber layer (RNFL) thickness. First, optic disc edema as a result of swollen axons increases RNFL thickness and may obscure retinal nerve fiber loss. GCL thickness detects optic nerve injury when optic disc edema is present and is helpful to predict prognosis and monitor treatment. However, when optic disc edema produces substantial peripapillary retinal edema, the SD-OCT GCL–IPL thickness algorithm may fail to provide proper segmentation resulting in falsely low values. Second, the RNFL thickness sector distribution for an anomalous optic nerve head may be altered and difficult to interpret, whereas macular GCL layer thickness is less likely to be affected. Third, macular GCL thickness may provide more precise topographical correlation with central visual field defects than peripapillary RNFL thickness. For instance, the corresponding optic nerve damage from homonymous hemianopia related to cerebral stroke is more apparent and correlates far better topographically with GCL thickness than RNFL thickness (5).

Macular GCL–IPL thickness is an additional clinical tool rather than a replacement for peripapillary RNFL thickness. The dynamic ranges of the 2 parameters in detecting an optic nerve abnormality are different in various clinical scenarios. The peripapillary RNFL thickness is sensitive in detecting optic disc edema. When optic disc edema is not present, RNFL thickness correlates reasonably well with visual field defects, particularly with sectoral or 2-dimensional en face analysis. Although macular GCL thickness may be sensitive in detecting early optic nerve damage, peripapillary RNFL thickness may be a better measure in more advanced optic neuropathies when macular GCL thickness has “bottomed out.” Because visual field defects may not occur until a considerable loss of axons has occurred, both GCL and RNFL thickness measures are especially helpful in scenarios where the visual field may be near normal (e.g., recovered optic neuritis, early compressive optic neuropathy). The GCL and RNFL measures also are useful when the patient cannot provide reliable visual fields. However, in advanced optic neuropathies, when both GCL and RNFL thickness have been maximally reduced, visual field testing remains the test of choice in following disease progression (e.g., severe optic nerve atrophy from idiopathic intracranial hypertension or from compressive optic neuropathy).

Macular GCL–IPL thickness analysis is obtained from typical macular SD-OCT without additional scanning time. Concurrent review of the retinal OCT is important because altered macular anatomy
from conditions such as epiretinal membrane and cystoid macular edema may reduce the accuracy of segmentation of the GCL-IPL layer. On occasion, the automated GCL–IPL analysis may fail even without an obvious retinal abnormality. Available GCL–IPL analysis is designed to detect neuronal injury in disorders such as glaucoma and divides the macula into 6 sectors respecting the horizontal but not vertical meridian. Given the findings of GCL thickness changes respecting the vertical meridian in homonymous hemianopia from cerebral ischemic injury (5), modification of the GCL–IPL analysis into sectors respecting both the vertical and the horizontal meridians would be beneficial.

To advance the clinical relevance of GCL thickness, prospective longitudinal studies with adequate sample size are needed to determine the prevalence, variability, and time course of GCL thickness changes in neuro-ophthalmic conditions. Case reports, case series, and cross-sectional studies have offered intriguing GCL thickness observations. In this issue of the journal, Meier and associates (1) documented a case of transsynaptic retrograde GCL thickness loss from a right occipital lesion; Rebolleda and colleagues (2) report a case series of 4 patients with anterior optic neuritis (papillitis) with GCL thinning occurring before RNFL thinning; and Sari et al (3) found decreased GCL thickness in patients with Parkinson disease in a cross-sectional study. In all 3 reports, longitudinal studies of large cohorts of patients are needed to determine how to apply these observations in the clinic and in future research. For instance, what is the prevalence and time course of transsynaptic retrograde GCL thickness loss in patients with homonymous visual field defects from damage to the occipital cortex and would this be pertinent to the testing of potential treatment strategies? Can GCL thickness in the early stages of optic neuritis serve as a predictor of the final visual outcome? If it is a valid predictor, GCL thickness may be an important measure in selecting patients for evaluation of neuroprotective interventions. Longitudinal studies also would determine the prevalence, onset, and progression of GCL thinning in patients with Parkinson disease and help to assess the efficiency of various treatment modalities.

In conclusion, SD-OCT macular GCL thickness is a valuable objective clinical measure of optic nerve damage. Clinicians as well as researchers will increasingly integrate its use as evidence-based knowledge accumulates.

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The Intersection of Optics and Neuro-Ophthalmology: The Enigma of Pseudophakic Dysphotopsia

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There is an expression “all that glitters is not gold.” Disturbing glittering sensations of light following cataract surgery may actually originate from the intraocular lens (IOL). Visual complaints of “glittering” following cataract surgery have been the subject of numerous reports linking the cause to optic edge design, material and shape of the IOL. Glittering (or shimmering) sensations and disturbing secondary images of light, producing rings, arcs, and central flashes, are commonly referred to as positive dysphotopsia as incoming light is internally reflected by the squared edges of the implant and projected onto the retinal surface. Off axis light striking the temporal cornea projects onto the nasal edge of the IOL and can create secondary images and disabling glare under scotopic conditions (1,2).

Distinguishing the etiology of abnormal visual sensations derived from complex optical aberrations induced by the edge of the IOL from those visual symptoms produced by neurological pathology creates an interesting intersection of commonality between the anterior segment ophthalmic surgeon and the neuro-ophthalmologist.

CASE 1

A 57-year-old man had cataract surgery on the left eye. Immediately postoperatively, he complained of seeing a double broken circle with dots around it and a secondary image. Light projected from the temporal field produced a secondary image nasally (Fig. 1A). Symptoms were worse at night when viewing a light source (Fig. 1B). The patient refused surgery in the fellow eye until the problem glare and secondary images was resolved in the left eye. A dilated examination was performed and appeared unremarkable. The patient was offered a second opinion with neuro-ophthalmology. Multiple tests were performed, including automated visual fields, macular optical coherence tomography, and multifocal electroretinography. All testing was normal. The patient was referred to another anterior segment specialist and an IOL exchange was performed with the insertion of an IOL with a round edge optic. Immediately following the IOL exchange, the quality of the symptoms improved slightly but his complaints have not totally resolved.

Visual dysfunction following implantation of an IOL after cataract surgery may also be manifested as a negative dysphotopsia. First described over 10 years ago (3), negative dysphotopsia appears as a temporal, dark, crescent-shaped shadow following in-the-bag posterior chamber IOL implantation (Fig. 2). Negative dysphotopsias have been linked to the square edge design of the IOL optic, shape of the IOL, high index of refraction, and the anterior capsule extending over the edge of the optic (1,2,4–7). Square truncated edges on many IOLs, originally designed to reduce posterior capsule opacification, may be the source of both positive and negative dysphotopsias. Negative pseudophakic dysphotopsias are caused by the absence of light in the extreme temporal field from the edge of the IOL causing a crescent shadow on the nasal retina where light would normally be transmitted by the crystalline lens of a phakic eye. Although articles demonstrating the crescent-shaped shadow with ray tracing studies are available and the clinical appearance of these symptoms has corresponded to the introduction of square edges, the topic is still debated (4,7). The circular IOL optic accounts for the crescent shape seen in positive and negative dysphotopsias.

Pseudophakic dysphotopsias are generally considered to be an annoyance of little functional significance. However, many patients become functionally or psychologically disabled from their
symptoms. These symptoms have a clear impact on daily visual function and generate the “unhappy 20/20 patient.” It is not uncommon that many of these patients seek second opinions from other ophthalmologists and, in fact, may be referred to a neuro-ophthalmologist for extensive evaluation to rule out neurologic causes of their complaints. The differential diagnosis of pseudophakic dysphotopsias includes a host of neurological conditions with symptoms such as visual field loss, halos, flashes, and entoptic phenomenon such as visual auras, scintillations, and visual hallucinations.

Krista et al (8) reported in a study of pseudophakic patients without confounding ophthalmic diseases and with excellent visual acuity, that a visual function questionnaire correlated strongly with patient dissatisfaction from pseudophakic dysphotopsia. This study revealed that subjective visual function may indeed be compromised because of pseudophakic dysphotopsias in otherwise normal 20/20 pseudophakic eyes. Not only is vision of 20/20 considered normal but also the entire ophthalmic examination of the eye is unremarkable. This places an increased burden on the ophthalmologist when examining symptomatic patients to correctly diagnose the symptoms because there are no objective tests to measure the severity of pseudophakic dysphotopsias.

Despite bitter complaints about their vision, it is not uncommon for patients who easily read the 20/20 line on a Snellen acuity chart following cataract surgery to be told there is nothing wrong with their eye or their vision. Ophthalmologists may advise patients that their symptoms will disappear over time, suggesting neural adaption may suppress the severity of their awareness of their symptoms. Osher (9) reported negative dysphotopsias in 15.2% on the first postoperative day, 3.2% at 1 year, and 2.4% at 2–3 years. In contrast, after being told there is nothing wrong

FIG. 1. Positive dysphotopsia. A. Patient drawing depicts a ring and secondary image (image of light) generated by a light source located at approximately 35° in the temporal visual field at a distance of 33 cm. The ring is probably produced from the edges of the intraocular lens. B. A glare source viewed by a pseudophakic eye will produce refracted and reflected images if light rays are able to reflect internally from the edge of the lens. The reflected glare imaged will appear as a thin crescent or partial ring on the side of the retina opposite the glare source [modified from Ref. (1)].

FIG. 2. Patient drawings of a variety of negative dysphotopsias and the model of intraocular lens implanted in each patient [modified from Ref. (1)].
producing on the side of her vision as if she was looking into the ciliary sulcus (14).

with their eyes, some patients may go years living with their symptoms without complaining.

An IOL exchange from a truncated edge design to a rounded edge design may relieve symptoms of patients with positive dysphotopsias. Several reports have demonstrated relief of symptoms from negative dysphotopsias following YAG laser of the anterior capsule (10,11), IOL exchange with a sulcus fixated IOL (12,13) or prolapsing the optic through the capsulorhexis into the anterior capsule (reverse optic capture), and piggyback IOL implantation into the ciliary sulcus (14).

CASE 2

A 71-year-old woman underwent uneventful phacoemul-

sification with IOLs in both eyes. Since surgery, she described a temporal “dark ring around both eyes” producing a sensation that she could not see and that she was going to step into a hole when she walked. She described “blinders and a dark spot” on the side of her vision as if she was looking through binoculars all of the time. Her symptoms were dismissed by 2 ophthalmologists and she was re-evaluated 8 months later. Visual acuity was 20/20 and J1 in each eye. On examination, there was extensive fibrosis of the anterior (not posterior) capsule extending over the anterior optic of the IOL by several millimeters. Bilateral YAG laser was performed to the anterior capsule allowing light to pass through the periphery of the lens optic, relieving the patient of her symptoms (Fig. 3).

In addition to the positive and negative dysphotopsias discussed above, there is another visual dysfunction commonly seen after cataract surgery following implantation of a multifocal IOL. Multifocal IOL intolerance not uncommonly results in patient dissatisfaction with the quality of vision despite having 20/20 eye in each eye. Referred to as “waxy” or “vaseline” vision, these patients may bitterly complain that they are unable to see clearly despite being able to read 20/20 high-contrast Snellen acuity. Concentric diffractive rings in multifocal IOLs create 2 simultaneous focal points and increase light scatter, resulting in reduced retinal image contrast. If the cornea has significant aberrations (>0.5 μm over a 6-mm zone) and is combined with the reduced retinal image contrast from the multifocal IOL, the result is poor quality of vision. Excessive corneal higher order aberrations of the Zernike third-order and fourth-order \( Z_3 + Z_4 \) terms have been statistically and clinically linked to multifocal lens intolerance and visual dysfunction (15). Light sources may also produce the presence of a halo (the simultaneously defocused image). Treatment options include refractive surgery to eliminate corneal higher order aberrations with limited success or an IOL exchange with a monofocal IOL.

The critical issue in arriving at the correct diagnosis of visual dysphotopsia is the temporal relationship of symptomatic onset after cataract surgery. Many patients complaining of undesired visual disturbances following cataract surgery may seek secondary and tertiary referrals for relief of their symptoms. 20/20 vision and a normal eye examination may pose a conundrum to the clinician to resolve these visual symptoms. All that glittering may not be gold, but it may be pseudophakic dysphotopsia.

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Homonymous Ganglion Cell Layer Thinning After Isolated Occipital Lesion: Macular OCT Demonstrates Transsynaptic Retrograde Retinal Degeneration

Paolo G. Meier, MD, Philippe Maeder, MD, Randy H. Kardon, MD, PhD, François-Xavier Borruat, MD

Abstract: A 48-year-old man was examined 24 months after medical and surgical treatment of an isolated well-circumscribed right occipital lobe abscess. An asymptomatic residual left homonymous inferior scotoma was present. Fundus examination revealed temporal pallor of both optic discs, and optical coherence tomography (OCT) revealed mild temporal loss of retinal nerve fiber layer in both eyes. No relative afferent pupillary defect was present. Assessment of the retinal ganglion cell layer demonstrated homonymous thinning in a pattern corresponding to the homonymous visual field loss. There were no abnormalities of the lateral geniculate nuclei or optic tracts on review of the initial brain computed tomography and follow-up magnetic resonance imaging. We believe our patient showed evidence of transsynaptic retrograde degeneration after an isolated right occipital lobe lesion, and the homonymous neuronal loss was detected on OCT by assessing the retinal ganglion cell layer.

Transsynaptic retrograde degeneration (TRD) of the visual pathways, that is loss of undamaged retinal ganglion cells occurring upstream from a retrogeniculate lesion, has been convincingly reported in experimental conditions (1–3). Some patients with occipital lesions sparing the lateral geniculate nucleus and optic tracts can develop TRD with bow tie optic atrophy in the eye contralateral to the lesion and temporal pallor in the fellow eye (4). However, optic nerve changes can be subtle and sometimes overlooked on ophthalmoscopy. Histological evidence of TRD in humans was provided by Beatty et al (5) who reported such a case 40 years after occipital lobectomy. The development of optical coherence tomography (OCT) allows measurement of the retinal nerve fiber layer (RNFL), and this technology has provided evidence of TRD after isolated occipital lesions (6–8). Additional evidence of TRD with occipital lesions has been demonstrated with magnetic resonance imaging (MRI), revealing atrophy of the ipsilateral optic tract (9,10).

The development of segmentation software of macular OCT provides thickness maps of the retinal ganglion cell layer–inner plexiform layer complex (RGCL-IPL). This approach is advantageous for discerning patterns of homonymous loss corresponding to TRD from postgeniculate lesions. We report homonymous thinning of RGC-IPL in the macula of a patient with an isolated occipital lobe abscess producing a corresponding homonymous visual field scotoma within the central 15°.

CASE REPORT

A 46-year-old man in good health reported a 10-day history of headaches and scintillating scotomata. The patient was afebrile with normal vital signs, and general physical examination was normal. Visual acuity was 20/20 bilaterally but visual field examination revealed a dense left homonymous hemianopia (Fig. 1). There was no relative afferent pupillary defect (RAPD). Ophthalmoscopy was normal. Brain computed tomography disclosed a well-demarcated lesion within the right occipital lobe with perifocal edema thought to represent a neoplasm (Fig. 2).
The patient was treated with intravenous methylprednisolone (125 mg 3 times a day) for 48 hours followed by craniotomy. At surgery, a cortical abscess was drained, and bacteriologic analysis revealed *Actinomyces Meyeri* and *Aggregatibacter aphrophilus*. Systemic intravenous antibiotic therapy (ceftriaxone 2 g twice a day and metronidazole 0.5 g 3 times a day) was given for 6 weeks. The patient was found to have a patent foramen ovale that was surgically closed. Six weeks after surgery, ophthalmic examination revealed partial resolution of the left homonymous hemianopia, absence of a RAPD, and no evidence of optic atrophy. Twelve months after initial presentation, MRI showed right occipital cortical atrophy with mild ipsilateral white matter gliosis (Fig. 3). Review of all MRI studies revealed no evidence of damage to the lateral geniculate nuclei or optic tracts.

Two years later, the patient was referred for neuroophthalmic evaluation. Visual acuity was 20/15 in each eye, pupils reacted normally, and color visual testing and slit-lamp examination were normal. There was temporal pallor of both optic discs (Fig. 4). Automated visual field testing showed a congruous left inferior homonymous congruous scotoma (Fig. 5).
Using spectral-domain OCT (Cirrus 4000 HD-OCT; Carl Zeiss Meditec, Dublin, CA), average RNFL thickness was normal in both eyes (right eye: 95 μm; left eye: 98 μm) with slight thinning of temporal quadrant in each eye. Macular OCT showed no significant thinning of the total retinal thickness. Analysis of the RGC-IPL complex with the Ganglion Cell Analysis module (Zeiss Cirrus software, version 6.5.0; Zeiss, Dublin, CA) disclosed a moderate homonymous thinning in both eyes on the total thickness RGC-IPL map and significant to less than the 1% level on the probability map (Fig. 6). The pattern of the RGCL thinning was homonymous, affecting the temporal retina in the right eye and the nasal retina in the left eye. The RGC-IPL thinning respected the vertical meridian. Although the homonymous visual field defect extended to approximately 16°, ganglion cell thinning appeared to extend to approximately 6°.

**FIG. 4.** Two years after initial presentation, color (top) and red-free (bottom) fundus photographs shows temporal pallor of both optic discs.

**FIG. 5.** Two years after initial presentation, automated static perimetry (Octopus, program G1, Haag Streit) discloses a residual left inferior homonymous scotoma.
FIG. 6. Optical coherence tomography performed 2 years after initial presentation (Cirrus 4000 HD-OCT; Carl Zeiss Meditec). 

A. Fundus diagram with the thickness map of RGCL-IPL for right eye (left) and left eye (right). Homonymous thinning of RGCL-IPL complex (i.e., loss of RGCL-IPL in the temporal retina of the right eye and in the nasal retina of the left eye indicated by arrows) is present in a pattern corresponding to the residual homonymous left visual field defect. 

B. Deviation maps of the RGCL-IPL loss demonstrates the homonymous defect of RGCL-IPL. Note that the extent of the RGCL-IPL thinning on the deviation maps (approximately 6°) does not extend as far peripherally as the visual field defect (16°). Sector maps illustrated the degree of homonymous RGCL-IPL thinning in each eye. 

C. Macular profiles with horizontal OCT B-scans through the fovea appear normal in both eyes. 

D. RNFL analysis shows loss of nerve fibers in the temporal quadrant of both optic discs more marked in the left disc. RGCL-IPL, retinal ganglion cell layer–inner plexiform layer complex; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer.
DISCUSSION

The combination of bilateral optic atrophy and homonymous visual field loss usually implies the presence of a lesion of the pregeniculate visual pathways. Typically, this results in temporal atrophy of the optic disc ipsilateral to the lesion and a bow tie atrophy of the contralateral eye. This pattern arises from loss of noncrossing fibers in the ipsilateral eye and the loss of crossing fibers in the contralateral eye (4). The presence of an RAPD in the contralateral eye indicates a lesion of the optic tract, whereas the absence of an RAPD signifies a lesion beyond the point where the pupillomotor fibers leave the optic tract.

OCT can demonstrate thinning of the RNFL in optic tract lesions, but the pattern of RNFL loss does not readily demonstrate a homonymous nature of the lesion. A bow tie pattern of RNFL loss also is not usually apparent. The availability of software to provide segmentation of the retinal layers in the macula allows the analysis of the RGC-IPL complex. Homonymous thinning of the RGC-IPL in a patient with an optic tract lesion due to neumyelitis optica has been published (11).

Our patient had a right occipital lobe abscess. Both before and after neurosurgical drainage, neuroimaging studies did not detect any abnormality of the optic tracts or lateral geniculate nuclei. The homonymous thinning of the RGC-IPL on OCT exhibited by our patient most likely represents TRD. Interestingly, the peripheral extent of the homonymous ganglion cell-inner plexiform layer thinning (6°) on the probability plot was not as extensive as the visual field defect (16°). Possibly, the central macular fibers near fixation are more likely to show TRD.

More than 50 years ago, Van Buren (1) created a focal surgically-induced lesion in 1 occipital lobe of the adult macaque monkey. Forty-eight months later, he demonstrated homonymous thinning of the retina supportive of the concept of TRD. Similar experiments in other nonhuman primates confirmed this observation (2,3). However, documentation of optic atrophy in humans after retrogeniculate lesion is rare, and the concept of TRD in human adults has been challenged (12). However, recent studies with OCT have demonstrated the possibility of TRD in adult humans with acquired retrogeniculate disorders. Jindahra et al (6) demonstrated thinning of RNFL in both eyes in a series of 26 patients with both congenital and acquired homonymous hemianopia. Patients exhibited a significant loss of RNFL mean thickness as compared to controls, and those with congenital lesions exhibited greater RNFL loss than individuals with acquired lesions. In a later study (7), the same investigators studied 38 patients with purely acquired retrogeniculate lesions and reported a decelerating rate of RNFL loss of 9.08 μm per log-years. Yet, no thinning of RNFL was detected when small visual field defects were present. Park et al (8) reported a constant pattern of RNFL loss in patients with cerebral infarction with the optic nerve ipsilateral to the lesion losing uncrossed (temporal) fibers and the fellow eye losing crossed (nasal) fibers.

In a cohort of patients with autosomal-demonstrated optic atrophy, Rönnbäck et al (13) showed that measurement of RGCL-IPL complex was more sensitive than RNFL thickness in detecting structural loss. The OCT results in our patient support a similar conclusion in patients with TRD due to a retrogeniculate lesion.

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Ganglion Cell–Inner Plexiform Layer Thickness in Patients With Parkinson Disease and Association With Disease Severity and Duration

Esin S. Sari, MD, Rabia Koc, MD, Alper Yazici, MD, Gözde Sahin, MD, Sitki S. Ermis, MD

Background: To evaluate the average, minimum, and 6-sectoral macular ganglion cell–inner plexiform layer (GC-IPL) thickness measured by spectral domain optical coherence tomography (SD-OCT) in patients with Parkinson disease (PD), as well as average and 4-sectoral retinal nerve fiber layer (RNFL) thickness and to determine whether thickness parameters are correlated to disease severity and duration.

Methods: Patients with PD (n = 54) and age-matched healthy controls (n = 54) were prospectively examined with SD-OCT. Randomly selected eyes of all subjects were included. The average, minimum, and 6-sectoral (superior, superotemporal, superonasal, inferonasal, inferior, and inferotemporal) GC-IPL thickness values were analyzed. Average and 4-sectoral (inferior, superior, temporal, and nasal) peripapillary RNFL thicknesses were also evaluated. Each parameter was compared between patients with PD and age-matched healthy controls. PD severity was quantified with the Hoehn and Yahr (HY) scale. A correlation analysis was performed to evaluate the association between SD-OCT measurements and the duration and severity of PD.

Results: The mean age of patients with PD and age-matched healthy controls was 66.62 ± 8.71 years and 66.68 ± 7.85 years, respectively. Disease duration ranged from 1 to 15 years with a mean of 5.12 years. The mean PD severity, according to the HY scale, was 2.26 (range, 1–5). SD-OCT measurements revealed significant differences in inferior and temporal peripapillary RNFL values between groups (P = 0.018 and P = 0.031, respectively). All GC-IPL thickness parameters were statistically lower in the patients with PD when compared with the healthy controls (P < 0.001). PD duration was not correlated to any of the RNFL thicknesses, but PD severity was correlated inversely only with inferior peripapillary RNFL thickness (P = 0.006). Average, inferior (P = 0.011), inferotemporal (P = 0.007), and superotemporal (P = 0.007) GC-IPL thicknesses were correlated inversely with both PD severity and duration.

Conclusions: Retinal dopaminergic neurodegeneration in patients with PD can be detected with macular GC-IPL thickness measurements. Macular GC-IPL thickness was correlated with PD severity and duration. It may be used to follow disease progression and efficacy of the neuroprotective treatment in patients with PD.

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Parkinson disease (PD) is a neurodegenerative disorder characterized by progressive loss of selective dopaminergic neurons, mainly in the nigrostriatal pathway (1). Clinical manifestations include comprised movement alterations and nonmotor symptoms such as dementia, depression, and autonomic dysfunction (2). Visual symptoms also are common among the nonmotor symptoms in patients with PD and manifest as visual acuity loss and reduced color discrimination and contrast sensitivity (3). Recognition of the nonmotor symptoms has gained importance in understanding the pathophysiology and early diagnosis of the disease (4).

It has been shown that the human retina contains dopaminergic amacrine cells, which provide visual input to the retinal ganglion cells through their rich interconnections in the inner plexiform layer (5). Ganglion cells act as the final common pathway in the flow of visual information to the optic nerve through the retinal nerve fiber layer (RNFL) (6). Retinal cells that produce the dopamine precursor (levodopa) seem to be reduced in patients with PD, leading to the thinning of the inner retinal layers, including the RNFL and the ganglion cell–inner plexiform layer (GC-IPL) (7).
The introduction of spectral domain optical coherence tomography (SD-OCT) has allowed detailed analysis of retinal structure and quantitative maps of retinal thickness with high spatial resolution (8). Although many studies have demonstrated peripapillary RNFL thinning in patients with PD using SD-OCT (4,7,9), the pathogenesis of disease involves degeneration of not only axons but also cell bodies and dendrites. Therefore, a more useful measure would be the thickness profile of the retinal GC-IPL. To date, there are few reports of measurements of ganglion cell layer thickness in patients with PD (10,11), all of which focus on average thickness. The Cirrus SD-OCT (Carl Zeiss Meditec Inc., Dublin, CA) macular GC-IPL thickness algorithm has the advantage of segmenting the layers automatically and provides 8-parameter measurements rather than average thickness alone. This option allows objective comparison and parameter selection.

The purpose of our study is to evaluate the thickness of macular GC-IPL and peripapillary RNFL in different sectors in patients with PD compared with age-matched controls. In addition, we assessed whether thickness parameters correlated with disease duration and severity. The latter is based on the Hoehn and Yahr (HY) scale.

METHODS

Patients

This prospective and observational study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee. All subjects provided informed consent to participate in the study. Consecutive patients diagnosed with PD and age-matched healthy controls were recruited from the Neurology Department in our hospital. Randomly selected eyes of all subjects were included in the study. All subjects underwent neurologic and ophthalmic examination, including best-corrected Snellen visual acuity (BCVA), intraocular pressure (IOP), and dilated ophthalmoscopy. The required inclusion criteria were as follows: BCVA of 20/40 or better; refractive error within ±5.00 diopters (D), (spheric equivalent) and 2.00 D astigmatism. Exclusion criteria were corneal opacity or cataract formation (nuclear color/opalescence and cortical or posterior subcapsular lens opacity >1, according to the Lens Opacities Classification System III system), glaucoma, history of previous intraocular surgery, diabetes, or other diseases or medications that affect vision, the visual field, or any portions of the neuro-ophthalmic system. The diagnosis of PD was based on criteria from the United Kingdom Parkinson Disease Society Brain Bank (12), and all patients were clinically stable on medical therapy. Medical records of patients with PD were reviewed, including duration and severity of disease. Disease severity was evaluated according to the HY scale by 1 neurologist (R.K.). The HY scale (13) is widely used to categorize the progression of PD symptoms and quantify the patients according to 5 stages. The first stage represents the early phase of the disease and is characterized by symptoms, such as tremor, muscle stiffness, slowness of movement, and postural problems, which appear only on 1 side of the body. The fifth stage corresponds to the advanced disease phase, where the patient is immobile and requires total assistance. The neurologist was masked to the results of optical coherence tomography (OCT) examinations.

Optical Coherence Tomography

All examinations were performed by the same physician with the Cirrus HD-OCT Model 4000 (Carl Zeiss Meditec Inc.,). Two scans obtained from each patient were averaged. In all cases, the pupil was dilated before the examination with tropicamide 1% (Tropicamid; Bilim, Istanbul, Turkey). While performing the OCT, the pupil was centered and focused in the iris viewport. The autofocus mode was used to obtain an optimized view of the retina with the line-scanning ophthalmoscope. To maximize the OCT signal, the Z-offset was optimized with the center mode and the scan polarization was optimized with the enhance mode. Motion artifacts that were detected by vascular discontinuity in the overlay images of the line-scanning ophthalmoscope, and OCT were avoided by repeated scanning. GCL-IPL thickness was calculated with the macular cube 512 × 128 analysis protocol. The macular GCL-IPL thickness was measured within a 14.13-mm² elliptical annulus area centered on the fovea, which has the following dimensions: vertical inner and outer radius of 0.5 and 2.0 mm, respectively, and horizontal inner and outer radius of 0.6 and 2.4 mm, respectively. The average, minimum, and 6-sectoral (superior, superotemporal, superonasal, inferonasal, inferior, and inferotemporal) GC-IPL thickness values were obtained from this elliptical annulus. Average and 4-sectoral (inferior, superior, temporal, and nasal) peripapillary RNFL thickness was evaluated using a previously described protocol (14). For GC-IPL and RNFL measurements, only SD-OCT scans with a signal strength of at least 6/10 were analyzed. Any image with inadequate fixation due to head movements or postural instability was re-evaluated. If the OCT examination could not be completed for any patient with PD after several attempts, they were excluded from the study.

Data Analysis

Data was calculated as mean ± SD (range). One eye from each subject was randomly selected for the analyses. The SPSS statistics software package version 15.0 for Windows (SPSS, Chicago, IL) was used for statistical analysis. Normality of all data samples was checked by means of the Kolmogorov–Smirnov test. When parametric analysis was possible, the Student t test for paired data was performed in all parameter comparisons between patients with PD and age-matched healthy controls. When parametric analysis was not possible, the Wilcoxon rank-sum test was used. In addition, correlation coefficients (Pearson or Spearman depending on whether normality condition could be assumed) were calculated to assess the correlation between
SD-OCT measurements and PD severity and duration. Intraclass correlation coefficient (ICC) also was performed for interobserver and intraobserver reliabilities. A P value less than 0.05 was considered statistically significant.

RESULTS

Initially, 59 consecutive patients with PD were recruited. Three patients with stage 5 and 2 patients with stage 4 disease who could not complete OCT examination due to inadequate fixation were excluded from the study. Therefore, 54 eyes of 54 patients with PD (30 men and 24 women), with a mean age of 66.62 ± 8.71 years (range, 50–81 y) and 54 eyes of 54 patients (28 men and 26 women) with a mean age of 66.68 ± 7.85 years (50–81 y) were included in the study. Disease duration ranged from 1 to 15 years with a mean of 5.12 years. The mean PD severity according to the HY scale was 2.26; 14 patients (25.9%) stage 1, 22 patients (40.8%) stage 2, 10 patients (18.5%) stage 3, 6 patients (11.1%) stage 4, and 2 patients (3.7%) stage 5. There was no statistically significant difference between the patient cohort and healthy controls in terms of age, gender, BCVA, and IOP (Table 1).

The intraobserver and interobserver reliabilities for SD-OCT examination were assessed with ICC, and the values were between 0.997 and 0.974 with high reproducibility. The differences in peripapillary RNFL thickness between patients with PD and age-matched healthy controls are shown in Table 2. SD-OCT measurements revealed significant differences only in inferior and temporal peripapillary RNFL values between groups (P = 0.018 and P = 0.031, respectively). Average peripapillary RNFL thickness did not significantly differ between the groups (P = 0.245). Average, minimum, and 6-sectoral GC-IPL thicknesses were also analyzed in this study (Table 2). All GC-IPL thickness parameters were statistically lower in the patients with PD when compared with the healthy controls (P < 0.001). Figures E1 and E2. Supple-

TABLE 1. Clinical characteristics of patients with PD and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>Healthy Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66.62 (8.71)</td>
<td>66.68 (7.85)</td>
<td>0.812*</td>
</tr>
<tr>
<td>Gender</td>
<td>30/24</td>
<td>28/26</td>
<td>0.645†</td>
</tr>
<tr>
<td>(male/female)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>15.34 (2.40)</td>
<td>15.17 (2.43)</td>
<td>0.712*</td>
</tr>
<tr>
<td>BCVA</td>
<td>0.69 (0.24)</td>
<td>0.71 (0.24)</td>
<td>0.091*</td>
</tr>
<tr>
<td>(Snellen decimal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>5.12 (2.92)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Disease severity†</td>
<td>2.26 (0.97)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Student t test.
†Chi-square test.
‡Disease severity with Hoehn and Yahr scale.
§BCVA, best-corrected visual acuity; IOP, intraocular pressure; PD, Parkinson disease.

TABLE 2. Comparison of pRNFL thickness and GC-IPL thickness between patients with PD and age-matched healthy controls

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>Healthy Control</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRNFL, µm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>89.66 (12.0)</td>
<td>92.95 (9.27)</td>
<td>0.245</td>
</tr>
<tr>
<td>Superior</td>
<td>110.38 (17.85)</td>
<td>112.55 (13.75)</td>
<td>0.442</td>
</tr>
<tr>
<td>Nasal</td>
<td>67.91 (12.19)</td>
<td>72.25 (7.65)</td>
<td>0.181</td>
</tr>
<tr>
<td>Inferior</td>
<td>109.67 (13.25)</td>
<td>115.02 (15.97)</td>
<td>0.018</td>
</tr>
<tr>
<td>Temporal</td>
<td>64.55 (18.38)</td>
<td>70.03 (7.74)</td>
<td>0.031</td>
</tr>
<tr>
<td>GC-IPL, µm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>68.58 (16.3)</td>
<td>81.27 (6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superior</td>
<td>71.42 (16.8)</td>
<td>82.09 (7.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superonasal</td>
<td>69.17 (17.1)</td>
<td>83.09 (7.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferonasal</td>
<td>66.84 (17.1)</td>
<td>82.18 (8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior</td>
<td>67.33 (18.0)</td>
<td>80.52 (7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferotemporal</td>
<td>70.64 (17.1)</td>
<td>81.27 (7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superotemporal</td>
<td>68.91 (17.9)</td>
<td>81.53 (6.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum</td>
<td>62.53 (21.5)</td>
<td>77.70 (7.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Student t test.
GC-IPL, ganglion cell inner plexiform layer; PD, Parkinson disease; pRNFL, peripapillary retinal nerve fiber layer.

DISCUSSION

A progressive retinal dopaminergic degeneration causes the loss of retinal amacrine cells that provide input to retinal ganglion cells (6). Macular GC-IPL thickness, which can be directly affected in PD, is a relatively new parameter that accurately reflects the thicknesses of macular ganglion cells and their axons. In this study, we found that average, minimum, and 6-sectoral macular GC-IPL thickness measurements within the macula in patients with PD and performed the correlation analyses between the measurements and disease severity and duration.

In 2004, RNFL damage in PD was first demonstrated by Inzelberg et al (9). The authors showed a reduction in the inferotemporal peripapillary RNFL thickness, which was topographically matched to the visual field defects in a small
number of patients. Some subsequent studies reported evidence of peripapillary RNFL thinning in patients with PD (15,16), although others did not (17,18). Moschos et al (16) found decreased inferior and temporal peripapillary RNFL thicknesses, and no difference in mean RNFL thickness in 32 eyes of 16 patients with PD compared with controls. In accordance with previous investigations, our findings revealed significant differences only in inferior and temporal peripapillary RNFL values between both groups. Average RNFL thickness was lower in patients with PD than in healthy controls but did not reach statistical significance.

Foveal and perifoveal thickness measurements have previously been used to estimate ganglion cell degeneration in patients with PD (15,19), because approximately 50% of the ganglion cells are localized within the 4.5 mm of the fovea (20). It is now possible to directly measure ganglion cell bodies and their dendrites with the GC-IPL analysis: program of the Cirrus SD-OCT device (21). Yet there are very few reports of GC-IPL measurements in patients with PD (7,11). Adam et al (11) investigated the internal retinal layer (RNFL + GC-IPL) thickness in 14 eyes of 28 patients with PD and observed significant differences between groups in the nasal, superior, temporal, and inferior quadrants of perifoveal locations. Hajee et al (7) also evaluated internal retinal layer thickness in 46 eyes of 23 patients with PD with the same device and reported similar results. More recently, Garcia-Martin et al (10) examined the thickness of 10 retinal layers using an average value of macular thickness and demonstrated that the average ganglion cell layer thickness was significantly reduced in the PD group. In all of these studies, sectoral analyses of GC-IPL thickness were not provided. In our study, average, minimum, and 6-sectoral thicknesses were measured, and all GC-IPL thickness parameters were statistically significantly lower in the patients with PD when compared with healthy controls. In contrast to peripapillary RNFL thickness measurements, GC-IPL thickness is reduced globally in patients with PD without any specific sectoral preference.

The question arises whether the thickness of retinal layers correlates with the severity and duration of disease. Altintas et al (15) showed a correlation of disease severity with inner foveal thickness but not with peripapillary RNFL thickness in 17 patients with PD. Another study with 52 patients reported that the average and RNFL quadrants, except the nasal sector, were significantly correlated with disease severity (22). These authors found that average, inferior, and nasal peripapillary RNFL thinning were the parameters, which correlated with disease duration. In this study, an inverse correlation was observed between inferior peripapillary RNFL thickness and PD severity, but no correlation existed for disease duration and any of the peripapillary RNFL parameters. Only 1 previous study specifically examined GC-IPL measurements and their correlation in patients with PD. Garcia-Martin et al (10) found that the average ganglion cell layer correlated inversely with HY scale and disease duration. However, that study did not provide sectoral analyses of GC-IPL thickness. We performed correlation analyses with 8 different GC-IPL parameters. Average, inferior, inferotemporal, and superotemporal GC-IPL thicknesses were inversely correlated with disease severity; similar results were observed regarding disease duration. It is difficult to speculate why the significant correlation was not observed in all sectors.

Laboratory studies in both human (23) and monkey (24) eyes have shown that in the macular area, inferior and temporal sectors have the thinnest GC-IPL thickness

<table>
<thead>
<tr>
<th>TABLE 3. Spearman Correlation Analyses in Patients With PD</th>
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<tbody>
<tr>
<td><strong>Correlation Coefficient</strong></td>
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<tr>
<td>----------------------------</td>
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<tr>
<td><strong>PRNFL, μm</strong></td>
</tr>
<tr>
<td>Average</td>
</tr>
<tr>
<td>Superior</td>
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<tr>
<td>Nasal</td>
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<tr>
<td>Inferior</td>
</tr>
<tr>
<td>Temporal</td>
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<tr>
<td><strong>GC-IPL, μm</strong></td>
</tr>
<tr>
<td>Average</td>
</tr>
<tr>
<td>Superior</td>
</tr>
<tr>
<td>Superonasal</td>
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<tr>
<td>Inferonasal</td>
</tr>
<tr>
<td>Inferior</td>
</tr>
<tr>
<td>Inferotemporal</td>
</tr>
<tr>
<td>Superotemporal</td>
</tr>
<tr>
<td>Minimum</td>
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</tbody>
</table>

*Hoehn and Yahr scale.
GC-IPL, ganglion cell-inner plexiform layer; PD, Parkinson disease; pRNFL, peripapillary retinal nerve fiber layer.
followed by the superior and nasal sectors, respectively. Interestingly, the inferior and temporal sectors were those found to be correlated with disease severity in this study. However, it is possible that our results might be biased due to the relatively small sample size.

Some limitations of this study must be addressed. First, our PD group consisted of patients in relatively early stages of the disease. The patients with PD in advanced stages often have impaired quality of OCT examinations and, therefore, such patients were excluded, possibly leading to selection bias. Second, the physician performing OCT was not masked because disease symptoms are evident.

In conclusion, we observed that macular GC-IPL thickness was significantly lower in patients with PD than controls. This may be due to loss of dopaminergic amacrine cell dendrites suggesting dopaminergic neurodegeneration. Macular GC-IPL thickness also correlated with disease severity and duration. Accordingly, macular GC-IPL measurements with SD-OCT may be a useful tool in the following patients with PD. Further large cohort studies are needed to possibly detect predictive parameters leading to early diagnosis of PD, before the appearance of serious motor and nonmotor impairment in PD.

STATEMENT OF AUTHORSHIP

REFERENCES
Retinal Atrophy in Eyes With Resolved Papilledema Detected by Optical Coherence Tomography

Brian E. Goldhagen, MD, M. Tariq Bhatti, MD, Pratul P. Srinivasan, Stephanie J. Chiu, PhD, Sina Farsiu, PhD, Mays A. El-Dairi, MD

Background: To apply automated spectral domain optical coherence tomography (SD-OCT) segmentation to eyes with resolving papilledema.

Methods: Ninety-four patients with idiopathic intracranial hypertension seen at the Duke Eye Center neuro-ophthalmology clinic between November 2010 and October 2011 were reviewed. Excluded were eyes with papilledema with Frisén grade ≥2, other optic neuropathies or retinopathies, and those that did not have SD-OCT imaging. The remaining 43 patients were split into 2 groups: non-atrophic papilledema and atrophic papilledema. Automated SD-OCT segmentation was performed on patients with non-atrophic papilledema and age-matched controls for each of the 9 regions of the Early Treatment Diabetic Retinopathy Study map. Bonferroni correction was used for multiple comparisons. All SD-OCT scans were reviewed for retinal structural abnormalities.

Results: Total macular thickness was significantly thinner within the fovea and inner macular ring in non-atrophic papilledema vs control eyes (266 vs 276 μm, P = 0.04; 333 vs 344 μm P < 0.01, n = 26 non-atrophic papilledema, 30 controls). SD-OCT demonstrated thinning within the fovea, inner macular ring, and outer macular ring of the outer plexiform layer plus nuclear layer in non-atrophic papilledema vs control (124 vs 131 μm, P < 0.01; 112 vs 118 μm, P = 0.03; 95 vs 100 μm, P = 0.03). Retinal structural changes were seen in 21/33 eyes with atrophic papilledema vs none of the eyes with non-atrophic papilledema or controls.

Conclusions: SD-OCT shows qualitative and quantitative changes in the macula of eyes with resolved papilledema.

doi: 10.1097/WNO.0000000000000210

Papilledema is defined as optic nerve swelling caused by increased intracranial pressure and can lead to profound irreversible vision loss due to secondary optic atrophy (1,2). One of the common causes of papilledema in young adults is idiopathic intracranial hypertension (IIH). In this study, IIH was defined using the Modified Dandy criteria (3). IIH is an ideal disease model to study optic nerve damage caused by papilledema since confounding causes of optic atrophy, such as compression or inflammation, are not present.

When papilledema occurs, there are changes in pressure gradients caused by increased subarachnoid pressure that lead to impairment of axoplasmic flow within the optic nerve resulting in swelling of axons (manifesting as optic disc edema) (4,5). The eventual resultant loss of axonal integrity leads to loss of axons and their retinal ganglion cells (i.e., optic atrophy) (6). There is no study to date that has been able to distinguish resolution of papilledema from superimposed axonal loss or optic atrophy in treated cases of IIH.

Automated spectral domain optical coherence tomography (SD-OCT) segmentation accurately identifies retinal layer boundaries in normal patients and patients with retinal pathology (7–10). This technique has been used in patients with neuro-ophthalmic disease, and it has been suggested that analysis of the ganglion cell layer plus inner plexiform layer (GCL-IPL) is more predictive of disease progression and visual loss than measurement of the retinal nerve fiber layer (RNFL) (11,12).

In this study, we evaluated the thickness of the macula and its layers using automated SD-OCT segmentation in eyes of adult patients with stable, mild chronic papilledema due to IIH. We hypothesized that automated SD-OCT segmentation could be used to detect subclinical retinal or optic atrophy in this patient cohort.
METHODS

This study was designed as a retrospective chart review. It was approved by the Duke University Medical Center Institutional Review Board and conducted in accordance with the standards of the Health Insurance Portability and Accountability Act. The Duke Enterprise Data Unified Content Explorer (D.E.D.U.C.E.) was used to identify patients aged 16 years and older seen at the Duke Eye Center neuro-ophthalmology clinic between November 2010 and October 2011 with the ICD-9 diagnosis of 377.00 (Papilledema NOS) and 348.2 (Benign intracranial hypertension).

Patients who did not have SD-OCT data collected by Heidelberg Spectralis (required for the automated SD-OCT segmentation protocol as described by Chiu et al (7,9)) were excluded. Also excluded from the study were patients who had other conditions that may affect the optic nerve head (ONH) including glaucoma, ONH drusen, and large refractive error (spherical equivalent of greater than ±5 diopters or astigmatism of greater than 3 diopters). One patient with fulminant IHH was excluded because she was lost to follow-up 2 weeks after optic nerve sheath fenestration.

Data gathered on each patient included age, gender, race, ocular and medical history, visual acuity, visual fields results using the Humphrey Field Analyzer/HFA II-i (Carl Zeiss Meditec, Dublin, CA), appearance of the ONH, color vision, and raw E2E data from Spectralis OCT (Heidelberg, Carlsbad, CA) horizontal linear scans of the macula and circular scan of the peripapillary region.

We included eyes with resolved or resolving papilledema looking for atrophic changes; eyes with moderate or severe papilledema (Frisén grade ≥2) were not included in this study. The eyes in our study were subdivided into 2 groups: atrophic papilledema and non-atrophic papilledema (Frisén grade ≤2) (Table 1). Atrophic papilledema was defined as visible ONH pallor. All patients with ONH pallor had some form of vision loss (i.e., reproducible visual field changes other than an enlarged blind spot and/or best corrected visual acuity <20/40). Non-atrophic papilledema was defined as stable disease without evidence of ONH pallor, RNFL thickness ≥80 μm, and normal visual field testing (mean deviation less than −3.0 dB on Humphrey 24-2 SITA standard visual field testing and no visual field defect other than an enlarged blind spot).

SD-OCT scans from both groups were reviewed for any retinal structural abnormalities. These structural abnormalities included epiretinal membranes (ERMs), inner or outer retinal layer cysts, and photoreceptor (PR) loss. SD-OCT scans from the non-atrophic papilledema group as well as the control group were segmented by Duke Optical Coherence Tomography Retinal Analysis Program (DOCTRAP) software using a graph-based automated segmentation analysis protocol which was previously validated for images of various disease pathologies (7–10). The eye with the more reliable OCT or thinner RNFL was selected for comparison in these patients, with the exception of when that eye had met 1 or more of the exclusion criteria. In instances where there were multiple visits during the period of November 2010 and October 2011, only scans from the most recent visit were used. Normal controls were age-matched to patients in the mild non-atrophic papilledema group (Table 1).

Thickness was determined for RNFL, GCL-IPL, inner nuclear layer (INL), outer plexiform layer plus outer nuclear layer (OPL-ONL), inner plus outer photoreceptor segments (IS-OS), and retinal pigment epithelium (RPE) (Fig. 1). The Early Treatment Diabetic Retinopathy Study (ETDRS) map was used to divide the macula into 9 regions consisting of 3 concentric circles with diameters measuring 1 mm (fovea), 3 mm (inner ring), and 6 mm (outer ring). Peripapillary RNFL thickness was acquired from the Heidelberg Spectralis OCT software.

![FIG. 1. Segmentation of spectral domain optical coherence tomography macular scans by Duke Optical Coherence Tomography Retinal Analysis Program (DOCTRAP) demonstrates the vitreous, nerve fiber layer (NFL), ganglion cell layer plus inner plexiform layer (GCL-IPL), inner nuclear layer (INL), outer plexiform layer plus outer nuclear layer (OPL-ONL), inner plus outer photoreceptor segments (IS-OS), retinal pigment epithelium (RPE), and choroid.](image)

TABLE 1. Demographic data of patients demonstrating atrophic papilledema, nonatrophic papilledema, and controls

<table>
<thead>
<tr>
<th></th>
<th>Atrophic Papilledema</th>
<th>Non-Atrophic Papilledema</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>Age, yr</td>
<td>37 (±16)</td>
<td>32 (±9)</td>
<td>33 (±15)</td>
</tr>
<tr>
<td>Gender</td>
<td>16 f/1 m</td>
<td>25 f/1 m</td>
<td>23 f/7 m</td>
</tr>
<tr>
<td>Race</td>
<td>4 w/5 b</td>
<td>7 w/18 b</td>
<td>14 w/7 b</td>
</tr>
<tr>
<td>Presenting ONH ≥3</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Presenting ONH &lt;3</td>
<td>3</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

Control group was age-matched to non-atrophic papilledema group. Presenting ONH refers to the nerve swelling on the Frisén scale when the patient initially presented for evaluation. SD values within the parenthesis.

b, black; f, female; m, male; ONH, optic nerve head; w, white.
Statistical analysis of data was performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA). Unpaired Student t tests were used to compare the mild non-atrophic papilledema group with the control group for each of the above-listed automated OCT scan thicknesses. Bonferroni correction was used for multiple comparisons (P-value for each ETDRS segment was multiplied by 8, P-values for each ring was multiplied by a factor of 2). Additionally, the automated DOCTRAP segmentation results were verified by manual evaluation and corrected using DOCTRAP in manual mode if necessary. The error rate comparing the total macular thicknesses within the fovea, inner macular ring, and outer macular ring between the DOCTRAP software and Spectralis software also was performed.

RESULTS

Ninety-four patients were identified from the D.E.D.U.C.E. query. Forty-five patients were excluded due to not having SD-OCT imaging using the protocol of the study, 4 patients due to ONH swelling >2 on the Frisén scale, and 2 patients due to the presence of ONH drusen. Of the remaining 43 patients, 26 had non-atrophic papilledema (Frisén grade ≤2) and 17 had atrophic papilledema. Thirty controls were age-matched to those in the non-atrophic papilledema group. Of the 26 patients in the non-atrophic papilledema group, 6 had nerve swelling on initial presentation ≥3 on the Frisén scale, whereas 20 had nerve swelling <3. Of the 17 patients in the atrophic papilledema group, 11 initially presented without pallor, of which, 8 had nerve swelling on presentation ≥3, whereas 3 had nerve swelling <3 on the Frisén scale (Table 1).

There was equivalence of the total macular thicknesses within the fovea, inner macular ring, and outer macular ring between the DOCTRAP software and Spectralis software (average difference 1.13%; range, 0.35%–3.4%). Of the 61 horizontal line scans per patient used to construct the ETDRS map, 35.7% of the scans required slight manual adjustment of at least one of the segmented layers. This adjustment was performed once in a masked manner and only if the DOCTRAP segmentation clearly did not follow the expected contour of a retinal layer. This did not create significant differences in the numerical results for any layer within any ETDRS segment when using the automated vs manually adjusted technique.

The total macular thickness was significantly thinner in all papilledema eyes as compared with control within the fovea, inner macular ring, and outer macular ring (263 vs 276 μm, P < 0.01; 323 vs 344 μm, P < 0.001; 288 vs 301 μm, P < 0.01, respectively). Non-atrophic papilledema eyes also showed thinner total macular thickness compared with controls within the fovea and inner macular ring (266 vs 276 μm, P = 0.04; 333 vs 344 μm, P < 0.01) (Table 2). Fully automated segmentation demonstrated no difference in layer thickness between all papilledema and control eyes within the RNFL, IS-OS, and RPE. Among these layers, the RNFL was significantly thinner in atrophic papilledema than normal controls within the inner and outer macular ring (25 vs 27 μm, P < 0.01; 36 vs 41 μm, P = 0.03), although there was no difference between non-atrophic papilledema and controls.

There was thinning of the GCL-IPL, INL, and OPL-ONL layers in patients with papilledema as compared with controls. Among these layers, the GCL-IPL was thinner among all papilledema patients compared with controls, particularly within the inner and outer macular rings (85 vs 97 μm, P < 0.01; 62 vs 67 μm, P < 0.02). In non-atrophic papilledema patients, there was a trend for reduced thickness within the GCL-IPL inner macular ring as compared with control (93 vs 97 μm, P = 0.12). Significant thinning was seen within the inner macular ring of the INL among all patients with papilledema compared with controls (37 vs 39 μm, P = 0.04). In non-atrophic papilledema patients, there was a trend for reduced thickness within the inner macular ring of the INL when compared with normal controls (37 vs 39 μm, P = 0.13). Within the OPL-ONL layer, there was thinning within the fovea, inner macular ring, and outer macular ring among all patients with papilledema vs controls (124 vs 131 μm, P < 0.01; 112 vs 118 μm, P = 0.01; 95 vs 100 μm, P < 0.01). This was also the case in each of these regions among those patients with non-atrophic papilledema when compared with controls (124 vs 131 μm, P < 0.01; 112 vs 118 μm, P = 0.03; 95 vs 100 μm, P = 0.03).

Total macular thickness and retinal layers in which there were statistically significant differences for patients with non-atrophic papilledema were further assessed by quadrant. For total macular thickness, the nasal and temporal quadrants of the inner macular ring were thinner as compared with controls (334 vs 348 μm, P < 0.01; 322 vs 335 μm, P < 0.01) (See Supplemental Digital Content, Figure e1, http://links.lww.com/WNO/A124). Within the INL, the nasal quadrant of the inner ring was thinner in mild papilledema as compared with controls (36 vs 38 μm, P = 0.03) (See Supplemental Digital Content, Figure e2, http://links.lww.com/WNO/A125). Within the OPL-ONL, there was only a trend of thinning in mild papilledema in each quadrant of each macular ring as compared with controls (See Supplemental Digital Content, Figure e3, http://links.lww.com/WNO/A126).

There was no difference in thickness between all papilledema and controls within the peripapillary RNFL, either centrally or for any quadrant. This also was the case when comparing non-atrophic papilledema vs controls. Thickness of the peripapillary RNFL in eyes with atrophic papilledema was significantly thinner centrally and within the nasal, inferior, and superior quadrants as compared with controls (80 vs 102 μm, P < 0.0001; 56 vs 76 μm, P < 0.01; 108 vs 134 μm, P < 0.05; 88 vs 124 μm, P < 0.0001).

Twenty-one of 33 eyes from 17 patients with atrophic papilledema had changes in their retinal architecture. Photoreceptor loss was seen in 17 eyes, INL cysts were
seen in 4, ERMs in 9, and a lamellar hole in 1 (Fig. 2). These structural changes persisted with follow-up OCT imaging. Eyes with atrophic papilledema that had retinal structural change had worse visual acuity than eyes with atrophic papilledema with normal retinal architecture (20/31 vs 20/23; \( P = 0.04 \)). All control eyes and those with non-atrophic papilledema had normal retinal architecture.

**DISCUSSION**

In this study, we demonstrated that patients with non-atrophic and atrophic papilledema have atrophic changes in the macula. In patients with atrophic papilledema, these changes occur within the inner nuclear, outer nuclear, and photoreceptor layers. Patients with non-atrophic papilledema did not demonstrate qualitative structural changes, but we detected quantifiable macular thinning within the inner and outer nuclear layers. Peripapillary RNFL thickness showed no significant difference between eyes with non-atrophic papilledema and normal controls, similar to previously reported studies (13,14). Our findings of thinner nuclear layers in the macula may be a reliable measure to quantify subclinical atrophy in eyes with resolving papilledema. The overall thinning of the macula in resolving papilledema has been reported previously, but segmentation of the individual layers was not performed (15,16).

Our secondary findings of outer retinal changes in eyes with atrophic papilledema are particularly intriguing because papilledema is most commonly thought of as a disease of the optic nerve. This would suggest that changes due to papilledema occur within the retina. Potential causes include: 1) mechanical changes at the time of the severe ONH swelling, 2) ischemic changes due to compression of retinal vessels, and 3) retrograde transsynaptic degeneration. Transsynaptic degeneration may occur when injured neurons cause subsequent damage of retinal ganglion cells and inner nuclear neurons, which may be followed by thinning of the OPL and cell loss within the ONL (17). Such changes are detectable on both OCT and electroretinography (18,19) and have been shown to occur after occipital lobe injury, optic neuritis in multiple sclerosis and neuromyelitis optica, and other neurological diseases (17,20–23).

Our study is limited by its retrospective and cross-sectional design. We were unable to assess early stages of IIH and control for treatment modality or treatment delay. In addition, we did not assess for mild visual impairment using low-contrast acuity with the Colenbrander Mixed Contrast Eye Chart or with multifocal electroretinography. Our study was also limited by having more than half of potential patients excluded due to not having Spectralis SD-OCT imaging performed as part of their evaluation and management. These

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**TABLE 2.** Average thickness (in micrometers) in 6 segmented layers of 3 macular rings in eyes with non-atrophic papilledema vs controls

<table>
<thead>
<tr>
<th>Layer</th>
<th>NFL (( \mu \text{m} ))</th>
<th>GCL-IPL (( \mu \text{m} ))</th>
<th>INL (( \mu \text{m} ))</th>
<th>OPL-ONL (( \mu \text{m} ))</th>
<th>IS-OS (( \mu \text{m} ))</th>
<th>RPE (( \mu \text{m} ))</th>
<th>Total (( \mu \text{m} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fovea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-atrophic papilledema</td>
<td>16.3 (2.1)</td>
<td>36.8 (12.7)</td>
<td>20.7 (4.1)</td>
<td>124.3 (9.3)</td>
<td>36.4 (2.6)</td>
<td>28.8 (3.2)</td>
<td>336 (16)</td>
</tr>
<tr>
<td>Control</td>
<td>16.4 (1.6)</td>
<td>37.0 (9.1)</td>
<td>21.4 (4.2)</td>
<td>131.5 (9.3)</td>
<td>37.7 (3.2)</td>
<td>30.1 (4.0)</td>
<td>346 (11)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.83</td>
<td>0.94</td>
<td>0.53</td>
<td>(&lt; 0.01)</td>
<td>0.10</td>
<td>0.72</td>
<td>(&lt; 0.01)</td>
</tr>
<tr>
<td>Inner ring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-atrophic papilledema</td>
<td>27.2 (1.9)</td>
<td>93.3 (8.0)</td>
<td>37.4 (2.8)</td>
<td>112.0 (9.1)</td>
<td>32.8 (2.6)</td>
<td>29.9 (2.5)</td>
<td>333 (17)</td>
</tr>
<tr>
<td>Control</td>
<td>27.4 (1.7)</td>
<td>96.6 (4.6)</td>
<td>38.8 (2.7)</td>
<td>117.7 (7.3)</td>
<td>33.4 (3.2)</td>
<td>30.1 (3.4)</td>
<td>344 (10)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>1.47</td>
<td>0.12</td>
<td>0.13</td>
<td>(&lt; 0.01)</td>
<td>0.86</td>
<td>1.53</td>
<td>(&lt; 0.01)</td>
</tr>
<tr>
<td>Outer ring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-atrophic papilledema</td>
<td>42.4 (5.1)</td>
<td>66.5 (6.4)</td>
<td>30.6 (2.5)</td>
<td>95.4 (8.1)</td>
<td>34.8 (3.4)</td>
<td>25.6 (3.0)</td>
<td>296 (16)</td>
</tr>
<tr>
<td>Control</td>
<td>41.2 (4.7)</td>
<td>67.2 (4.7)</td>
<td>31.0 (2.5)</td>
<td>100.4 (6.8)</td>
<td>35.1 (2.6)</td>
<td>26.1 (3.1)</td>
<td>301 (12)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.77</td>
<td>1.29</td>
<td>1.20</td>
<td>(&lt; 0.01)</td>
<td>1.32</td>
<td>1.17</td>
<td>0.35</td>
</tr>
</tbody>
</table>

SD values within the parenthesis. \( P \) values are Bonferroni corrected. Significant (\( P < 0.05 \)) are bolded.

GCL-IPL, ganglion cell layer plus inner plexiform layer; INL, inner nuclear layer; IS-OS, inner photoreceptor segment plus outer photoreceptor segment; NFL, nerve fiber layer; OPL-ONL, outer plexiform layer plus outer nuclear layer; RPE, retinal pigment epithelium.

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**FIG. 2.** Arrows indicate changes in retinal architecture seen in patients with atrophic papilledema. **A.** Photoreceptor loss. **B.** Inner nuclear layer cysts.
limitations could be overcome by performing a continuation study which would involve prospectively enrolling patients, observing them over time from onset of papilledema, and evaluating outcomes with different treatment modalities. Our findings shed light on retinal changes that occur due to papilledema and may help to explain the etiology of vision loss in some patients. Further longitudinal and prospective studies may help to create a model to predict the visual outcome of patients presenting with papilledema.

REFERENCES


Background: This study sought to correlate the clinical features of patients with giant cell arteritis (GCA) who present with ophthalmic symptoms and signs, with 2 specific histopathological findings—the presence of giant cells and arterial wall neoangiogenesis. The goal was to assess if these pathological features might be useful in guiding the approach to patient management.

Methods: Medical charts were retrospectively reviewed from 58 patients who underwent a temporal artery biopsy at a single institution. Detailed information was collected about the clinical presentation and course, with an emphasis on visual function. Histopathological and immunohistochemical techniques were used to examine temporal artery biopsies for evidence of inflammation. Correlations were made between the clinical data and the presence of giant cells and neoangiogenesis.

Results: Twenty-one (34%) biopsies were positive for inflammation consistent with GCA. Although the percentage of positive biopsies with giant cells was high, neither the presence of giant cells nor neoangiogenesis was predictive of a patient’s presenting visual symptoms, severity and bilaterality of vision loss, other ophthalmic manifestations of GCA, presence of headache or jaw claudication, or erythrocyte sedimentation rate. Giant cells were more common in patients with recent weight loss. Immunohistochemistry confirmed diagnoses but did not alter the clinical course or treatment plan.

Conclusions: There was no correlation between the clinical, specifically visual, features of GCA and the presence or absence of giant cells or neoangiogenesis in temporal artery biopsy specimens. Although the presence of neoangiogenesis may be important in the pathogenesis of GCA, our study showed no correlation between this finding and the clinical course.

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Giant cell arteritis (GCA) is a systemic vasculitis that can cause permanent visual loss in older adults, although the majority of patients with GCA do not have visual symptoms (1–5). Despite some controversy, biopsy of the temporal artery is the gold standard to establish a diagnosis of GCA (6,7). The typical defining characteristics of positive biopsies include T lymphocytes, epithelioid histiocytes, and possibly multinucleated giant cells, although the latter are not required for the diagnosis (6,8). A positive biopsy may additionally demonstrate intimal hyperplasia, luminal narrowing, neoangiogenesis, and internal elastic lamina fragmentation (9,10). More recently, the use of immunohistochemical stains to identify inflammation has been suggested as a strategy to help to resolve diagnostic uncertainty (11,12). However, the question remains whether specific histopathological features, such as giant cells or neoangiogenesis, have clinical significance or implications for patient management.

The goal of our study was to provide assessment of any correlations between the visual outcomes of patients with GCA and histopathological findings of temporal artery biopsy. Such data are important as new steroid-sparing therapies are being explored that target specific immune mechanisms (13).

METHODS

Permission for review and analysis of medical records and biopsy specimens for this study was granted by the Institutional Review Board at Massachusetts Eye and Ear Infirmary (MEEI), Boston, MA. A retrospective blinded chart review was undertaken without knowledge of the biopsy results for all patients with complete medical records.
from MEEI who underwent temporal artery biopsy between January 2008 and April 2013. All patients had been examined either in the neuro-ophthalmology or oculoplastic clinic and had temporal artery biopsies performed by MEEI oculoplastic surgeons. All initial histopathological diagnoses had been rendered by 1 of 3 MEEI ocular pathologists. Data about ophthalmic presentation and findings included initial visual acuity, visual acuity at last follow-up visit, color vision, funduscopic examination, visual field test result, presence of an ischemic disease involving the eye or visual pathways, or ocular motor cranial nerve palsies. Presenting symptoms were categorized according to the presence or absence of permanent visual loss, transient visual loss, or diplopia. Ophthalmic signs were detailed about visual acuity worse than 20/400, bilaterality of vision loss, optic neuropathy, and central retinal artery occlusion (CRAO). The range of normal values for C-reactive protein varied significantly because many of the initial tests were performed in different laboratories.

The specimen slides from all 58 biopsies were re-evaluated in a blinded fashion by 2 of the authors (R.C.S., A.L.G.) with no knowledge of the previous diagnoses or clinical presentation. All specimens were evaluated with hematoxylin and eosin and an elastin stain. In some cases, immunohistochemistry had already been obtained at the time of diagnosis. All other specimens were stained with the same battery of immunohistochemical stains used for the other specimens, which included CD3 (DAKO, Carpinteria, CA) for T cells and CD68 (Leica, Wetzlar, Germany) or CD163 (Leica) for histiocytes. Neoangiogenesis was highlighted by staining for CD31 (DAKO), which is an endothelial cell marker. A positive diagnosis was made according to accepted criteria (9,12), based on the presence of intimal hyperplasia and transmural inflammation and confirmed using immunohistochemistry-assisted modified criteria (12).

To determine statistical significance, student 2-tailed t tests were performed for continuous variables, and Fisher exact tests were used for dichotomous variables.

RESULTS

Clinical Data

Of the 58 biopsies available for review, 21 were positive and 37 were negative; the diagnoses made upon our rereview matched the diagnoses that had been assigned at the time of the initial evaluation. The overall diagnosis of positive or negative GCA also did not change with the information provided by immunohistochemical staining. All histopathological diagnoses concurred with clinical diagnoses that were made by the treating physician.

Clinical data and statistical analyses for patients with positive and negative biopsies are summarized in Table 1. A significant difference was found in the degree of vision loss between categories: 11 patients (82%) with positive biopsies had acuities in the affected eye of 20/400 or worse, whereas 9 patients (35%) with negative biopsies had acuities of 20/400 or worse. Three patients with positive biopsies had bilateral vision loss, whereas none of the patients with negative biopsies had bilateral vision loss. There also was a statistically significant difference in the prevalence of jaw claudication, erythrocyte sedimentation rate, and platelet count.

In the 21 patients with positive biopsies, the most common cause of visual loss was ischemic optic neuropathy, which was found in 10 patients (48%), followed by CRAO, found in 3 patients (14%) (Table 1). Four patients with negative temporal artery biopsies were diagnosed with “biopsy-negative” GCA based on clinical suspicion. Of the remaining 33 patients with negative temporal artery biopsies, final diagnoses were available for 18 patients. The most common alternative diagnosis to explain vision loss was a CRAO due to atheroembolic disease, which was diagnosed in 9 patients (17%) (i.e., 50% of patients with known alternative diagnoses) and nonarteritic ischemic optic neuropathy was diagnosed in 3 patients.

All 21 patients (100%) with positive biopsies were treated with corticosteroids, either methylprednisolone or prednisone. Twenty-eight patients (76%) with negative biopsies had been treated with prednisone before or on the day of their biopsy. The time lag between treatment and biopsy was not significantly different between the 2 groups. Only 1 patient in the positive biopsy group had any improvement in vision. This patient had a CRAO and had been started on 60 mg of prednisone 2 weeks after her acuity was found to be 20/400. After 2 weeks of prednisone, her vision improved to 20/90 and remained stable for 4 months during the period of prednisone taper.

Histopathological Findings in Positive Biopsies and Clinical Correlations

Positive biopsies were divided into categories based on the presence or absence of giant cells and neoangiogenesis. The mean length of the postfixation biopsy specimen was 1.4 cm. There also was no statistical difference in length of positive biopsy specimens with or without giant cells or neoangiogenesis. There also was no significant difference in time lag from the introduction of corticosteroid treatment to biopsy between any compared categories.

Inflammatory changes included giant cells detected with routine staining techniques (Fig. 1A) and with immunohistochemistry (Fig. 1B). Use of immunohistochemical stains confirmed and localized inflammation for 4 positive biopsies in which inflammation was more subtle (Fig. 1C and 1D). Immunohistochemical stain CD31 highlighted neoangiogenesis that may not have been apparent with hematoxylin and eosin (Fig. 1E).
None of the negative biopsies had notable inflammation within the vessel wall, including any giant cells or signs of neoangiogenesis even after immunohistochemical staining.

Within the group of patients with positive biopsies, there were 17 specimens (80%) that contained giant cells and 4 specimens (20%) that did not. There were no significant clinical differences between the 2 groups regarding the following variables: age, gender, presenting ophthalmic symptom, presence of concurrent headache, jaw claudication, history of polymyalgia rheumatica, history of stroke, erythrocyte sedimentation rate, time from steroid treatment to biopsy, percentage of patients with vision loss to an acuity of 20/400 or worse, bilateral vision loss, or percentage of patients with the diagnosis of ischemic optic neuropathy or CRAO (Table 2). Platelet values were not available for 3 of the 4 patients with negative biopsies, so this parameter was not statistically compared. The only statistically significant finding was the presence of weight loss, which was found in 11 patients who had positive biopsies containing giant cells but in no patient with giant cell−negative inflammation. Similar results were seen when comparing groups with and without neoangiogenesis. Specifically, 15 specimens (71%) had neoangiogenesis within the vessel wall, and 6 specimens (29%) did not. As above, there were no significant clinical differences (Table 2), and weight loss was not found to be significantly different in this comparison.

When comparing other histological parameters from the positive specimens, there was a statistically significant association between giant cells and neoangiogenesis ($P=0.05$) (Table 2). The converse was also true. All but 3 specimens had visible inflammation in all 3 layers of the vessel wall; statistically, transmural inflammation was not more common in specimens with giant cells or neoangiogenesis. However, there was a trend without significance of transmural inflammation with neoangiogenesis ($P=0.07$). No statistical correlation was seen for the presence or absence of accessory vessel inflammation regarding giant cells or neoangiogenesis. The internal elastic lamina was fragmented in all positive biopsies.

### DISCUSSION

Our study is one of a small number attempting to correlate clinical and histopathological findings in temporal artery biopsy specimens from an ophthalmic and neuro-ophthalmic perspective (12,14,15). Our patient population and focus of clinical examinations differs significantly from

### TABLE 1. Clinical data of patients with positive and negative temporal artery biopsies

<table>
<thead>
<tr>
<th></th>
<th>Positive Biopsy</th>
<th>Negative Biopsy</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>21</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Age, mean, yr</td>
<td>76</td>
<td>73</td>
<td>0.17</td>
</tr>
<tr>
<td>Female/male</td>
<td>14/7 (67%/33%)</td>
<td>18/19 (49%/51%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Presenting visual symptom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent vision loss</td>
<td>13 (61%)</td>
<td>26 (70%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Bilateral vision loss</td>
<td>3 (14%)</td>
<td>0</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Transient vision loss</td>
<td>3 (14%)</td>
<td>6 (16%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diplopia</td>
<td>3 (14%)</td>
<td>3 (8%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9 (43%)</td>
<td>17 (46%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Jaw claudication</td>
<td>9 (43%)</td>
<td>4 (11%)</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Weight loss</td>
<td>11 (52%)</td>
<td>10 (27%)</td>
<td>0.09</td>
</tr>
<tr>
<td>History of polymyalgia rheumatica</td>
<td>3 (14%)</td>
<td>2 (5%)</td>
<td>0.34</td>
</tr>
<tr>
<td>History of stroke</td>
<td>4 (19%)</td>
<td>3 (8%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Examination finding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual acuity ≤20/400</td>
<td>11 (82%)*</td>
<td>9 (35%)*</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Optic neuropathy</td>
<td>10 (48%)</td>
<td>3 (17%)*</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>CRAO</td>
<td>3 (14%)</td>
<td>9 (50%)*</td>
<td>0.07</td>
</tr>
<tr>
<td>Laboratory studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mean)</td>
<td>77</td>
<td>44</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Platelet count, $\times 1000$ (mean)</td>
<td>386</td>
<td>287</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Number of days from initiation of steroid treatment to temporal artery biopsy (mean, median)</td>
<td>4, 2</td>
<td>9, 3</td>
<td>0.11</td>
</tr>
<tr>
<td>Length of biopsy specimen, postfixation, cm (mean)</td>
<td>1.4</td>
<td>1.5</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Bold values are statistically significant.

*Percentages based on the number of patients with permanent vision loss.
†Percentages based on the 18 patients who had known diagnoses other than biopsy-negative GCA.
CRAO, central retinal artery occlusion.
FIG. 1. Histopathological and immunohistochemical staining of positive temporal artery specimens. A. Change in the vessel wall includes lymphocytic and granulomatous inflammation with giant cells (arrowheads) at the intima–media junction. New vessel formation is present (arrows), and there is severe luminal narrowing (asterisk) (hematoxylin and eosin, × 200). B. T lymphocytes are present throughout the vessel wall (CD3 immunostain, × 200). C. In this specimen, inflammation is obvious in the adventitia (arrow) but not elsewhere (hematoxylin and eosin, × 100). D. Immunostaining of the vessel shown in (C) reveals inflammation along the internal elastic lamina (inset, arrow) (CD163 immunostain, × 100). E. In another specimen, immunohistochemical staining confirms the presence of neoangiogenesis in the vessel wall (CD31 stain, × 100).
most other research in this area, which typically mines data from general medical or rheumatological clinics, where only 30%–50% of patients report visual complications (1,2,4,16,17).

In our survey, 54 of 58 patients were referred for visual symptoms, and 67% of our patients had permanent visual loss. However, the patients we studied otherwise matched the profile generally reported in the medical literature for GCA, having similar demographics of age and gender, similar clinical manifestations, and visual symptoms and signs (1,3–5,15,17–19). The absence of visual recovery seen among all but 1 of our patients is consistent with the poor visual prognosis in GCA (1,3,20). Although the prevalence of headache was less than reported from other studies (5,17,18,21,22), our patient cohort is quite similar to those described in the literature.

This study sought to correlate the clinical features of patients having GCA with 2 specific histopathological findings, the presence of giant cells and arterial wall neoangiogenesis, to assess if these pathological features might be useful in guiding the approach to management. Giant cells and CD68+ macrophages at the media–intima junction may be the major source of vascular endothelial growth factor (VEGF), which has been implicated in causing neoangiogenesis of the temporal artery (10,23). It has also been suggested that neoangiogenesis may be a protective measure, perhaps lowering the risk of ischemic complications (23,24). However, one study suggests the contrary, that neoangiogenesis is associated with risk of permanent vision loss (2). We chose to focus on the specific histopathological parameters of giant cells and neoangiogenesis because of their potential roles in inflammation and/or protection and also to help resolve the different viewpoints on whether they portend a better or worse prognosis. Our results show that in patients referred to an ophthalmologist, the presence or absence of giant cells or neoangiogenesis are not indicators of clinical presentation or course. Our study also demonstrates for the first time that the presence

### TABLE 2. Clinical and histopathological parameters associated with giant cells and neoangiogenesis within the temporal artery specimens

<table>
<thead>
<tr>
<th></th>
<th>With Giant Cells</th>
<th>Without Giant Cells</th>
<th>P Value</th>
<th>With NA*</th>
<th>Without NA*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>17</td>
<td>4</td>
<td>0.74</td>
<td>15</td>
<td>6</td>
<td>0.82</td>
</tr>
<tr>
<td>Age, mean, yrs</td>
<td>76</td>
<td>75</td>
<td>0.00</td>
<td>76</td>
<td>75</td>
<td>0.82</td>
</tr>
<tr>
<td>Female</td>
<td>12 (71%)</td>
<td>3 (75%)</td>
<td>1.00</td>
<td>10 (67%)</td>
<td>4 (67%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Presenting symptom</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent vision loss</td>
<td>12 (71%)</td>
<td>1 (25%)</td>
<td>0.25</td>
<td>10 (67%)</td>
<td>3 (50%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Bilateral vision loss</td>
<td>3 (18%)</td>
<td>0</td>
<td>1.00</td>
<td>2 (13%)</td>
<td>1 (17%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Transient vision loss</td>
<td>1 (6%)</td>
<td>2 (50%)</td>
<td>0.48</td>
<td>2 (13%)</td>
<td>1 (17%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diplopia</td>
<td>1 (6%)</td>
<td>2 (50%)</td>
<td>0.08</td>
<td>2 (13%)</td>
<td>1 (17%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Concurrent symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8 (47%)</td>
<td>1 (25%)</td>
<td>0.60</td>
<td>7 (47%)</td>
<td>2 (33%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Jaw claudication</td>
<td>7 (41%)</td>
<td>2 (50%)</td>
<td>1.00</td>
<td>8 (53%)</td>
<td>3 (17%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Weight loss</td>
<td>11 (65%)</td>
<td>0</td>
<td>0.04</td>
<td>9 (60%)</td>
<td>2 (33%)</td>
<td>0.36</td>
</tr>
<tr>
<td>History of polymyalgia rheumatica</td>
<td>2 (13%)</td>
<td>1 (25%)</td>
<td>0.48</td>
<td>2 (13%)</td>
<td>1 (17%)</td>
<td>1.00</td>
</tr>
<tr>
<td>History of stroke</td>
<td>3 (18%)</td>
<td>1 (25%)</td>
<td>1.00</td>
<td>3 (20%)</td>
<td>1 (17%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Examination finding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual acuity ≥20/400†</td>
<td>10 (83%)†</td>
<td>1 (100%)†</td>
<td>1.00</td>
<td>8 (53%)†</td>
<td>3 (50%)†</td>
<td>1.00</td>
</tr>
<tr>
<td>Optic neuropathy</td>
<td>7 (41%)</td>
<td>1 (25%)</td>
<td>1.00</td>
<td>7 (47%)</td>
<td>3 (50%)</td>
<td>1.00</td>
</tr>
<tr>
<td>CRAO</td>
<td>3 (18%)</td>
<td>0</td>
<td>0</td>
<td>3 (20%)</td>
<td>0</td>
<td>0.52</td>
</tr>
<tr>
<td>Laboratory studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mean)</td>
<td>77</td>
<td>60</td>
<td>0.43</td>
<td>81</td>
<td>64</td>
<td>0.11</td>
</tr>
<tr>
<td>Platelet count, × 1000 (mean)</td>
<td>†† ‡‡ ‡</td>
<td>4, 2</td>
<td>0.98</td>
<td>4, 2</td>
<td>2, 1</td>
<td>0.31</td>
</tr>
<tr>
<td>Days from initiation of steroid treatment to temporal artery biopsy (mean, median)</td>
<td>4, 2</td>
<td>4, 2</td>
<td>0.98</td>
<td>4, 2</td>
<td>2, 1</td>
<td>0.31</td>
</tr>
<tr>
<td>Transmural inflammation</td>
<td>17 (100%)</td>
<td>3 (75%)</td>
<td>0.19</td>
<td>15 (100%)</td>
<td>4 (50%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Accessory vessel involvement</td>
<td>8 (47%)</td>
<td>1 (25%)</td>
<td>0.60</td>
<td>5 (33%)</td>
<td>4 (67%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Giant cells</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>14 (93%)</td>
<td>3 (50%)</td>
<td>0.05</td>
</tr>
<tr>
<td>NA</td>
<td>14 (82%)</td>
<td>1 (25%)</td>
<td>0.052</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Bold value is statistically significant.
*NA, neoangiogenesis.
†Percentages based on the number of patients with permanent vision loss.
‡Not analyzed due to insufficient data (see text).
CRAO, central retinal artery occlusion.
of angiogenesis is not a guaranteed reprieve from devastating visual complications.

Some additional positive findings among the data were discovered: giant cells and neoangiogenesis were correlated (albeit not to a significant extent). This may be related to the increased levels of vasogenic substances, such as VEGF and interferon-γ that are found in arteries infiltrated with macrophages (10). We also found one constitutional symptom that was associated with histopathology: weight loss was correlated with giant cells. Interestingly, weight loss was found to be negatively associated with irreversible vision loss in another study (1), so the significance of this finding remains to be elucidated.

Our overall findings are consistent with but expand upon several other studies. Bevan et al (16) found that giant cells were not correlated with vision loss. Similar studies also showed that giant cells were not indicative of visual symptoms or optic nerve involvement, but these reports did not provide measurements of visual function (15,24,25). Yet another study suggested that the depth of inflammation in the temporal artery was possibly related to visual symptoms, although the presence of giant cells was not (14). Another report came to an opposite conclusion that giant cells were related to permanent vision loss (2). However, in this series of more than 300 patients, fewer than 10% of patients had vision loss and 40% of patients had negative biopsies.

There are several potential limitations to our study. Although our specimens were of standard length for histopathological analysis, focal areas of inflammation can be as small as 330 μm (26), and variability within an artery is common (26). Because of the possibility of “skip lesions,” it is thought that a longer specimen increases the biopsy yield (27). However, various surgical subspecialists may have different surgical approaches to temporal artery biopsies. For example, in one survey from 3 institutions, ophthalmologists who performed temporal artery biopsies sampled longer specimens than other types of surgeons (28). In our study, all biopsies were obtained by ophthalmic plastic surgeons trained in ophthalmology. The mean specimen length in our survey, 1.4 cm postfixation, exceeded the critical value found to be associated with a meaningful result (28). Notably, specimen lengths were not provided in other studies that correlated clinical presentation with histopathological findings.

Interobserver and intraobserver variability in temporal artery biopsy diagnosis has been reported to be as high as 25% (9) and could be another limitation to our study. In our series, all pathological diagnoses were confirmed by a second blinded review and the interpretations matched the original diagnoses of whether there was evidence or not of active inflammation in the temporal artery. This high correlation might be due, in part, to the use of immunohistochemistry supporting the findings of Zhou et al (12). In our series, immunohistochemistry confirmed and did not change the diagnosis when the original biopsy was reviewed without special stains.

One potential confounding factor that might have influenced our results involves treatment: patients with vision loss were often treated with corticosteroids at the first hint of the diagnosis and biopsied on average 2 days later. This short duration of treatment is unlikely to alter the histopathological diagnosis because the inflammatory response is usually robust within the first 2 weeks (20,29). There were no significant differences in treatment periods for all groups compared in this study.

In summary, patients with GCA who present with visual symptoms show no correlation between the clinical features of their presentation and the presence or absence of giant cells or neoangiogenesis of the temporal artery biopsy specimen. Our study is the first to show that neoangiogenesis, which has been suggested to be a protective measure, does not correlate with the severity of the visual or general clinical presentation. As often discussed (13), identification of biomarkers (either in the temporal artery biopsy or blood) would potentially provide an advantage in tailoring therapy, but this goal remains elusive.

STATEMENT OF AUTHORSHIP


REFERENCES


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Effect of Diabetes Mellitus on Giant Cell Arteritis

Anne S. Abel, MD, Arseniy P. Yashkin, PhD, Frank A. Sloan, PhD, Michael S. Lee, MD

Background: To determine if Type 2 diabetes mellitus (DM) is protective against giant cell arteritis (GCA) and to estimate the incidence of GCA diagnosis from Medicare claims.

Methods: Medicare 5% claims files from 1991 to 2011 were used to identify beneficiaries diagnosed with DM, but not GCA, within a 3-year ascertainment period. Propensity score matching was used to define a control group of non-diabetics with comparable demographic covariates. Competing risk regression was then used to assess the impact of DM diagnosis on GCA diagnosis. To allow for a 3-year ascertainment period, the analysis sample was limited to beneficiaries older than 68 years at baseline.

Results: A total of 151,041 beneficiaries diagnosed with DM were matched to an equal number of controls. Mean study follow-up was 67.75 months. GCA was diagnosed among 1116 beneficiaries with DM (0.73%) vs 465 (0.30%) controls. The risk of receiving a GCA diagnosis among patients with DM was increased by 100% (sub-hazard ratio, 2.00; 95% confidence interval, 1.78–2.25). The annual incidence of GCA diagnosis among claims for US Medicare beneficiaries older than 68 years old was 93 in 100,000.

Conclusions: A DM diagnosis is not protective against a GCA diagnosis in the Medicare population. Our data suggest that a DM diagnosis increases the risk of GCA diagnosis within 5.7 years for Medicare beneficiaries older than 68 years.

doi: 10.1097/WNO.0000000000000218

Giant cell arteritis (GCA) is a T-cell-dependent vasculitis of medium and large arteries, almost exclusively affecting patients older than 50 years (1). Histologically, GCA causes panarteritis with infiltration of the vessel wall by activated T cells and macrophages (1). Destruction of the internal elastic lamina and intimal hyperplasia lead to an occlusive vasculitis, which can result in irreversible blindness, myocardial infarction, or stroke if untreated. Diagnosis of GCA requires careful consideration of clinical presentation and serum inflammatory markers. Ultimately, the diagnostic gold standard for GCA remains temporal artery biopsy (TAB).

Clinically, the diagnosis can be quite challenging, especially in the absence of headache, jaw claudication, or other systemic GCA symptoms. Physicians must weigh their clinical index of suspicion in the context of serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet levels to decide when to start corticosteroids and proceed with TAB. Unfortunately, ESR and CRP are not 100% sensitive or specific, and equivocal serum inflammatory markers can occur in biopsy-proven GCA. Conversely, chronically elevated ESR and CRP can occur in patients without GCA who have diabetes mellitus (DM), cardiovascular disease, and metabolic syndromes (2–7).

Previous reports have identified a potentially protective effect of DM against GCA (5,8,9). Proposed mechanisms include an altered cytokine profile, impaired T-cell response, and impaired dendritic cell function due to excessive antigen glycosylation (5,8,9). One recent retrospective study found a lower prevalence of DM among patients with a positive TAB than with a negative TAB (5). A meta-analysis of 8 GCA studies found a low prevalence of biopsy-positive GCA among patients with DM (5). The authors suggested that DM may actually lower the risk of GCA. Additionally, they implied that elevated ESR and CRP may result from DM and may not increase the likelihood of GCA diagnosis. If this is true, our GCA practice patterns for patients with DM may change dramatically.

We sought to explore this hypothesis in a larger patient population. Given the low incidence of GCA, it is not
practical to study the relationship between DM and GCA prospectively (10–19). Therefore, we queried the Medicare 5% claims and enrollment data and then followed beneficiaries through time to compare the incidence of GCA diagnosis among individuals with and without a DM diagnosis.

METHODS

Institutional Review Board approval was obtained for this study from Duke University Medical Center.

Data

Medicare is a national health insurance program that serves Americans who live within the geographical borders of the United States. Most Medicare beneficiaries qualify at age 65 years. Younger individuals with a qualifying disability may also be enrolled. The Medicare 5% claims data set is a nationally representative random sample of the overall Medicare beneficiary population containing information on services paid for by Medicare Part A (covering hospital and other facility-based services) and Medicare Part B (covering professional services, mostly provided by physicians). Claims information is not available for beneficiaries who enroll in a MA plan, a private alternative to traditional Medicare. The 5% Medicare claims and enrollment data from 1991 to 2011 was queried for diagnoses of DM and GCA. Demographic characteristics, enrollment information, International Classification of Diseases, Ninth Revision (ICD-9) codes, and Current Procedure Terminology (CPT) codes were available for the entire sample. Beneficiaries enrolled in MA plans were excluded because the 5% sample does not include claims for care provided by MA.

Sample Selection

To assess the incidence of GCA diagnosis, study inclusion required an ascertainment period of 3 years during which a diagnosis of GCA was not documented. Because TAB results are not part of the Medicare 5% sample data, GCA was defined as 1) any beneficiary who received a GCA diagnosis (ICD-9, 446.5) after a TAB (CPT 37609) or 2) any patient who received 2 GCA diagnoses (ICD-9, 446.5) within 180 days. To ensure the availability of a 3-year ascertainment period, beneficiaries were required to be at age 68 years or older at baseline. This ascertainment period has been used in other studies (20,21). Baseline was defined as the date of the first Type 2 DM diagnosis (ICD-9, 250.xx). For the DM group and the first date, after the beneficiary’s 68th birthday, a Medicare claim appeared in the claims data. All beneficiaries diagnosed with DM received this diagnosis before being diagnosed with GCA. The non-DM control group was identified using propensity score matching (PSM) to select a matched sample of beneficiaries who were never diagnosed with Type 2 DM during the 3-year ascertainment period or during follow-up.

Current standards of PSM research accept a standardized difference of roughly 10% between the treatment and control groups for all covariates of interest (22–25). Matching covariates were gender, black race, other race (white race omitted), baseline year, age at baseline, and binary variables for hypertension (ICD-9, 401.xx) and hyperlipidemia (ICD-9, 272.xx–272.xx) at baseline. We used logistic regression to estimate the propensity score and the nearest neighbor matching (without replacement) within a caliper of 0.001 to identify the match. The size of the caliper was well below the 20% of the SD of the propensity score guideline suggested in the literature (26).

Beneficiaries meeting the inclusion criteria were followed until they were 1) diagnosed with GCA, 2) died, or 3) otherwise censored. Beneficiaries were censored if they 1) joined a MA plan, 2) moved outside the United States, or 3) had no Medicare claims during follow-up.

Statistical Analysis

The DM and non-DM group were compared using a competing risk regression model based on the method of Fine and Gray (27). The underlying rationale for competing risk regression has been discussed elsewhere (28–30). Briefly, competing risk regression uses the cumulative incidence function to model probability of failure from a specific cause (the primary risk) in the presence of other events that could prevent the outcome of interest (the competing risks). GCA diagnosis was the primary risk, and death was the competing risk. The subhazard ratios (SHR) are interpreted like hazard ratios in Cox regression. Given the advanced age and morbidity of the Medicare population, competing risk regression was chosen over Cox regression, because the risk of death from all other causes could potentially censor the observations of interest prematurely.

The incidence of GCA was calculated by dividing the number of GCA diagnoses for the PSM-matched cohort by the total number of person-years, which was calculated by multiplying the number of PSM-matched beneficiaries by the average study time.

RESULTS

A total of 151,041 beneficiaries with a Type 2 DM diagnosis were matched to an equal number of beneficiaries without a Type 2 DM diagnosis. In the absence of PSM, the beneficiary mix in the DM and non-DM groups was not comparable with respect to hyperlipidemia, hypertension, and baseline year, as these covariates exceeded the 10% standardized difference criterion (20–23). PSM substantially improved the comparability of both groups, bringing all covariates well within the 10% guideline (Table 1).

In the pooled sample, the majority of subjects were white (82.3%) and female (58.8%). A total of 9.9% were black, and 7.8% were identified as other race. The mean beneficiary age at baseline was 77.7 years. The mean age for black and non-black beneficiaries was 77.6 and 77.7 years, respectively (P < 0.01). Substantial beneficiary fractions were diagnosed with hyperlipidemia (26.8%) and hypertension (59.1%).
Mean study time was similar for the DM and non-DM groups (67.4 months and 68.1 months, respectively). Median follow-up was 56 months for the DM group and 57 months for the non-DM group. In the DM group, GCA was diagnosed in 1116 (0.73%) beneficiaries vs 465 (0.30%) beneficiaries in the non-DM group. Death, the competing risk event, occurred in 94,273 (62.42%) of the DM group and 80,512 (46.39%) of the non-DM group. The risk of receiving a GCA diagnosis among beneficiaries diagnosed with Type 2 DM increased by 100% (SHR: 2.00; 95% confidence interval [CI], 1.78–2.25). Non-white race and male gender were primarily protective. Hyperlipidemia and hypertension increased the risk of GCA (Table 2, Fig. 1).

Of the 302,082 PSM-matched beneficiaries included in this study, 1581 were diagnosed with GCA (GCA group). The majority (85%) of the GCA group had a GCA diagnosis after TAB, whereas only 15% of the GCA group had 2 diagnoses of GCA within a 180-day period but no TAB. We conducted a sensitivity analysis omitting the 2 diagnosis-only group and observed no significant difference in the results. The mean study time for the entire matched cohort was 67.8 months or 5.7 years. The annual incidence of GCA diagnosis was 92 diagnoses per 100,000 beneficiaries. The incidence of GCA diagnosis was significantly higher among white beneficiaries than black beneficiaries (98 per 100,000 vs 77 per 100,000, respectively [P < 0.001]).

**DISCUSSION**

Contrary to previous reports suggesting a protective effect of DM on GCA, we found that Medicare beneficiaries older than 68 years with a Type 2 DM diagnosis were more likely to receive a GCA diagnosis than beneficiaries older than 68 years without a DM diagnosis. Type 2 DM does not appear protective against GCA in this population, and our data showed that it increased the risk of GCA by 100%.

**TABLE 2. Risk factors for giant cell arteritis**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>SHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>2.00* (1.78–2.25)</td>
</tr>
<tr>
<td>Male</td>
<td>0.47* (0.41–0.53)</td>
</tr>
<tr>
<td>Black</td>
<td>0.76† (0.62–0.93)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.27* (1.12–1.42)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.22† (1.09–1.36)</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>0.97* (0.96–0.98)</td>
</tr>
<tr>
<td>Baseline year</td>
<td>0.98* (0.97–0.99)</td>
</tr>
<tr>
<td>N</td>
<td>302,082</td>
</tr>
<tr>
<td>% With condition</td>
<td>0.52</td>
</tr>
</tbody>
</table>

These are adjusted risk factors. Other race, including Hispanic ethnicity was also controlled for in the analysis.

*P < 0.01 confidence intervals are reported at 95%.

†P < 0.05.

CI, confidence interval; GCA, giant cell arteritis; SHR, subhazard ratio.
Cumulative incidence of giant cell arteritis in Medicare beneficiaries with and without a DM diagnosis.

Pathophysiologic links between DM and GCA have been proposed but not well defined. Previous studies have suggested that an impaired T-cell response in DM is protective against GCA (5,8,9). Our results suggest the opposite (5,8,9). The study by Matthews et al (5) was a retrospective study of 215 patients at one academic institution. One strength of this study was that all subjects underwent TAB. Only 44 patients had biopsy-positive GCA, and only 4 of these patients had DM. Cid et al (8) studied 200 biopsy-positive patients with GCA at 3 hospitals, and Gonzalez-Gay et al (9) studied 215 biopsy-positive patients at 1 hospital. The relatively small sample sizes in these studies compared with our sample of more than 300,000 Medicare beneficiaries may explain our conflicting results. Moreover, our random sampling of the national database removes the selection bias inherent in the single center studies. Because our inclusion criteria did not mandate TAB results like the aforementioned studies, we acknowledge that our GCA incidence may be overestimated. However, the overwhelming majority (85%) of our GCA group received a GCA diagnosis after TAB, implying that the biopsy was positive.

Mounting evidence suggests a common abnormality between cell-mediated immune dysfunction in patients with DM and GCA, which may support our findings. Specifically, regulatory T-cell (Treg) deficiency has been implicated in various autoimmune and metabolic disorders, including rheumatoid arthritis, atherosclerosis, diabetes Type-1, metabolic syndrome, and multiple sclerosis (31). Patients with GCA and polymyalgia rheumatic may have decreased serum levels of these immunosuppressant Treg cells (32). Conceivably, an impaired immune response, possibly due to Treg deficiency, may represent a common thread between DM and GCA that could explain the increased risk of GCA diagnosis we found in Type 2 diabetic Medicare beneficiaries older than 68 years.

The annual incidence of GCA has been previously reported in geographically and ethnically homogenous populations older than 50 years. Retrospective studies of primarily Scandinavian populations from Northern Europe and Olmsted County, Minnesota, indicate an annual incidence around 20 per 100,000 individuals older than 50 years (10–15). A lower GCA incidence of 10 per 100,000 was reported in Mediterranean populations older than 50 years (14,16–19). An accurate annual incidence of GCA across the entire US population has not been firmly established. Our study found an overall incidence of GCA diagnosis of 92 per 100,000 US Medicare beneficiaries older than 68 years. This cannot be compared directly with previously published series because of the different ages of the populations studied.

GCA rarely occurs among black individuals (19,33), and our results suggest this observation. The reasons for this difference are unclear, and additional research is needed to determine the effect of race on GCA diagnosis.

We acknowledge the inherent limitations of using billing records to measure disease incidence. Medicare claims data are designed for administrative rather than for clinical purposes. However, use of these data has been shown to provide valid measures of underlying clinical phenomena (34). We also recognize that not all providers use strict diagnostic criteria when coding for GCA. We assumed that 1) a GCA diagnostic billing code after a TAB CPT code implies that the TAB was positive and 2) 2 GCA ICD-9 codes within 180 days indicates the presence of GCA. Conceivably, we may be overestimating the incidence of GCA by including beneficiaries with 2 GCA diagnoses within 180 days and not requiring a GCA diagnosis after TAB for study inclusion. This study’s retrospective design is also a limitation. Finally, PSM does not completely eliminate selection bias or replace random assignment (35).

In conclusion, we found that DM is not protective against GCA in the Medicare population. Our data suggest that a diagnosis of DM increases the risk of GCA diagnosis in Medicare beneficiaries older than 68 years. Contrary to previous studies, our results suggest that elevated ESR and CRP are just as concerning in patients with diabetes as they are in patients without diabetes undergoing GCA evaluation. Ideally, a prospective study would further clarify the relationship between DM and GCA. To our knowledge, this is the largest population-based study to report the incidence of GCA in the Medicare population.

**STATEMENT OF AUTHORSHIP**


Category 2: a. Drafting the manuscript: M. S. Lee, F. A. Sloan, A. S. Abel. b. Revising it for intellectual content: M. S. Lee, F. A. Sloan, A. P. Yashkin, A. S. Abel.


**REFERENCES**


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Abstract: Background: Cranial nerve schwannomas are radiologically characterized by nodular cranial nerve enhancement on magnetic resonance imaging (MRI). Schwannomas typically present with gradually progressive symptoms, but isolated reports have suggested that schwannomas may cause fluctuating symptoms as well.

Methods: This is a report of ten cases of presumed cranial nerve schwannoma that presented with transient or recurring ocular motor nerve deficits.

Results: Schwannomas of the third, fourth, and fifth nerves resulted in fluctuating deficits of all 3 ocular motor nerves. Persistent nodular cranial nerve enhancement was present on sequential MRI studies. Several episodes of transient oculomotor (III) deficits were associated with headaches, mimicking ophthalmoplegic migraine.

Conclusions: Cranial nerve schwannomas may result in relapsing and remitting cranial nerve symptoms.

CASE REPORTS

Case 1

A 41-year-old woman with diabetes mellitus presented with a pupil-involving left third nerve palsy associated with severe headache. She had a history of "migraine headaches" since age 23 years. Brain computed tomography (CT) and cerebral angiography were normal. She was diagnosed with ophthalmoplegic migraine. Her symptoms gradually resolved over the next 6 months.

Ten years later, the left third nerve palsy and headache recurred. Serologic and cerebrospinal fluid (CSF) studies were normal. Brain magnetic resonance imaging (MRI) revealed a thickened and enhancing 3-mm nodular lesion of the left third nerve within the interpeduncular cistern, consistent with a schwannoma. She was empirically treated with a short course of oral prednisone. Gradually, over the next 6 months, the third nerve palsy resolved. A follow-up MRI, 12 years after her initial presentation, showed no change in the size or nodular enhancement of the third nerve lesion (Fig. 1A).
She had a third episode 13 years after her initial presentation. A repeat brain MRI was unchanged, and magnetic resonance angiography revealed no vascular abnormalities. Once again, her third nerve deficits resolved slowly over time, and she has remained asymptomatic for the past several years.

**Case 2**

A 23-year-old woman developed a complete pupil-involving right third nerve palsy accompanied by a severe headache. She reported having experienced a total of 5 similar stereotyped episodes beginning at age 7, with normal intervening neurologic and ophthalmologic examinations and had previously been diagnosed with “ophthalmoplegic migraine.” Brain MRI revealed a 4-mm nodular enhancing lesion of the right oculomotor nerve within the interpeduncular cistern. Her headache was treated with analgesic medications, and the right oculomotor nerve palsy resolved within 1 week (previously reported (5)).

Seven years later, she had her seventh episode of “ophthalmoplegic migraine.” On brain MRI, the appearance of the right third nerve lesion was unchanged (Fig. 1B). Once again, her third nerve palsy resolved spontaneously. Six months after resolution of her symptoms, a third brain MRI revealed continued nodular enhancement of the right oculomotor nerve lesion.

**Case 3**

A 42-year-old man presented with a partial pupil-involving left third nerve palsy accompanied by headache and periorbital pain. For the previous 15 years, he had been experiencing similar left periorbital headaches once or twice a year that were unaccompanied by other symptoms.

Brain MRI showed focal enlargement and nodular enhancement of the left third nerve at its brainstem exit. Six weeks later, the ptosis and extraocular movements in the left eye had improved significantly. Ten months later, only minimally decreased elevation of the left eye was noted. Repeat brain MRI at that time showed no change in the nodular enhancement of the left third nerve lesion.

**Case 4**

A 43-year-old man with isolated complete paralysis of the right medial rectus muscle was evaluated with serologic testing and CSF analysis that were unremarkable. Brain MRI revealed nodular enlargement and enhancement of the inferior division of the right third nerve. He received a 10-day course of oral prednisone. The right medial rectus paresis gradually improved over a 3-month period leaving only a small esophoria that increased on left gaze. Repeat MRI scans 6 months and 2 years later showed no interval change.

The patient returned 9 years later with recurrence of isolated complete paralysis of the right medial rectus muscle. Repeat MRI again showed similar nodular enlargement and enhancement of right inferior division of the third nerve (Fig. 2A). The diplopia and ophthalmoplegia resolved in over 5 months. Repeat MRI 10 months after his second presentation and 6 months after symptom resolution showed no interval change (Fig. 2B). Follow-up examination was normal except for a small exophoria that increased on left gaze.

**Case 5**

A 36-year-old man with diplopia was diagnosed with a right fourth nerve palsy. His medical history was significant only for asthma. Serologic testing and CSF studies were normal. Brain MRI showed focal enlargement and enhancement of the right trochlear nerve adjacent to the midbrain (Fig. 3A). The diplopia gradually resolved over several months, but brain MRI 3 years later was unchanged (previously reported (2)).

He remained asymptomatic for many years, except for 2 episodes of mild transient diplopia. Repeat brain MRI 10 years after initial presentation showed no change in the enhancing right fourth nerve lesion (Fig. 3B).

**Case 6**

A 60-year-old man with diabetes mellitus and hyperlipidemia developed a right fourth nerve palsy. Serologic testing was normal. A noncontrast brain MRI revealed a small isointense lesion of the right trochlear nerve adjacent to the

![FIG. 1. Two Cases of “ophthalmoplegic migraine.” Contrast-enhanced T1 axial brain magnetic resonance imaging reveals enhancing lesions (arrow) of the left (A, case 1) and right (B, case 2) third nerve in the interpeduncular cistern.](https://example.com/fig1.png)
midbrain. His diplopia gradually resolved without treatment, and on follow-up examination 3 months after presentation, there was no residual vertical misalignment (previously reported (2)).

Approximately 6 months later, he reported recurrence of binocular vertical diplopia and examination revealed a right fourth nerve palsy. Contrast-enhanced brain MRI demonstrated nodular enhancement of the previously identified trochlear nerve lesion, consistent with a schwannoma. The diplopia gradually resolved without treatment. Repeat examination 1 year later revealed a slight left head tilt and a small right hyperphoria.

Case 7
A 48-year-old man with a right fourth nerve palsy had serologic studies and an edrophonium test that were negative. Brain MRI showed an enhancing right trochlear nerve lesion. Over the next year, his diplopia resolved spontaneously, leaving no residual findings on examination (previously reported (2)).

He remained asymptomatic, and his examination remained normal on follow-up 7 and 9 years after initial presentation. More than a decade after presentation, brain MRI showed continued enhancement of the right fourth nerve lesion.

Case 8
A 66-year-old man reported a 6-month history of binocular vertical diplopia. Examination showed a right fourth nerve palsy, and brain MRI revealed an enhancing lesion of the right fourth nerve. After attempts at prism correction were unsuccessful, he was referred to a strabismus surgeon, but by the time he was seen, approximately 8 months later, his symptoms had spontaneously resolved.

He has remained asymptomatic, but follow-up MRI 4 years after his initial presentation showed that the enhancing fourth nerve lesion was still present.

Case 9
A 43-year-old man with a history of pulmonary sarcoidosis and diabetes mellitus was found to have a right sixth nerve palsy. Laboratory studies including CSF analysis were normal. Whole-body SPECT gallium scanning was unremarkable. Brain MRI demonstrated an enhancing lesion within Meckel cave on the right, extending to the cavernous sinus (Fig. 4A).

Although his diplopia resolved spontaneously, he received an 8-week course of oral corticosteroids. Brain MRI after steroid treatment revealed no interval change in the enhancing lesion. His examination remained normal at a 6 month follow-up visit.

FIG. 2. Case 4: Schwannoma of the inferior division of the right third nerve. Contrast-enhanced T1 coronal magnetic resonance imaging shows nodular enhancement and enlargement of the inferior branch of the right third nerve (A) and a similar appearance 10 months later (B).

FIG. 3. Case 5: Fourth nerve schwannoma. Initial postcontrast T1 axial magnetic resonance imaging (A) and scanning performed 10 years later (B) reveals unchanging nodular enhancement of the right fourth nerve.
Approximately 2 years after his initial presentation, the patient returned with a right fourth nerve palsy. His diplopia gradually resolved over 6 weeks without treatment, and his examination returned to normal. He remained asymptomatic for the next 5 years with a normal examination. Follow-up brain MRI 7 years after initial presentation (Fig. 4B) showed no change in the appearance of the enhancing trigeminal nerve lesion.

Case 10

A 43-year-old woman presented with a right sixth nerve palsy. Identical events had taken place as many as 10 times in the previous 14 years. Each attack would come without warning, regress spontaneously after 6 to 12 weeks and occur approximately once a year. She had been free of attacks for as long as 4 years but had also once had 2 attacks in the same year.

Six weeks after her presentation, her diplopia resolved and a follow-up examination was normal. A detailed physical examination revealed a nodule on her left leg that appeared to be a schwannoma. Although the patient had no subjective hearing complaints, an audiogram revealed left sensorineural hearing loss. Brain MRI performed 2 years previously showed multiple enhancing lesions within the frontal lobes, cerebellopontine angles, and Meckel cave. The frontal lobe lesions were most consistent with meningiomas; the other lesions appeared to be left vestibular and right fifth nerve schwannomas. During follow-up over several years, there was no change in the intracranial abnormalities. The patient was diagnosed with neurofibromatosis type 2. She has subsequently had 2 other identical episodes of horizontal diplopia, both of which resolved spontaneously.

DISCUSSION

In our case series, the oculomotor symptoms from schwannomas were transient or recurring (Table 1). Of our 10 patients, 4 involved the third nerve, 3 of which were clinically suggestive of ophthalmoplegic migraine. Four cases involved the fourth nerve in isolation and 2 involved the fifth nerve within Meckel cave, leading to palsies of the sixth nerve in 2 cases, one of which had a fourth nerve palsy as well. In all 9 cases with follow-up MRI studies, the location of the lesions...
and the persistent nodular enhancement, even when asymptomatic, were most consistent with schwannoma.

In patients with involvement of the cisternal segment of the third nerve, ptosis and diplopia were accompanied or preceded by headache, often with migrainous features, creating a clinical picture indistinguishable from ophthalmoplegic migraine. Many reported cases of ophthalmoplegic migraine are associated with focal thickening and enhancement of the third nerve at its brainstem exit and, because both the focal swelling and enhancement typically resolve once the oculomotor palsy remits, it has been argued that the pathology in this migraine disorder is transient inflammation or demyelination (15). Some have dismissed the idea that schwannoma can present with recurrent symptoms (16). In our patients, both focal enlargement and enhancement persisted even during periods of clinical remission, favoring the possibility that schwannoma may be the underlying pathology in at least some cases of ophthalmoplegic migraine.

Although a diagnosis of schwannoma can often be made presumptively based on neuroimaging characteristics, a definitive diagnosis requires tissue examination. Our patients had MRI during the acute palsy and after resolution, and these were all carefully reviewed by neuroradiologists to rule out dynamic changes.

An unexpected finding was that schwannoma of the sixth nerve within Meckel cave was associated with conjunctival congestion, which we believe is not a known feature of schwannoma (17). This has been noted in other cases in which sixth nerve palsy was an initial manifestation of sixth nerve schwannoma (17). No definitive explanation is available for the clinical fluctuations that we observed, particularly given the relative stability of the MRI lesions. There are other reports of clinical improvement with mass lesions whose size remained unchanged over time (10–13). Proposed mechanism for remissions or fluctuations includes regression of tumor-associated edema, remyelination, and hemo-dynamic changes.

The expected clinical course of schwannoma is one of stability or slow progression, but as we and others have demonstrated, it may be one of fluctuating signs and symptoms (2–8). Clinicians should be aware of the possibility of schwannoma as a cause of oculomotor cranial nerve palsy with a relapsing or remitting clinical course.

STATEMENT OF AUTHORSHIP

REFERENCES
Ipilimumab-Associated Bilateral Optic Neuropathy

Oliver L. Yeh, MD, Courtney E. Francis, MD

Abstract: Ipilimumab is a novel monoclonal antibody targeting the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) receptor that has been shown to improve survival in metastatic melanoma. Previous case reports have documented its association with drug-induced uveitis. We report a patient who developed bilateral optic neuropathy with disc edema while taking this medication.

CASE REPORT

A 67-year-old man who underwent excisional biopsy of a melanoma from his left thigh with lymph node dissection (1/6 nodes involved) was diagnosed with Stage III (T4N1) metastatic melanoma. Initially, he opted for observation, but the disease progressed, and 3 years later, monotherapy was begun with ipilimumab infusion (3 mg/kg) every 21 days. One year before treatment, the patient had a normal eye examination including assessment of retinal nerve fiber layer (RNFL) thickness on optical coherence tomography and normal automated visual fields.

Three weeks after his third ipilimumab infusion, the patient reported several episodes lasting 10–15 minutes when he saw "white outs" in his entire left visual field. Ophthalmic examination was unremarkable, but evaluation for transient visual loss revealed atrial fibrillation. Elective cardioversion was scheduled but, in the interim, the patient reverted to normal sinus rhythm.

Six weeks after his third ipilimumab infusion, the patient complained of photopsias in the temporal visual field of each eye and blurred vision bilaterally. Visual acuity was 20/20 in each eye and color vision and pupillary reactions were normal. Slit lamp examination showed 1+ anterior chamber cell and posterior synechia bilaterally. There was mild bilateral optic disc edema. Treatment with topical prednisolone and atropine drops in both eyes was initiated. Brain magnetic resonance imaging without and with contrast showed only small vessel ischemic changes.

Seven days after the fourth ipilimumab infusion, visual acuity was 5/200 in right eye and 20/30 in left eye. Color vision was reduced in the right eye but intact in the left eye. Automated visual fields showed bilateral visual field loss more marked in the right eye (MD: -13.90 dB) than the left eye (MD: -3.30 dB) (Fig. 1). There was bilateral optic disc edema, more pronounced in the right eye.

Over the next 3 days, the patient’s vision stabilized, his anterior uveitis improved, but his optic disc edema worsened.

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Lumbar puncture showed an opening pressure of 23.5 cmH$_2$O, and cerebrospinal analysis was normal.

The patient returned 8 days later with improved vision in the right eye of 20/70 but worsened in the left eye to 20/80. Slit lamp examination demonstrated 2+ cellular reaction in the anterior chamber of both eyes and persistent bilateral disc edema (Fig. 2) with subfoveal fluid (Fig. 3). Topical prednisolone frequency was increased to every 2 hours in both eyes. A trial of systemic corticosteroids was discussed but not instituted given spontaneous improvement in visual acuity of the right eye, lack of published treatment guidelines and the patient’s preference.

Over the next 3 months, the patient’s visual acuity gradually improved to 20/30 in both eyes with resolution of anterior uveitis. At 4 months after the fourth ipilimumab infusion, both discs were pale, with global RNFL thickness of 78 μm with severe superior and moderate inferior thinning in the right eye, and 79 μm with moderate inferior thinning.
in the left eye. The patient’s vision was 20/25 bilaterally at 6 months after his fourth ipilimumab treatment, although there were persistent visual field defects (Fig. 4), with MD: −7.74 dB in right eye and MD: −6.12 dB in left eye.

**DISCUSSION**

A human T-lymphocyte cell requires 2 signals for activation: presentation of an antigen by an antigen-presenting cell (APC) and binding of the CD28 receptor on the T cell with CD80 and CD86 ligands on the APC. Another molecule, CTLA-4, functions as a feedback mechanism preventing unwanted autoimmunity and establishing tolerance to self-antigens by competitively binding the CD28 receptor, thereby downregulating T-cell response (4). Melanoma cells can evade immune surveillance through multiple mechanisms, and it is
thought that they can express CTLA-4 ligands, thereby attenuating the adaptive immune responses and inducing T-cell inactivation (7). The novel agent ipilimumab targets this aspect of melanoma oncogenicity.

Presumably by downregulating systemic T-cell function (regulatory T cells), ipilimumab produces a novel class of immune-related adverse events ranging from the common such as dermatitis, enterocolitis, hepatitis, to the uncommon of uveitis, pancreatitis, and peripheral neuropathy. One recent case report documented the first known case of euthyroid Graves’ ophthalmopathy in a 53-year-old woman with no previous thyroid disease and baseline normal free thyroxine (free T4) and thyroid-stimulating hormone (TSH) levels (8). After her fourth infusion of ipilimumab, the patient developed bilateral proptosis and bilateral enlarged extraocular muscles; although her TSH and free T4 remained normal, anti-TPO and thyroglobulin antibody were markedly elevated. Ipilimumab was discontinued, and after several courses of high-dose IV steroids followed by a slow oral prednisone taper, the orbitopathy almost completely resolved.

In our patient, early signs and symptoms of optic neuropathy including bilateral disc edema were present after the third infusion of ipilimumab, but definitive diagnosis was not achieved until after the fourth infusion. Serial observation revealed gradual improvement over 6 months.

With the development of novel treatments for melanoma, it is imperative that the ophthalmologist be aware of potential immune-related adverse events including uveitis and optic neuropathy. Our patient recovered his vision with only topical steroid treatment for his anterior uveitis. Further study is necessary to determine whether systemic steroids with or without immune-modulating agents will prove to be of benefit.

REFERENCES


Topiramate-Induced Palinopsia: A Case Series and Review of the Literature

Samuel H. Yun, MD, Patrick J. Lavin, MD, Martha P. Schatz, MD, Robert L. Lesser, MD

Background: To report palinopsia as a possible side effect of topiramate.

Methods: Case series and review of the literature.

Results: Nine patients in our series, and 4 previously reported patients, who developed palinopsia while on topiramate, are reviewed. All patients were women, and comorbidities included migraine, idiopathic intracranial hypertension, and bulimia nervosa. Palinopsia resolved in 8 patients after stopping or decreasing the dose of topiramate. The lowest dose of topiramate causing palinopsia was 25 mg twice a day. More than half of our patients reported exacerbation of visual disturbance in early morning or late evening.

Conclusions: Topiramate-induced palinopsia may be underdiagnosed because physicians do not inquire about such visual symptoms.

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Palinopsia is the persistence or recurrence of visual images after the initial stimulus has been removed and is believed to be caused by failure to suppress after images (1,2). It may be due to dysfunction of the coordinate systems of the parietal lobes (3). Typical symptoms of palinopsia include echoing, ghosting, multiple images, smearing, streaming, trailing, or vibrating of the initial image.

Palinopsia may occur in otherwise normal patients (4) or those with migraine (5), epilepsy (6), mitochondrial disease (7), diseases affecting parieto–occipital pathways (8), multiple sclerosis (9), non-Hodgkin’s lymphoma (10), stroke (11), glioma (12) metabolic disorders (carbon monoxide poisoning [13] and nonketotic hyperglycemia [14]), drugs including marijuana (15), mescaline (16), lysergic acid diethylamide (LSD) (17), methylenedioxymethamphetamine (MDMA) (18), interleukin (19), trazodone (20), zonisamide (4), nefazodone (21), clomiphene (22), and topiramate (23–25).

Topiramate is an antiepileptic drug with multiple mechanisms of action including: 1) blocking the repetitive action of sodium channels and L-type calcium channels, 2) potentiating gamma-aminobutyric acid inhibition, 3) modulating glutamate receptors, and 4) inhibiting carbonic anhydrase (26,27). It is frequently used to treat epilepsy, migraine prophylaxis (28), and, occasionally, for idiopathic intracranial hypertension (29).

Common side effects of topiramate therapy include paresthesia, fatigue, anxiety, cognitive impairment, and dizziness (27). Ocular side effects include increasing myopia and angle closure glaucoma (30).

We report 9 cases of topiramate-induced palinopsia (Table 1) and present 3 illustrative cases.

CASE REPORTS

Case 1

A 42-year-old woman with history of migraine since adolescence, on topiramate for about a year, complained of “tracer vision.” She reported that after moving her arm, she continued to see images of the arm moving for a few seconds. The images were noticeable particularly with movement of her arms but not with movement of her legs or other objects. Her symptoms were worse in the morning and improved later in the day. The symptoms improved, but did not resolve completely, after stopping topiramate.

She had no history of seizures, significant head injury, or illicit drug use. She had taken trazodone for many years but...
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<td>Case 1</td>
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<td>Migraine with aura</td>
<td>NR</td>
<td>Improved after cessation</td>
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<td>Case 2</td>
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<td>F</td>
<td>Idiopathic intracranial hypertension</td>
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<td>NA†</td>
<td>NR</td>
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<td>Migraine</td>
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<td>Resolved at 100 mg BID</td>
<td>Evenings</td>
<td>“Trailing or smearing”</td>
<td>Migraine</td>
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<tr>
<td>Case 9</td>
<td>49</td>
<td>F</td>
<td>Migraine</td>
<td>25 mg BID</td>
<td>Resolved spontaneously</td>
<td>NR</td>
<td>NR</td>
<td>Migraine/trazodone</td>
</tr>
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</table>

*Lowest dose of topiramate in which palinopsia was observed.
†Description of palinopsia in patient’s own words.
‡Patient preferred to stay on the medication.
BID, twice daily; d, days; NA, not applicable; QAM, every day before noon; QD, every day; QHS, every night at bedtime; NR, not reported; TID, three times a day.
did not develop palinopsia until on topiramate. Magnetic resonance imaging (MRI) of the brain was normal.

Case 3
A 40-year-old woman presented with a diagnosis of migraine without aura and history of a pretectal glioma. She had tried multiple medications to control headache including tricyclic antidepressants, beta-blockers, ergotamine, antiepileptics, calcium-channel blockers, nonsteroidal anti-inflammatory medications, triptans, serotonin receptor inhibitors, muscle relaxants, narcotics, steroids, benzodiazepines, and neuroleptics. She developed palinopsia when she was prescribed topiramate, 200 mg daily. She reported that objects left a trail as in cartoons and persistence of an image when she looked away from it. In addition to palinopsia, she complained of poor concentration and memory and word-finding difficulty. At her 5 years follow-up appointment, she reported significant improvement of symptoms, although she was still taking topiramate 100 mg daily.

Case 6
A 58-year-old woman with history of left frontal meningioma and migraine presented with palinopsia. After her topiramate dose was increased from 50 mg twice a day to 3 times a day, she reported seeing “multiple snap shots” of hands as from the movie “Look Who’s Talking.” This occurred every other day, most notably early in the morning after awakening from sleep. Once the dose of topiramate was decreased to 50 mg twice a day, her palinopsia resolved. Brain MRI showed a left frontal meningioma that was unchanged from previous scans.

DISCUSSION
Our 9 patients and the 4 patients previously reported developed palinopsia while on topiramate. All patients were women, 76.9% had migraine, 15.4% had idiopathic intracranial hypertension, and 7.7% had bulimia nervosa (Table 1). The preponderance of women in our series is likely due to clinician often being asked for by the clinician.

Topiramate, like other systemic drugs that induce palinopsia, may inhibit neural activity. Palinopsia may occur in patients with a predisposition to decreased speed of visual processing with additional decreased neural activity from a central nervous system suppressant such as topiramate. Alternatively, Dubois and Vanrullen (31) proposed failure of motion streak suppression as a possible mechanism of palinopsia.

Topiramate affects sodium and calcium ion channels, impairs glutamate transmission and carbonic anhydrase function, and also potentiates gamma-aminobutyric acid inhibition (26,27). The pathophysiology of palinopsia has been proposed to be an increase in serotonergic activity secondary to 5-HT$_2$ receptors. Several drugs associated with palinopsia affect 5-HT$_2$ receptor including LSD, MDMA, nefazodone, trazodone, risperidone, zonisamide, and mitrazapine (18,23,25,32). Weight loss seen in patients on topiramate also may be secondary to 5-HT$_2$ receptor activation (16,33). Topiramate also inhibits CYPD6 gene (34), which may precipitate the serotonin syndrome (35).

Some of our patients presented with potential confounding risk factors for developing palinopsia. Case 1 was on trazodone chronically. Although the patient developed palinopsia only after starting on topiramate, trazodone may have potentiated the effect of topiramate. Case 9 also had taken trazodone before starting topiramate, but with symptoms again developing only after starting topiramate. Seven patients also had migraine as a potential confounding factor.

In 8 of 9 patients, symptoms either improved after decreasing the dose or resolved after lowering the dose or stopping topiramate. Two patients (Cases 2 and 5) preferred to stay on topiramate to control their headache despite persistent palinopsia. In one patient, palinopsia did not resolve after stopping the medication, perhaps because of use of trazodone. The time between starting topiramate and onset of palinopsia could not accurately be documented. In most cases, the time course was either omitted or described as “briefly” or “soon after.” In Case 4, the time of onset was documented as 3 months after starting the medication.

Topiramate-induced palinopsia is likely uncommon considering how often the medication is prescribed. However, it may go unrecognized because patients may not report the symptom, unless specifically asked for by the clinician.

REFERENCES
Superoxide Generation Explains Common Features of Optic Neuropathies Associated With Cecocentral Scotomas

Leonard A. Levin, MD, PhD

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The pathophysiology of some of the more common optic neuropathies associated with cecocentral scotomas might be explained by a unifying hypothesis. This hypothesis is based on clinical features of these optic neuropathies, laboratory studies of the pathophysiology of how retinal ganglion cells (RGCs) die, some of which is unpublished, and biochemistry of reactive oxygen species generation within some of these disorders.

OPTIC NEUROPATHIES AND CECOCENTRAL SCOTOMAS

Diseases of the optic nerve are associated with abnormalities of vision, primarily visual acuity, color vision, contrast sensitivity, and most relevant to this discussion, the visual field. The nature of the visual field defect usually reflects the location at which the disease affects the optic nerve. For example, glaucomatous optic neuropathy primarily affects RGC axons at the optic nerve head. A focal thinning of the optic disc will affect those axons which originated from RGCs defined by the pattern of the retinal nerve fiber layer (1). Compression of the chiasm from a pituitary adenoma that affects primarily crossing fibers will generate unilateral or bilateral temporal visual field defects.

Cecocentral scotomas are distinctive in that there is visual field loss centrally, but there is involvement that includes the blind spot, that is, a temporal predominance. This is different from pure central loss which only involves the blind spot as a result of the defect itself being large enough to subsume it. What is interesting about diseases associated with cecocentral scotomas is that they are relatively few in number and share common clinical...
features. The main optic neuropathies with cecocentral scotomas are:

1. Leber hereditary optic neuropathy (LHON)
2. Nutritional optic neuropathy
3. Toxic optic neuropathy
4. Other hereditary optic neuropathies.

My focus will be on the first 3, creating a hypothetical framework for understanding their pathophysiology.

**CLINICAL PRESENTATION OF CECOCENTRAL SCOTOMAS**

The optic neuropathies associated with cecocentral scotoma are painless and bilateral, and usually progressive. LHON is an exception in that the visual loss frequently starts unilaterally but eventually becomes bilateral in all cases. When only 1 eye is affected initially, the fellow eye follows within weeks to months although sometimes longer.

Optic disc edema is unusual in the optic neuropathies associated with cecocentral scotomas. In LHON, there may be a swollen optic nerve head with telangiectatic small vessels, but it is not true disc edema because it does not show evidence of vascular leakage on fluorescein angiography. Occasionally, acute toxic or nutritional optic neuropathies show elevation of the disc.

**CECOCENTRAL SCOTOMAS AND PATHOPHYSIOLOGY**

A cecocentral scotoma is a visual field defect that can be thought of as representing a biomarker of an underlying pathophysiological process. The retinotopic distribution of the cecocentral scotoma classically has been believed to reflect damage to the papillomacular bundle. However, the papillomacular bundle is not a single well-defined set of axons but rather a concentration of axons that are primarily small in diameter and are within the area between the optic disc and the perifoveal macula (2). As pointed out by Plant and Perry (2) and others, the concept of the papillomacular bundle was a reverse induction from the clinical and histological findings associated with toxic optic neuropathy. It is tautologous that the papillomacular bundle is involved in similar diseases, that is, those with cecocentral scotomas. For the sake of convenience and common usage in the rest of this article, I will use the term papillomacular bundle to refer to the set of fibers arising from the foveal and parafoveal regions and approaching the temporal part of the optic disc, both directly and through an arcuate pathway.

The critical assumption underlying the framework being developed is that the common clinical presentation of optic neuropathies associated with cecocentral scotomas implies a common pathophysiological process. Specifically, my hypothesis is that these disorders have in common the generation of superoxide anion, or superoxide (\(O_2^-\)). Superoxide is an oxygen-containing free radical generated within cells in various processes. Relevant to this hypothesis, one of the main sources of superoxide is the reaction of molecular oxygen (\(O_2\)) with a free electron.

\[ O_2 + e^- \rightarrow O_2^-. \]

Superoxide is reactive, and among its reactions is that with nitric oxide (NO) to form peroxynitrite (ONOO\(^-\)). Peroxynitrite can react with other molecules, such as tyrosines, resulting in their nitration. Superoxide also reacts directly with macromolecules such as proteins and nucleic acids. The scavenging of superoxide typically occurs through superoxide dismutases of which there are 3 major types: intracellular (SOD-1 [Cu/Zn-SOD]), mitochondrial (SOD-2 Mn-SOD), and extracellular (SOD-3).

Besides causing oxidative damage, superoxide has an important role as a signaling molecule. Cells use small molecules such as NO to activate or suppress various processes within the cell. Superoxide has been recognized for many years to be such a molecule. For example, it is known to initiate mitosis in certain cells (3).

Over the last decade, our group demonstrated that superoxide plays a special role relevant to RGCs. Specifically, we showed that it signals the death of the cell body, or soma, when the axon is injured (4,5). In other words, injury to the axon of the RGC caused an increase in superoxide within its soma. This finding was accomplished by imaging superoxide using specialized fluorescent probes in rat retinas after optic nerve transection. The increase in superoxide could be seen a few days after axonal injury, followed a day later by death of the RGC.

Using a variety of techniques, we established that the superoxide was not simply a result of the cell in the final throes of death but, rather, a signal that both preceded and was necessary for death. We did this by showing that other drugs that decrease the levels of superoxide (e.g., pegylated superoxide dismutase); both decreased the levels of superoxide and prevented the death of the RGC. Based on these studies, we concluded that superoxide was a signal for RGC death after axonal injury (5,6).

**SUPEROXIDE AND CECOCENTRAL SCOTOMAS**

How is superoxide relevant to optic neuropathies in which cecocentral scotomas occur? The next sections will discuss 3 specific optic neuropathies in turn, namely, LHON, the optic neuropathy associated with vitamin B\(_{12}\) deficiency and the toxic...
optic neuropathy caused by ethambutol. Each of these is associated with cecocentral scotomas, and for each of these, we have evidence that superoxide is generated at increased levels.

**Leber Hereditary Optic Neuropathy**

In at least 95% of patients with LHON, there is a mutation at 1 of 3 sites within the mitochondrial DNA (mtDNA). The most common is the 11778 mutation, followed by the 3460 and 14484 mutations. There is a slow-to-rapid development of loss of vision in 1 or both eyes. If only 1 eye is involved initially, the second eye follows within weeks to months. The loss of vision typically occurs in the late teens or early 20s, but it can occur at any age. There is a strong male predominance, which is as yet unexplained, especially as mtDNA is present in all cells (except mature erythrocytes) of both genders.

All of the 3 primary mutations that produce LHON are contained in mtDNA coding for components of the complex I of the mitochondrial electron transport chain. Complex I serves as an NADH:ubiquinone oxidoreductase. In other words, NADH, a product of the Krebs cycle, is oxidized at the same time that ubiquinone, a molecule that carries electrons between complexes, is reduced. Functionally, 2 electrons are transported from NADH to ubiquinone at the same time that 4 protons (H\(^+\)) are transported across the inner membrane of the mitochondria into the mitochondrial intermembrane space.

This set of reactions has 2 results. First, electrons are transported to various loci in the electron transport chain. Second, protons are pumped across the inner membrane to form a voltage gradient. The voltage gradient, or electro motive potential, is the basis for another complex, complex V, to generate adenosine triphosphate (ATP) in the process of transferring protons back across the inner membrane into the mitochondrial matrix.

For many years, it was assumed that the mechanism by which LHON mtDNA mutations in complex I caused visual loss was a deficiency of ATP, for example, by decreased pumping of protons or some other mechanism. This made sense, given that ATP is essential for cellular function, and RGCs, with their very long axons relative to the size of their somas, would presumably have high ATP demands. However, there are some flaws in this assumption, related to the fact that RGCs are specifically affected in LHON, whereas other cells are less commonly involved. We pointed out several years ago that diseases characterized by decreased ATP production from mutations in mtDNA usually are not associated with death of RGCs (7). Instead, they are associated with death of photoreceptors, as occurs in mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS; mtDNA position 3243) or neuropathy, ataxia, and retinitis pigmentosa (NARP; mtDNA position 8993). Frequently, there is abnormal extraocular muscle function, as well as other systemic involvement such as abnormal cardiac conduction deficits and pancreatic dysfunction. Tissues such as photoreceptors and extraocular muscles are highly energy-consuming, and any disruption of ATP production in MELAS or NARP usually will affect patients early in the course of their disease. Therefore, if there were a deficiency in ATP production in LHON, there should be effects on photoreceptors and not, or at least not only, on RGCs.

The second reason to suspect that ATP production is less relevant to LHON than previously believed is that studies of LHON cybrids demonstrate only a relatively small effect on ATP production. Cybrids are cells in which the mitochondria are from one cell source, usually having mutant mtDNA, whereas the rest of the cell is from another source, usually a wild-type dividing cell. This allows study of the specific effects of mtDNA mutations without affecting other aspects of cellular function. Surprisingly, the respiration deficits that would decrease ATP production are not particularly marked (8–12), although this is not always the case (13). Note that it is currently not possible to make cybrids from isolated RGCs because a dividing cell is necessary, and RGCs, like other neurons, do not divide.

Superoxide is produced in LHON cybrids that are made in neuronal cell lines (14). For example, Wong and colleagues showed an approximate doubling of superoxide production in LHON 11778 or 3460 cybrids compared with control, nonmutant cybrids (14). They suggested that this effect was specific to differentiated neurons. However, they used a neuronal cell line that was different from RGCs, and thus, their findings would not explain the specific damage to RGCs in LHON.

How do LHON mutations result in an increase in superoxide? As mentioned previously, the function of complex I is as an NADH/ubiquinone oxidoreductase. If the transfer of electrons to ubiquinone is disrupted, then complex I will retain the extra electron, which then can react with free oxygen to form superoxide. In other words, the problem with the LHON mutations and their effects on complex I is less likely due to decreased ATP production, but instead due to an accumulation of superoxide from failure to transfer electrons down the electron transport chain to other complexes. This, in turn, results in those electrons reacting with molecular oxygen to form superoxide.

Why should an increase in superoxide in LHON lead to RGC death but not death of other cells? Mitochondria are present in all cells in the body except mature erythrocytes, and therefore, superoxide should be increasing in those cells as well. The specificity to RGCs is, therefore, unexpected.

The answer is that superoxide is not only a free radical that can react with other molecules to cause oxidative damage, but it also is a signaling molecule. As discussed
previously, superoxide is a signal for RGC bodies to die after the axon is injured. Our hypothesis (7) is that the increased superoxide “tricks” the soma of the RGC into thinking that axon injury has occurred, although it has not. The RGC soma then initiates the process of apoptosis, misled by the aberrant superoxide signal, and eventually dies. Other cells in the body may not use superoxide as a signal for cell death and, therefore, remain unaffected.

Partial support for this theory can be found in a study of mice in which superoxide dismutase-1 is knocked out, resulting in the levels of superoxide within the cell bodies being higher than normal (15). These animals have decreased numbers of RGCs, consistent with the premise (relevant to LHON) that increasing superoxide levels in cells other than RGCs nevertheless causes the RGCs to die, even when there is no axon injury and no direct injury to the RGCs.

In summary, LHON likely represents a disease in which superoxide is abnormally produced because of mutations in complex I of the mitochondrial electron transport chain. RGCs may be specifically sensitive to increased superoxide because it is a signaling molecule for cell death after axon injury. The increased superoxide ultimately would result in specific loss of RGCs, with relative preservation of other cells within the nervous system and elsewhere in the body.

**Vitamin B12 Deficiency Optic Neuropathy**

**Clinical Background**

“Nutritional amblyopia” is a term used for the optic neuropathy that arises from malnutrition. Examples include starved prisoners of war in Asia during World War II, severe malnutrition in alcoholics, those on inadequately supplemented vegan diets, patients with various gastrointestinal disorders or who have had intestinal surgery resulting in inadequate absorption of needed nutrients, and pernicious anemia in which, antibodies to intrinsic factor decrease inadequate absorption of needed nutrients, and pernicious disorders or who have had intestinal surgery resulting in

**Nutritional amblyopia** is similar to those seen in patients with LHON.

**Vitamin B12 as a Superoxide Scavenger**

As part of a collaboration with Professor Zeev Gross of the Technion in Haifa, Israel, we assessed novel chemical entities to serve as superoxide scavengers for decreasing RGC death after axon injury. We tested metallocorroles, molecules that Gross and his laboratory had invented for redox chemistry. We tested their role as potential neuroprotective compounds and showed that some metallocorroles served as excellent superoxide scavengers in RGCs (17). They also were effective in decreasing RGC death after optic nerve transection in adult rats (18).

We noticed that the chemical structures of metallocorroles and vitamin B12 were very similar, with both having a corrin ring. Based on this similarity, we hypothesized that vitamin B12 could serve as a superoxide scavenger. A literature search found an article from the laboratory of Nicola E. Brasch at Kent State University showing that cobalamin is a superoxide scavenger with catalytic activity approaching that of superoxide dismutase (19). We therefore embarked on a series of experiments to examine the ability of vitamin B12, in the form of cyanocobalamin, to scavenge superoxide in RGCs and rescue them from cell death. While our results have been submitted for publication, the main findings are:

1. In the test tube, vitamin B12 is an excellent scavenger of superoxide produced by reacting xanthine with xanthine oxidase.
2. Superoxide scavenges RGCs in neuronal-like cells (we used the RGC-5 photoreceptor-derived cell line that, despite its name, is not an RGC).
3. Intraretinal vitamin B12 scavenges superoxide produced in RGCs after axon transection.
4. Intravitreal superoxide decreases RGC death after optic nerve transection.

Implications for Understanding Vitamin B<sub>12</sub>
Optic Neuropathy
We hypothesize that vitamin B<sub>12</sub> has, in addition to its enzymatic cofactor roles with respect to methionine synthase and methylmalonyl-CoA mutase, a role as an endogenous superoxide scavenger in RGCs. Its deficiency would be specifically deleterious to RGCs because, as noted in the previous section on LHON, RGCs use superoxide as an intracellular signaling molecule for inducing soma apoptosis after axon injury. Given that superoxide is continuously being generated within cells as part of the mitochondrial electron transport chain, if superoxide is a signaling molecule, an RGC would require strict control of intracellular concentrations. Otherwise, the deregulated superoxide might induce aberrant cell death. The usual superoxide scavengers within cells, such as the various superoxide dismutases, theoretically should be sufficient, as they are for other cells. Given that RGCs do not divide and therefore cannot be replenished if they die, it is not surprising that they would develop a system for regulating superoxide levels that is more stringent than that of other cells.

We have suggested a role for vitamin B<sub>12</sub> as an additional superoxide scavenger. This is hypothetical, and further work will be needed to prove that this is indeed a mechanism relevant to RGCs. It is very difficult to induce optic neuropathy from vitamin B<sub>12</sub> deficiency in rats, and even more than 12 months of such deficiency does not cause an obvious loss of RGCs. Thus, it is possible that vitamin B<sub>12</sub> does not play the same role in rats as it does in humans. This is akin to other differences between rats and humans with respect to optic neuropathies, for example, rats given methanol develop primarily a photoreceptor toxicity not an RGC toxicity. Another possibility is that rats are able to upregulate other superoxide scavenging molecules within cells in response to vitamin B<sub>12</sub> deficiency. Overall, this is an area of active research.

In summary, these data are consistent with the hypothesis that vitamin B<sub>12</sub> deficiency, the known cause of nutritional optic neuropathy, is due to an abnormality in superoxide scavenging and that elevated levels of superoxide within RGCs would be responsible for the progressive bilateral visual loss associated with cecocentral scotomas that occurs from RGC death in this disease.

Ethambutol Optic Neuropathy
Ethambutol is commonly used to treat tuberculosis and other mycobacterial infections, especially multiple drug-resistant tuberculosis. Ethambutol is the most common cause of toxic optic neuropathy (20,21) and is characterized by progressive bilateral loss of visual acuity, acquired dyschromatopsia, cecocentral scotomas, and optic disc pallor. In some cases, there is a significant temporal preponderance of the visual field defect that sometimes respects the vertical meridian, suggesting that the damage is occurring primarily at or near the optic chiasm. This is different from the classic cecocentral scotoma associated with presumed involvement of the papillomacular bundle.

The potential for ethambutol to produce an optic neuropathy limits its use in patients who have visual symptoms, underlining the need to understand this optic neuropathy and find mitigating strategies. Major problems are that it is difficult to predict who will develop the optic neuropathy, how it can be detected before RGCs are irreversibly damaged, and, once present, how to treat the visual loss other than by stopping the medication. In many cases of ethambutol optic neuropathy, there is reversibility when the visual loss is detected early. However, the literature is replete with cases demonstrating failure to completely or even partially reverse the loss of vision. Two studies demonstrated that 40%–50% of patients with ethambutol-related optic neuropathy had no visual improvement after ethambutol was discontinued, an unacceptable high failure rate for the only known therapeutic intervention (22,23).

A priori, there is no specific reason to suspect that ethambutol toxicity is associated with superoxide induction. However, in preliminary experiments that we have performed in rats, we found increased levels of superoxide after intravitreal injection of ethambutol, using the oxidation of hydroethidine as a marker for superoxide induction.

In Vitro Detection of Superoxide Induced by Ethambutol by Fluorescent Microscopy
We purified rat RGCs by sequential immunopanning and plating on poly-d-lysine/laminin-coated plates to provide a substrate for adherence and neurite outgrowth. The cells were then exposed to 3 mM ethambutol for 1 hour, with hydroethidine (1 mM) added in the last 30 minutes to detect superoxide generation. Hydroethidine reacts with superoxide to form 2-oxy-ethidium, which has specific excitation and emission characteristics. The cells then were imaged by fluorescent microscopy or with a fluorescent plate reader.

The addition of ethambutol resulted in a robust fluorescence signal, compared with vehicle control. To prove that ethambutol led to superoxide generation and not generation of some other reactive oxygen species that might also oxidize hydroethidine, some wells were incubated simultaneously with pegylated superoxide dismutase (500 U/mL), which enters cells and scavenges only superoxide and not other reactive oxygen species. This eliminated the ethambutol-induced fluorescence, implying that the fluorescence reflected an increase in superoxide alone.
The interpretation of these experiments is that ethambutol induces superoxide in cultured rat RGCs.

### In Vivo Detection of Superoxide Induced by Ethambutol Using In Vivo Confocal Imaging

One eye of adult Long-Evans rats under anesthesia received an intravitreal injection of ethambutol (final concentrations 0, 0.3, 1, or 3 mM), along with hydroethidine (final concentration 100 μM) to detect superoxide. The other eye was not injected and acted as control. Rats were imaged 24 hours later with a Heidelberg HRA-2 confocal scanning laser ophthalmoscope using the 488-nm laser for excitation and a broad-spectrum 500–600 nm filter for emission detection. Eyes injected with 3 mM ethambutol demonstrated small but definite production of superoxide in cells within the RGC layer that were not fluorescent before ethambutol injection, whereas equivocal induction was seen in eyes injected with the 0.3 or 1 mM concentrations of ethambutol. No fluorescence evidence of superoxide induction was seen in control eyes.

These data suggest that ethambutol can induce superoxide in RGCs and presumably lead to their death. Note that these experiments used an acute exposure to high concentrations of the drug. Chronic exposure experiments need to be performed to allow translational validation in patients. Furthermore, chronic exposure experiments to very high doses of ethambutol in rats demonstrated chiasmal lesions (24), and whether or not this chiasmal predilection is related to superoxide production is unclear. Finally, the mechanism for ethambutol causing an increase in superoxide is currently unknown but could be related to zinc chelation effects of ethambutol and the interaction of zinc with complex I (25).

### ISSUES RELATED TO THE SUPEROXIDE HYPOTHESIS FOR CECOCENTRAL SCOTOMAS

#### Why the Papillomacular Bundle?

Even if superoxide is a common pathophysiological factor for LHON, vitamin B12–deficiency optic neuropathy, and ethambutol optic neuropathy, this does not explain why a cecocentral scotoma develops. In other words, why should the papillomacular bundle be preferentially involved, and why should axons or their RGCs elsewhere in the retina be relatively spared?

The answer probably relates to the fact that the axons in the papillomacular bundle are smaller than average. Although there is controversy regarding this issue (2), there is strong evidence to suggest that 1) RGCs forming the papillomacular bundle are predominantly midget cells with small axons, 2) the axons are small for most of their course toward the disc, and 3) these features are different from fibers approaching the disc from other directions (26–28).

Sadun and colleagues have made convincing arguments that the size of RGC axons is relevant to the effects of a decrease in ATP production in the setting of LHON, with a greater mismatch between the ATP produced and the ATP needed in small vs large fibers of RGCs (29,30). However, as indicated above in the section on LHON, a deficit in ATP production is unlikely to be the main causative factor in this disorder, and presumably, also in vitamin B12–deficiency optic neuropathy or ethambutol optic neuropathy.

Instead, a parallel analytical process used by Pan et al (30) for comparing small and large axons can be applied to the dynamics of superoxide production, as follows:

1. Most of the ATP needed for axon conduction is for renormalizing the sodium and potassium concentrations at the nodes of Ranvier, primarily after an action potential has occurred. Sodium enters the axon and potassium leaves the axon as the 2 major ionic fluxes associated with the formation of an axon potential. The Na+-K+-ATPase re-normalizes these concentrations by shuttling sodium and potassium ions to the extracellular and intracellular spaces, respectively.

2. The renormalization of sodium and potassium concentrations is an ATP-dependent step, and therefore, the amount of ATP being consumed will be proportional to the amount of ionic flux, which takes place at the surface of the axon, at the nodes of Ranvier.

3. Superoxide is a byproduct of ATP production in the mitochondrial electron transport chain, and therefore, the amount of superoxide being produced will largely be proportional to the amount of ATP needed to support the ionic flux that takes place at the axon surface.

4. The detoxification of superoxide should be proportional to the axon volume, given that most superoxide is detoxified by intracellular superoxide dismutases.

5. The area/volume ratio is greater in small fibers than in large fibers because the surface area is proportional to the radius and the volume is proportional to the square of the radius.

6. Given that the amount of superoxide production is proportional to sodium and potassium flux at the axon surface area and that the superoxide detoxification is proportional to axon volume, there will be relatively more superoxide production than detoxification in small fibers compared with large fibers.

In other words, there should be a relatively greater mismatch between superoxide production (relative to ATP synthesis used to maintain axon conduction) and detoxification in small RGC axons than in large axons. This would support a preferential involvement of small axons in the papillomacular bundle. However, as pointed out by others (2), it is not fiber size alone that would explain the concentrated.

damage in this area. It is possible that the packing density of the axons in the retinal nerve fiber layer near the temporal disc or where the axons enter the disc that is the critical factor.

**Chiasmal Involvement**

There are occasional cases of ethambutol optic neuropathy in which the visual field defects are suggestive of chiasmal involvement. There is also a pathological study in rats showing chiasmal axon damage (24). Interestingly, there are cases of LHON in which there is predominantly chiasmal involvement based on clinical, magnetic resonance imaging, or pathological evidence (31,32).

These findings are not directly explained by aberrant superoxide levels causing death of RGCs. One possible reason for preferential involvement of the chiasm is that the crossing fibers within the chiasm theoretically undergo a small deformation as they cross under and over each other, in the same way that a weave deforms the fibers as they cross each other. Under those circumstances, the surface/volume relationship described above would be exacerbated in those locations where the chiasm is flattened. The surface/volume ratio of a flattened fiber is greater than one with a more circular cross-section. The factor of packing density and relation with adjacent fibers also may be relevant.

**Other Optic Neuropathies With Cecocentral Scotomas**

This hypothesis discusses 3 specific optic neuropathies, but there are other optic neuropathies, such as dominant optic atrophy and methanol-related optic neuropathy, in which the same clinical pattern occurs. The following is highly speculative and is included only in the interest of completeness.

Dominantly inherited optic atrophy is associated most often with mutations in the OPA1 and OPA3 genes, both of which are important for mitochondrial function. Studies in *Drosophila* have shown evidence that OPA1 deficiency increases reactive oxygen species levels, causes a variety of ocular abnormalities, and is rescued by superoxide dismutase (33). It would not be surprising if OPA1 deficiency in patients with dominant optic atrophy leads to increased superoxide levels in most cells, with preferentially more toxicity in RGCs for the same reason that it occurs in LHON.

Methanol intoxication is another example in which there may be a role for superoxide. Methanol is metabolized to formate, which inhibits mitochondrial cytochrome c oxidase (complex IV). This inhibition leads to electrically reduced upstream complexes in the mitochondrial electron transport chain. The electron-rich reduced complexes can react with molecular oxygen to form superoxide. In experiments conducted in rodents, methanol intoxication does not cause the predominant RGC death that it does in humans, but instead results in primarly photoreceptor death (34). Therefore, it is unclear if studies in rodents can help to clarify the precise mechanism by which methanol causes an optic neuropathy.

**Implications for Treatment of Optic Neuropathies Associated With Cecocentral Scotomas**

From the foregoing discussion, one might conclude that drugs that reduce superoxide levels within RGCs might be effective treatments for any or all of these diseases. This is a reasonable assumption, but there are several caveats. The most important is that it is the level of intracellular superoxide that is critical, and unless a superoxide scavenger is able to actually enter the RGC, it may not be effective. It also has to enter the cell at high levels. For example, loading patients with high levels of vitamin B₁₂ makes theoretical sense, but unless the intracellular concentration is maintained at a sufficiently high level for the long term, it may not be a sufficiently effective superoxide scavenger to be clinically beneficial. Drugs that our laboratory has studied, such as pegylated superoxide dismutase and metallocorroles, (5,17,18) are theoretically potent, but their use in humans would require a lengthy drug development process.

There has been much interest in drugs such as in idebenone for LHON. A formal clinical trial was performed but did not meet its primary end point for preventing vision loss in LHON (35). However, much of the data from the trial were encouraging because it was a separate nonrandomized study (36). Idebenone was designed as a drug that would serve to shuttle electrons, serving as a synthetic ubiquinone electron carrier. However, biochemical studies show that idebenone also is a superoxide scavenger (37,38). It may actually be efficacious because it reduces intracellular superoxide and not because it restores mitochondrial electric transport in LHON. On this basis, one could speculate whether or not drugs such as idebenone could be used in other optic neuropathies associated with cecocentral scotomas.

**SUMMARY**

I have presented above a hypothesis that ties together several disparate optic neuropathies, all characterized by a similar clinical presentation. The hypothesis is predicated on the formation of intracellular superoxide within RGCs as a common pathological pathway for the type of cell death that occurs. The anatomical predisposition of the papillo-macular bundle to have elevated superoxide levels is tied to the size of the fibers involved, a hypothesis that also implicates the crossing fibers of the chiasm. Much of this work is speculative and is an interpretation of several experimental studies that have been performed to date. Hopefully, this hypothesis will be developed further, and its validity tested in both experimental models and, ultimately, in humans.

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Almasieh, Rachel Beaubien, Maria-Magdalena Catrinescu, Wesley Chan, Megan Crowe, Laura Frassetto, Alireza Ghaffariyeh, Akiyau Kamomori, Chris Lieven, Karrina Mears, Nicholas Niemuth, Jonathan Ribich, Colin Scott, and Emily Seidler. I am also grateful for helpful discussions with many of my colleagues, including Simmons Lesell, Alfredo Sadun, and Helen Danesh-Meyer.

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The second consideration is how to plan a clinical trial (4,5). Clinical trials first require an assessment of drug safety. Only when safety has been established, trials with different concentrations of drug can be evaluated for efficacy. Thus, the first issue is whether a drug already approved for human use is available. If so, that drug already has a safety profile, and it may be used in a trial without a major safety arm, assuming that it is to be given in doses and routes for which it has already been approved. If the drug has not been approved

Developing a Human Clinical Trial From a Scientific Hypothesis

Neil R. Miller, MD

In this issue of the journal, Leonard Levin, MD, PhD has proposed a potentially unifying hypothesis regarding the pathogenesis of 3 apparently disparate optic neuropathies that are characterized in part by cecocentral scotomas: Leber hereditary optic neuropathy (LHON), vitamin B12-deficiency (nutritional) optic neuropathy, and ethambutol-related (toxic) optic neuropathy (1).

This hypothesis, based on theoretical grounds as well as both in vitro and murine experiments, is that these diseases have, as a common final pathway, the generation of superoxide free radicals within retinal ganglion cells (RGCs), leading to RGC death. Dr Levin further hypothesizes that because of their small size compared with fibers from RGCs elsewhere in the retina, the axons comprising the papillomacular (PM) bundle are more likely to be damaged from superoxide free radicals than their larger counterparts. This occurs because, according to Sadun (2), the energy expenditure of an axon is related to its surface area, whereas its content of mitochondria is constrained by the cell volume. Thus, the small P-cell axons of the PM bundle, which have the smallest ratio of volume to surface area, have the least margin for error in the setting of energy depletion and, hence, may be at the greatest disadvantage in energy dependence for maintaining efficient axon transport. Dr Levin also implicates the anatomy of the crossing fibers of the chiasm, emphasizing that these fibers may undergo a small deformation as they cross under and over each other, rendering them more susceptible to metabolic compromise than their noncrossed counterparts. He concludes his manuscript by emphasizing the speculative nature of his hypothesis (it is, after all, a hypothesis) and the need to validate it.

Dr Levin’s hypothesis is complex, implicating at least 3 different factors for the development of these 3 apparently disparate optic neuropathies: the development of superoxide free radicals, and the susceptibility of the small axons of the PM bundle as well as the crossing fibers in the chiasm to metabolic and other forms of stress. The experiments that he and his colleagues have performed provide circumstantial evidence supporting this hypothesis. So how do we validate it?

The first decision to be made is whether data from an animal model more closely related to humans are needed. Data obtained from many animals (e.g., rat, mouse) may or may not be pertinent to human disease as these animals often have different responses from humans to inflammation and other types of insults (3). For example, substances that showed significant experiment promise in providing neuroprotection in rats after cerebrovascular insults failed to provide the same protection in humans. The same issues may apply to the use of oxygen free radical scavengers. Therefore, it may be more appropriate to test the hypothesis in nonhuman primates, the optic nerves of which are more closely related to those of humans, and the responses to various insults are more similar to those of humans than those of rats or mice.

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Reference


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The second consideration is how to plan a clinical trial (4,5). Clinical trials first require an assessment of drug safety. Only when safety has been established, trials with different concentrations of drug can be evaluated for efficacy. Thus, the first issue is whether a drug already approved for human use is available. If so, that drug already has a safety profile, and it may be used in a trial without a major safety arm, assuming that it is to be given in doses and routes for which it has already been approved. If the drug has not been approved
for human use, it will require an assessment of its safety (Phase 1 trial). This, in turn, requires a statistical analysis to determine the number of subjects required to determine with a high probability that the drug is safe. One of the major errors of some clinical trials is that a statistician is consulted after the trial has been performed. In such cases, the trial results may be spurious because the drug has been evaluated in an inadequate number of subjects. Similar considerations apply when assessing the efficacy of a drug. One must consider the number of subjects required to provide adequate information regarding efficacy, whether assessed (with or without dose escalation) against a known treatment or a placebo (Phase 2 and 3 trials). This number is dependent on many factors, particularly the natural history of the disorder. For example, patients with LHON who harbor the 11778 mutation in their mitochondria have, at most, a 4% likelihood of spontaneous visual recovery. Thus, fewer subjects would be needed for a clinical trial of a superoxide radical scavenging drug than would be needed for, for example, a clinical trial of a drug for the treatment of nonarteritic anterior ischemic optic neuropathy (NAION), which has about a 40% spontaneous rate of visual recovery of 3 lines or more. However, just because a drug works in a group of subjects with a specific disorder does not mean that it will work in another. Dr Levin postulates that LHON, vitamin B12-deficiency optic neuropathy, and ethambutol optic neuropathy have a common pathogenesis. To prove this, not only does a particular drug or target need to provide benefit in patients with LHON but also in patients with the other 2 optic neuropathies. Proving his hypothesis will require more than a trial in patients with LHON.

This brings up a final consideration: a clinical trial must be economically feasible. One always hopes that the results will save society money in the long run, either by identifying optimum treatment for a previously untreatable or poorly treatable disorder or by showing that a current treatment either is ineffective (think systemic corticosteroids for NAION) or even potentially harmful (think optic nerve sheath fenestration for NAION).

Several years ago, at the request of a pharmaceutical company, several members of the Neuro-Ophthalmology Research Disease Investigator (NORDIC) put together a proposal for a clinical trial of a substance to treat patients with LHON. When the company was shown the proposed budget necessary to perform the study in what the NORDIC committee thought was an appropriate manner, the company’s executives decided that the study was too costly for what it would accomplish.

Ultimately, evidence-based medicine clearly is the best way to provide optimum medical care for our patients, and in most cases, the evidence is best derived from controlled clinical trials. Although such trials are not always straightforward and may be extremely costly, this is what translational research is all about.

REFERENCES

Signet Ring Cell Adenocarcinoma and Bilateral Leptomeningeal Involvement of Optic Nerve Sheaths

Joyce N. Mbekeani, MD, FRCS, FRCOphth, Mohammed Q. Haseeb, MD, FRCS, Asma M. Tulbah, MD, Salem H. Hamed, MD, Selwa A. Al Hazzaa, MD, FRSC, Mohammad A. Dogar, MD

Abstract: Signet ring cell adenocarcinoma has a propensity for leptomeningeal carcinomatosis, and although bilateral optic nerve involvement is rare, this may occur with or without obvious signs of diffuse leptomeningeal involvement. We describe a 41-year-old woman who presented with a brief history of simultaneous bilateral visual deterioration and a distended abdomen. Examination revealed bilateral no light perception vision and bilateral optic disc edema. Radiologic work-up showed large multiple pelvic masses involving the ovaries, multifocal bone deposits, and widespread central nervous system carcinomatosis, involving the optic nerves and the first, fifth, and eighth cranial nerves. Biopsy of an ovarian mass demonstrated islands of signet cells. Signet cell adenocarcinomatous infiltration of the leptomeningeal space should be considered in cases of bilateral simultaneous vision loss with signs suggestive of leptomeningeal infiltration of the optic nerve sheath.

FIG. 1. Contrast-enhanced fat-suppressed T1 axial magnetic resonance imaging shows optic nerve sheath enhancement posteriorly. Note the demarcation line (arrow) between infiltrated and noninfiltrated optic nerve sheaths and diffuse leptomeningeal thickening and enhancement along the folia of cerebellum.

A previously health 41-year-old woman was referred with a 2-month history of abdominal distension, intractable vomiting, frontal headaches, and declining vision. She reported bilateral blindness for the previous 6 days. Her medical history was significant for infertility after one successful pregnancy. On examination, the patient was lethargic but oriented. She had no light perception in each eye, and pupils were large and sluggishly reactive to light with no relative afferent pupillary defect. Extraocular movements were normal and were the anterior segments of each eye with intraocular presence of 10 mmHg bilaterally. Ophthalmoscopy revealed bilateral optic disc edema without retinal abnormalities. Systemic examination
was significant for a large distended abdomen with discernible pelvis masses. Neurologic, cardiorespiratory, and breast examinations were normal.

Acute phase reactants were elevated with erythrocyte sedimentation rate of 54 mm/h and C-reactive protein of 120 mg/dL (normal <10 mg/dL). Tumor marker values were cancer antigen (CA) 125 of 467.1 IU/mL (normal <35 IU/mL) while CA 15-3, CA 19-9, and carcinoembryonic antigen were normal. Cerebrospinal fluid (CSF) fluid analysis failed to disclose malignant cells but revealed decreased glucose of 0.47 mmol/L (normal: 2.8–4.4 mmol/L), elevated protein of 1.333 mg/dL (normal: 15–50 mg/L), and pleocytosis. The opening pressure was not recorded.

Contrast-enhanced MRI of the brain and orbits revealed widespread leptomeningeal thickening and enhancement. This involved the intraorbital optic nerves (Fig. 1), the first, fifth, seventh, and eighth cranial nerves and the brainstem and cerebellum (Fig. 2). In addition, T2 images demonstrated transependymal resorption of CSF indicating intracranial hypertension.

Postcontrast computed tomography of the abdomen and pelvis revealed bilateral adnexal masses. There was associated ascites, nodular mesenteric and peritoneal deposits, partial small bowel obstruction, and dilated appendix, likely because of peritoneal carcinomatosis (Fig. 3A). Boney metastatic deposits in the sternum, mandible, clivus, and multiple vertebrae also were present.

Biopsy specimen of an abdominal mass revealed multiple islands of signet ring cells within normal ovarian tissue. These cells displayed large deposits of intracytoplasmic mucin displacing hyperchromatic nuclei (Fig. 3B). Confirmatory immunohistochemistry stains with cytokeratin 7 disclosed strong diffuse positivity (Fig. 3C). Ascites fluid cytology revealed similar adenocarcinoma.

The patient, classified as stage IV malignancy, was deemed too unwell for therapeutic intervention and was offered palliation. Her condition deteriorated rapidly, and she died 2 weeks after admission from multiple organ failure.

Once believed to be extremely rare, the incidence of leptomeningeal carcinomatosis (LC) is increasing, primarily because of improved patient survival rates and advanced early detection methods. Various neuropathies may occur most often after a detection of a primary cancer and, rarely, as the presenting manifestation. Although the
primary tumor site was unknown in our case, signet ring cell adenocarcinoma commonly arises from the stomach, colon, breast, prostate, and lungs (1). It can have multiple primary foci and replicate along the natural contours of an organ, such as the stomach, completely encasing it as one sheet of neoplastic tissue, called linitis plastica. Known for rapidly metastasizing, patients often present with widespread disease. From the cytopathology and large tumor masses within the abdomen, the most plausible primary site in our patient was the abdomen. Its spread to other intra-abdominal tissues and bones including the spine was likely hematogenous. Tumor cells gained access to the CSF by direct spread from the spine or by penetrating epidural veins (2).

Optic nerve infiltration from LC has been reported in several cases of adenocarcinoma from various sources (2–6). It may lead to severe visual failure, including bilateral blindness (7–10). Along with reports by Suto et al (9) and Hayashi et al (10), our patient experienced simultaneous bilateral optic nerve sheath infiltration, confirmed by contrast-enhanced MRI. The symmetric demarcation from posterior infiltrated and anterior un-infiltrated optic nerves (Fig. 1) lends credence to the possibility that an intracranial sheet of signet ring cells extended into the orbits to encase the optic nerves in a similar fashion to linitis plastica in the abdomen.

The mechanism of vision loss in LC has yet to be elucidated and may have been multifactorial in our patient. She had headaches and MRI evidence of increased intracranial presence so the profound vision loss likely resulted from intracranial hypertension and variable contributions from meningeal cuf ting, parenchymal infiltration, and vascular disruption. The discrepancy between sluggish pupillary light responses and no perception of light vision may have resulted from residual melanopsin ganglion cell activity.

Cerebrospinal fluid cytology, the gold standard for diagnosis of LC, was negative in our patient. Detection of malignant cells is only 50%–70% positive in initial specimens, increasing to 100% with sequential CSF samples (8,11). Identification of signet ring cells in the abdomen and characteristic neuroimaging findings were deemed adequate for diagnosis and staging of LC in our patient.

STATEMENT OF AUTHORSHIP

ACKNOWLEDGMENTS
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REFERENCES
Ganglion Cell Layer Analysis Unmasks Axonal Loss in Anterior Optic Neuritis

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Abstract: Optical coherence tomography is a valuable tool for evaluating patients with neuro-ophthalmic disorders. In the acute phase of anterior optic neuritis (ON), peripapillary retinal nerve fiber layer (pRNFL) measurements can underestimate the amount of damage as axonal swelling could mask the true degree of RNFL loss. Contrary to pRNFL evaluation, we hypothesize that macular ganglion cell layer analysis could detect true neuronal loss before swelling resolution in anterior ON. We describe 4 patients with anterior ON in whom ganglion cell layer and inner plexiform layer (GCIPL) thinning was detected earlier than pRNFL loss. GCIPL analysis may provide more accurate information than pRNFL thickness and serve as an early structural indicator of irreversible neuronal loss.

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Spectral-domain optical coherence tomography (SD-OCT) has proven to be an essential imaging tool for neuro-ophthalmic pathologies. This technique evaluates neuronal integrity since it can demonstrate both retinal ganglion cell layer and peripapillary retinal nerve fiber layer (pRNFL) thinning in chronic optic nerve injury (1,2).

In anterior optic neuritis, pRNFL measurements obtained during the acute episode can underestimate axonal loss due to swelling that masks the true degree of pRNFL damage (3).

Macular thickness measurements have been reported to be useful to estimate and monitor the amount of ganglion cell loss in patients with papilledema (4). We hypothesize that macular ganglion cell layer and inner plexiform layer (GCIPL) analysis can detect structural changes masked within pRNFL analysis due to optic disc swelling. If correct, this analysis could help to establish a therapeutic window before irreversible neuronal loss occurs and identify patients needing more aggressive treatment.

METHODS

To assess this hypothesis, we prospectively evaluated 4 eyes of patients with anterior optic neuritis and collected the GCIPL macular thickness and pRNFL thickness with SD-OCT (Cirrus-OCT; Carl-Zeiss Meditec, Inc, Dublin, CA). We performed all examinations within 1 week of onset of optic neuritis. Visual fields were performed using standard automated perimetry (Humphrey Field Analyzer II 750; 24-2 Swedish interactive threshold algorithm; Carl-Zeiss Meditec).

All patients were evaluated and treated during the acute episode with intravenous steroids followed by a taper of oral steroids.

CASE REPORTS

Case 1

A 41-year-old woman, with no ocular history, complained of painful sudden vision loss in her left eye. Visual acuity was 20/20 in right eye and 20/30 in left eye. Fundoscopy revealed a swollen left optic disc. She had a severe depression of her left visual field (mean deviation [MD]: −26.5 dB), and average left pRNFL was 129 μm and average left GCIPL was 78 μm eye (minimum: 75 μm). Two weeks later, average left pRNFL was 134 μm, whereas average GCIPL was decreased to 62 μm (minimum: 59 μm). This GCIPL thinning was detected while the left optic disc was still swollen.

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The authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the full text and PDF versions of this article on the journal’s Web site (www.jneuro-ophthalmology.com).

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Left pRNFL analysis did not demonstrate axonal loss until 6 weeks later (pRNFL average: 69 μm) (See Supplemental Digital Content, Figure e1, http://links.lww.com/WNO/A128). At that time, acuity remained 20/30 in left eye, and MD of the left visual field was −23.57 dB.

Case 2
A 44-year-old woman presented with pain and sudden vision loss in her right eye. Visual acuity was 20/200 in right eye and 20/30 in left eye. In the right eye, average pRNFL was thickened (169 μm), and average GCIPL was 90 μm (minimum: 89 μm). Three weeks later, right pRNFL average was 111 μm, but right GCIPL analysis revealed thinning (average: 71 μm; minimum: 66 μm). Six weeks after the acute episode, right optic disc edema had resolved, and average pRNFL thickness was still within normal limits (99 μm) while GCIPL showed thinning (average: 66 μm; minimum: 59 μm). Significant temporal pRNFL thinning was not apparent until 2 months later (See Supplemental Digital Content, Figure e2, http://links.lww.com/WNO/A129). Visual acuity improved to 20/20 in the affected eye, but the visual field did not improve during follow-up (MD: −27.75 dB).

Case 3
A 35-year-old woman, diagnosed with relapsing–remitting multiple sclerosis, complained of blurred vision in her left eye. Visual acuity was 20/20 in right eye and 20/25 in left eye. The left optic disc was swollen, and pRNFL average was 109 μm. SD-OCT revealed abnormal color-coded GCIPL thinning. Left visual field testing showed a superior nerve fiber bundle defect (MD: −1.60 dB). Four months later, the left optic disc was no longer swollen, visual acuity was 20/20 and SD-OCT pRNFL analysis showed corresponding axonal loss. In this case, GCIPL was thinned at initial examination. Therefore, we could not assess if neuronal damage was due to the acute episode optic neuritis or a result of subclinical loss seen in some patients with multiple sclerosis.

Case 4
A 36-year-old woman, with no previous visual complaints, was diagnosed with anterior optic neuritis in her left eye. Visual acuity was 20/20 in right eye and 20/25 in left eye. In the left eye, SD-OCT showed pRNFL thickening (average: 175 μm), but average GCIPL was within normal limits (average: 88 μm; minimum: 84 μm). A small para-central scotoma was present in the left visual field (MD: −1.3 dB). Two weeks later, left pRNFL was 169 μm, and average GCIPL was 86 μm (minimum 81 μm), and at 8 weeks after onset, left optic edema persisted (average pRNFL thickness: 122 μm). Although GCIPL thickness was within normal limits, according to internal color-coded normative database, GCIPL thickness decreased in the superonasal and inferonasal sectors (by 9 μm and 10 μm, respectively). Three months later, GCIPL thinning (73 μm) in superonasal sector was color-coded as abnormally thinned (P < 0.5%), with reduced pRNFL thickness (average: 86 μm) (See Supplemental Digital Content, Figure e3, http://links.lww.com/WNO/A130). Visual acuity and visual field returned to normal in the left eye.

RESULTS
Changes in RNFL and GCIPL measurements at baseline and at last follow-up and the percentage change in the involved eye vs uninvolved eye are shown in Table 1. During the acute episode, mean average RNFL was significantly thicker in the involved eye vs uninvolved eye (P = 0.033). At the last visit, all the parameters, average GCIPL, minimum GCIPL, and average RNFL were thinner in involved eyes than in uninvolved eyes (P = 0.05, P = 0.09, and P = 0.06, respectively).

The difference in the percentage of change between involved and uninvolved eye ranged from 12.5% to 30% of thinning for average GCIPL, 9.5%–35% for minimum GCIPL, and from 32.4% to 59.1% for average RNFL thickness. The mean percentage of change between thicknesses at baseline and last follow-up was statistically higher in involved than in uninvolved eye for average GCIPL and average RNFL thickness (P = 0.013 and P < 0.001, respectively).

DISCUSSION
In our 4 patients with anterior optic neuritis, GCIPL thinning was detected within 1 month of presentation,

### TABLE 1. Comparison between involved and uninvolved eyes, for GCIPL and RNFL measurements at baseline and at the last follow-up

<table>
<thead>
<tr>
<th></th>
<th>Acute Episode</th>
<th>Last Visit</th>
<th>Percentage of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ON Eyes</td>
<td>Non-ON Eyes</td>
<td>P</td>
</tr>
<tr>
<td>Average GCIPL</td>
<td>83.25 (6.7)</td>
<td>83.5 (9.7)</td>
<td>0.968</td>
</tr>
<tr>
<td>Minimum GCIPL</td>
<td>77.5 (11.8)</td>
<td>79.5 (14.2)</td>
<td>0.836</td>
</tr>
<tr>
<td>Average RNFL</td>
<td>150.5 (37.7)</td>
<td>97.3 (8.6)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD), GCIPL, ganglion cell–inner plexiform layer; ON, optic neuritis; RNFL, retinal nerve fiber layer.

several weeks earlier than pRNFL loss. During the acute phase, optic disc and axonal swelling obscured axonal damage using pRNFL analysis. As pRNFL thickness returned to normal, it was not possible to determine whether this is due to decreasing axonal edema or axonal loss. In all cases, GCIPL analysis predicted neuronal damage several weeks before pRNFL analysis demonstrated axonal loss.

In this study, patients having more severe GCIPL thinning at baseline (Cases 1 and 2) had greater visual field damage at last follow-up. However, in Cases 3 and 4, with milder GCIPL loss, there was less visual field damage and the fields returned to normal. Quantification of GCIPL changes during the acute phase is likely to enhance our knowledge of the pathophysiology and natural history of optic neuritis. GCIPL analysis seems to be more sensitive in detecting neuronal damage and may provide more accurate information than pRNFL analysis during the acute phase of optic disc edema. GCIPL should be considered as a biomarker of early structural damage in anterior optic neuritis.

REFERENCES
Isolated Extraocular Muscle Infiltration With Plasmacytoma Treated With Localized Injection of Dexamethasone

Sally L. Painter, MA, MB, BChir, FRCOphth, Emmy Dickens, MBBS, BSc, MRCP, John S. Elston, MD, FRCOphth

Abstract: Plasmacytoma of the orbit secondary to multiple myeloma is rare and has not previously been reported limited to an extraocular muscle. Conventional treatment is either localized radiotherapy or systemic chemotherapy. We report a case of plasmacytoma within the medial rectus muscle, which regressed completely with localized infiltration of dexamethasone.

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Plasmacytoma of the orbit is an uncommon pathology with fewer than 60 cases reported in the literature (1). Most often, a bony lesion infiltrates the extraconal space causing proptosis and diplopia. Extraocular muscle infiltration is usually associated with surrounding soft tissue involvement and is rarely an isolated finding (2). Localized treatment of orbital involvement previously has been limited to radiotherapy (3–5). We present a case of plasmacytoma limited to an extraocular muscle, which regressed after a localized injection of dexamethasone.

CASE REPORT

A 74-year-old man was evaluated for a 3-week history of a red right eye. He had a 14-month history of immunoglobulin G lambda multiple myeloma. At first relapse, he was treated with 3 cycles of bortezomib, cyclophosphamide, and dexamethasone. Because of treatment toxicity (proximal muscle weakness and peripheral neuropathy) and evidence of disease progression with widespread soft tissue plasmacytomata, his regimen was changed to a lenalidomide-based regime with reduced dose oral steroids.

On examination, visual acuity was 20/25, right eye and 20/40, left eye. Color vision was intact, and pupillary reactions were normal. The right eye had 3-mm axial proptosis with a palpable mass in the medial orbit and localized medial conjunctival injection but no associated lid swelling (Fig. 1A). There was limited abduction of the right eye (Fig. 1B), and the patient reported diplopia in right gaze. Intraocular pressures were 10 and 11 mm Hg in his right and left eyes, respectively. The right optic disc was swollen nasally, and the left fundus was normal as was automated perimetry in each eye.

FIG. 1. On initial presentation, there is proptosis and medial injection of the right eye (A) and limitation of abduction (B).
Orbital computed tomography (CT) showed marked enlargement of the right medial rectus muscle causing mild proptosis and compression of the optic nerve in the orbital apex (Fig. 2). The remainder of the orbital soft tissue and bone structures was normal. The patient underwent right medial rectus biopsy with intramuscular injection of 2 mg dexamethasone. The biopsy showed extensive infiltration with plasma cells that were CD20−CD79−VS38c+ and lambda light chain restricted, consistent with plasmacytoma (Fig. 3). The patient responded well to the intramuscular dexamethasone and recent change in chemotherapy. Abnormalities on clinical examination completely resolved within 4 weeks (Fig. 4A, B), and radiotherapy was not required. A repeat CT scan showed that the medial rectus had returned to normal caliber (Fig. 4C). However, the patient’s condition worsened, and he died 5 months after presentation to the eye department.

**DISCUSSION**

Plasmacytoma is a soft tissue mass composed of clonal plasma cells, which can arise anywhere in the body, and may infiltrate orbital or ocular structures. Plasmacytoma may be the presenting feature of myeloma or occur in established disease. Solitary plasmacytoma of bone (SBP) and, even more rarely, solitary extramedullary plasmacytoma (SEMP) may arise in the absence of other features of myeloma. In SEMP, progression to myeloma occurs in approximately 30% of patients with a median time to progression of 2–3 years (6). This is in contrast to patients with SBP where the progression rate is 70%. A new diagnosis of plasmacytoma warrants a full investigation for systemic disease. Plasma cell malignancy typically responds well to radiotherapy and steroid treatment (7).

Presenting signs in myeloma with orbital involvement include proptosis, reduced vision, diplopia, periorbital swelling, and ptosis. Uncommonly, patients may have ecchymosis, cellulitis, or necrobiotic xanthogranuloma. Most orbital lesions arise in the superotemporal quadrant (75%), with 90% occurring extraconally. Bone involvement with local infiltration is often present. Extraocular muscle involvement has a prevalence of 0.3% (2) and has not previously been described as an isolated finding. In all reported cases, extraocular muscle involvement has been associated

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**FIG. 2.** Noncontrast axial (A) and coronal (B) orbital computed tomography shows enlargement of the right medial rectus muscle.

**FIG. 3.** Plasmacytoma of medial rectus muscle. A. There is a pleomorphic cell infiltrate within striated muscle (hematoxylin & eosin, ×4). Inset of tumor cells (×60). B. VS38 immunostaining reveals strong and uniform positivity consistent with plasma cell infiltrate (×10). Immunostaining for kappa light chains is negative (C) but positive for lambda light chains (D) (C and D, ×10).
with infiltration of tissues adjacent to the muscle including lacrimal gland, orbital bone, or contiguous eyelid (3–5).

Treatment options for plasmacytoma include localized radiotherapy, high-dose oral steroids, systemic chemotherapy, or a combination. Newer agents such as proteasome inhibitors (e.g., bortezomib) and immunomodulatory agents (e.g., thalidomide, lenalidomide) are now in routine use. Our patient was treated with chemotherapy and direct injection of dexamethasone into the extraocular muscle to prevent further optic nerve compression. Marked symptomatic improvement was noted within days of the injection, with complete regression of clinical signs and neuroimaging findings within weeks, despite a significant dose reduction in his oral steroid therapy. Orbital involvement in myeloma carries a poor prognosis with an average survival of 20 months, whereas median survival time for SEMP is 8.3 years (8). Previous reports indicate that patients often succumb to systemic disease before orbital involvement can be controlled, making the complete regression of signs and symptoms in this case particularly encouraging.

STATEMENT OF AUTHORSHIP

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REFERENCES
Primary Intrinsic Chiasmal Germinoma

Nauman S. Chaudhry, MD, Faiz U. Ahmad, MD, Elizabeth Whittington, MD, Norman Schatz, MD, Jacques J. Morcos, MD

Abstract: Intracranial germinomas are typically present in the suprasellar or pineal location, and their origin within the optic nerve or chiasm is extremely rare. We report a 25-year-old woman with an exophytic primary optic chiasm germinoma who underwent partial resection followed by radiation and had no detectable tumor on magnetic resonance imaging at 1-year follow-up.

Germinomas arising from the optic nerve or chiasm are extremely rare. According to our literature search, there are only 7 reported germinomas, all nonexophytic. Our patient appears unique as she had a primary exophytic optic chiasm germinoma.

CASE REPORT

A 25-year-old woman was referred for progressive visual loss for over 1 year associated with diabetes insipidus (DI). Visual acuity was 20/70 right eye, nasal letters only and 20/25 left eye, nasal letters only. Color vision was reduced in the right eye and intact in the left eye. There was a right relative afferent pupillary defect. Confrontation fields revealed that she could count fingers in all quadrants except the superotemporal quadrants bilaterally. Funduscopic examination was unremarkable. Her medications were prednisone and desmopressin.

Hematologic studies revealed an elevated prolactin of 199 ng/mL (normal: 4.8–23.3 ng/mL). Lumbar puncture, chest radiograph, and abdominal ultrasound were normal. Magnetic resonance imaging (MRI) of the brain revealed a 1.8 × 1.2 cm enhancing mass of the optic chiasm, suggestive of a glioma (Fig. 1).

A right frontal craniotomy was performed with a subfrontal approach. Gross inspection of the optic chiasm revealed an exophytic abnormal grayish mass bulging from within the chiasm. The chiasm itself was swollen, and the tumor was completely within the confines of the optic chiasm. The mass was not well circumscribed; rather, it was infiltrative making it difficult to distinguish between normal optic nerve fibers and abnormal tissue at the periphery of the lesion. Beginning with an incision at the center of the mass, the resection was limited only to the very abnormal grayish-appearing portion without breaching any myelinated fibers. A conservative partial resection was achieved. The tumor did not extend into the optic nerves or below the chiasm but rather was expanding the chiasm. The operation was without complications, and the patient awoke with no further neurological deficits.

Histologic examination revealed a tumor composed of large epithelioid cells with large pleomorphic nuclei and a prominent lymphoplasmacytic infiltrate. Immunohistochemical staining of the tumor cells was positive for C-kit, placental alkaline phosphatase, and D2-40 and negative for keratin and S100. CD45 immunostain highlighted the lymphocytes (Fig. 2). This was consistent with a diagnosis of germinoma (Fig. 2).

The patient underwent fractionated radiation therapy (24 Gy to the periventricular area with a boost of 45 Gy to the primary tumor in 30 cycles). She did develop panhypopituitarism. One year after surgery, the patient’s vision was counting fingers, right eye and 20/40, left eye. Her left visual field showed a temporal hemianopia. Both optic discs were pale. There was no evidence of tumor by MRI (Fig. 3).

DISCUSSION

The majority of intracranial germ cell tumors (GCTs) have been reported in suprasellar, pineal, or basal ganglia.
locations (1). Some have been reported with unique presentations including metastasis (2,3), orbital involvement (4), and cranial nerve involvement (5,6). There are several debated theories of the genesis of intracranial GCTs, but they all share the same principle in which germ cells during embryogenesis migrate aberrantly into the head or are misplaced within the mesoderm in the region of the optic nerves.

FIG. 2. Germinoma. A. Tumor is composed of large epithelioid cells with large nuclei (arrows) and prominent lymphocytes and plasma cells (arrowheads) (hematoxylin and eosin, ×40). Tumor cells are positive for immunohistochemical stains C-kit (B), PLAP (C), and D2-40 (D) (×40). Immunohistochemical stains for keratin (E) and S100 (F) are negative (×40).

FIG. 3. T2 axial (A) and postcontrast T1 sagittal (B) magnetic resonance imaging 7 months after radiation therapy shows no evidence of tumor.
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Age, y</th>
<th>Sex</th>
<th>Presentation</th>
<th>Examinations</th>
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<td>Chiasm (exophytic)</td>
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<td>R frontal craniotomy (subfrontal)</td>
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<td>Xia et al (7)</td>
<td>30</td>
<td>F</td>
<td>Vision loss, galactorrhea, vomiting, 2° amenorrhea, DI, vision loss, elevated PRL</td>
<td>No light perception in L eye; R eye only right nasal field intact, 20/25</td>
<td>Chiasm (nonexophytic)</td>
<td>Heterogenous ring enhancing lesion on chiasm</td>
<td>R pterional craniotomy</td>
<td>RT</td>
<td>&gt;1 y</td>
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<tr>
<td>Rath et al (3)</td>
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<td>Vision loss</td>
<td>Left funduscopy showed infiltrative lesion and dilated, tortuous retinal vessels with hemorrhage</td>
<td>Chiasm and R + L ON</td>
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<td>Krolak-Salmon et al (9)</td>
<td>35</td>
<td>M</td>
<td>Visual loss, periorbital pain, LP with oligoclonal banding and immunoglobulin G synthesis</td>
<td>R optic disc swelling</td>
<td>Chiasm and R ON</td>
<td>Hyperintense T2</td>
<td>Craniotomy</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bowman and Farris (1)</td>
<td>44</td>
<td>M</td>
<td>Vision loss, weight gain, DI, hypotestosteronism, hypothyroidism</td>
<td>Atrophy of L and R ON</td>
<td>Chiasm (L)</td>
<td>Diffuse high-intensity signal of optic chiasm L &gt; R</td>
<td>L frontal craniotomy (nonresectable)</td>
<td>RT 6 wk</td>
<td>&gt;1 y</td>
</tr>
<tr>
<td>Wilson et al (10)</td>
<td>9</td>
<td>M</td>
<td>Bilateral vision loss, fatigue, weight gain</td>
<td>Bilateral pale optic discs; R temporal VF defect; L centronasal VF defect</td>
<td>Chiasm and R + L ON</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nadkarni et al (11)</td>
<td>11</td>
<td>M</td>
<td>Vision loss (L), hormones normal</td>
<td>Optic atrophy</td>
<td>L ON</td>
<td>Thickened L optic nerve</td>
<td>Pterional craniotomy</td>
<td>RT only</td>
<td>&gt;6 mo</td>
</tr>
<tr>
<td>Izuka et al (12)</td>
<td>31</td>
<td>M</td>
<td>Vision loss only; no hypopit</td>
<td>—</td>
<td>R ON</td>
<td>Thickened R optic nerve</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

DI, diabetes insipidus; dx, diagnosis; F, female; L, left; LP, lumbar puncture; M, male; MRI, magnetic resonance imaging; ON, optic nerves; PRL, prolactin; RT, radiation therapy; VF, visual fields.
According to our literature search, there are only 2 reports of germinomas within the optic nerve(s) and 7 optic chiasmal germinomas, all of which were nonexophytic (Table 1). The mean age at diagnosis in reported cases is approximately 24 years, with 90% found in men.

Patients with a suprasellar GCT typically present with a triad of DI, visual changes, and endocrine abnormalities. Of the cases reported with optic nerve and chiasm germinoma, 100% suffer from visual deficits, 54.5% were diagnosed with DI, and 63.6% reported some form of endocrine abnormalities. DI often starts before the visual changes are detected (1). Laboratory studies reveal endocrine abnormalities, such as prolactinemia, hypotestosteronemia, hypothyroidism, and panhypopituitarism. Alpha fetal protein, beta human chorionic gonadotropin (bHCG), and lactate dehydrogenase have been reported within normal limits, except for 1 study with elevated bHCG (2). Sodium levels have been reported to be either high or low. Lumbar puncture, when performed, is usually unremarkable except for 1 study with a peculiar finding of oligoclonal banding and persistent immunoglobulin G synthesis in the cerebrospinal fluid independent of a demyelinating process (9).

Magnetic resonance imaging in all studies revealed the tumor to be of high signal intensity on T2, with either marked enhancement or a heterogeneous ring enhancing lesion on the optic chiasm and/or optic nerves. Similarly, our patient’s MRI findings were characterized by an enhancing mass involving the optic chiasm.

The MRI findings alone yield a broad differential diagnosis including chiasmal glioma, craniopharyngioma, ectopic pituitary adenoma, infundibuloma, neurosarcoidosis and tuberculosis sella meningioma. The GCT often appears well circumscribed on imaging but in reality it may actually infiltrate the surrounding nerve fibers of the optic nerves/chiasm without clear distinction. With biopsy, it is important to restrict the sampling to the obviously abnormal tissue without causing further damage to the surrounding visual pathways.

Surgical biopsy was performed in 82% reported cases of optic nerve and chiasm germinoma of which the vast majority also received radiation therapy. One third of the reports used a concomitant chemotherapy regimen of carboplatin etoposide and ifosfamide (2,8). Recurrence was reported in 2 patients who were treated with combined radiation and chemotherapy without surgery (2).

Visual function may or may not improve (1), and given the paucity of reported cases, it is still unclear whether radiation therapy causes significant damage to the optic fibers. Vision is more likely to improve in true suprasellar GCT’s after surgery and radiation therapy, in contrast to optic nerve and chiasmatic GCT’s with an infiltrative lesion, because removal of the tumor in the former case leads to the loss of the compressive mass effect it had caused (8,9,11).

REFERENCES
Midbrain Infarction Presenting With Monocular Elevation Palsy and Ptosis: Topographic Lesion Analysis

Yun-Ju Choi, MD, Seung-Han Lee, MD, PhD, Man-Seok Park, MD, PhD, Byeong C. Kim, MD, PhD, Myeong-Kyu Kim, MD, PhD

Abstract: A combination of monocular elevation palsy and ptosis is usually characteristic of an extra-axial lesion of the superior branch of the third nerve. We report an unusual case of monocular elevation palsy and ipsilateral ptosis due to midbrain infarction involving the third nerve fascicle. In addition, we conducted a review of the literature of similar cases and produced an overlay image of the magnetic resonance scans from these reports. The overlapping regions primarily were located in the midbrain between the red nucleus and cerebral peduncle. This correlated with involvement of the lateral portion of the third nerve fascicle containing fibers to the superior rectus and levator palpebrae.

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A partial third nerve palsy may due to involvement of the fascicular portion of the nerve within the brainstem (1,2). Reports following midbrain stroke include pupil-sparing third nerve palsy, isolated abduction palsy, isolated ptosis and mydriasis, and monocular elevation palsy with ipsilateral ptosis (3–8). We describe a patient with findings mimicking a superior division third nerve palsy and review similar reported cases with associated magnetic resonance imaging (MRI) abnormalities.

CASE REPORT

A 75-year-old woman presented with a 2-day history of right ptosis and diplopia. She had a 13-year history of diabetes mellitus and hypertension. There was no ocular injection or pain, visual loss, or proptosis. Examination revealed complete right ptosis and limitation of supra-duction in the right eye with no abnormalities of adduction, infraction, or pupillary reactivity (Fig. 1). The red glass test revealed vertical diplopia that increased in upward gaze and disappeared in downward gaze. Other cranial nerves, including the trigeminal and motor, sensory, and cerebellar systems were normal. Brain MRI did not reveal abnormalities in the right superior orbital fissure/cavernous sinus, orbit, or periorbital area. However, diffusion-weighted images showed abnormal high-signal intensity in the right medial midbrain near the cerebral peduncle compatible with acute infarction (Fig. 2). Her symptoms gradually improved over 3 months.

METHODS FOR LITERATURE REVIEW AND IMAGE OVERLAPPING

We conducted a review of the literature of similar clinical manifestations and collected MRI scans of these cases. This was performed by a web-based search for both English (www.ncbi.nlm.nih.gov/pubmed) and Korean (www.koreamed.org) publications using the following terms: oculomotor nerve; third cranial nerve; stroke; hemorrhage; ischemia; infarct; elevation; paresis, palsy; midbrain; mesencephalon. Our search was conducted up to July, 2014. Articles were selected using predetermined criteria. These criteria excluded reports that lacked original patient data, did not provide description of ocular motor symptoms, and did not indicate MRI findings. We identified 30 articles, 23 of which were excluded due to the presence of only experimental data (n = 12) and other associated ophthalmologic abnormalities, such as oscillpsia and horizontal gaze palsy (n = 11).

After a full-text review, we found 4 cases of monocular elevation palsy with ipsilateral ptosis in 3 (7–9). Four articles were excluded due to the lack of MR images. The demographics and clinical characteristics of the cases are shown in Table 1, and schematic diagrams of the MRI lesions appear in Figure 3.
**FIG. 1.** Nine cardinal positions of gaze reveal right ptosis and impaired elevation of the right eye.

**FIG. 2.** Axial (A), coronal (B), and sagittal (C) diffusion-weighted scans demonstrate a right paramedian midbrain infarction.

**TABLE 1.** Reports of superior division third nerve palsy due to midbrain stroke

<table>
<thead>
<tr>
<th>Author</th>
<th>Age/Gender</th>
<th>Other Neurologic Deficits</th>
<th>MRI Findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celebisoy et al. (7)</td>
<td>62/F</td>
<td>None</td>
<td>Right ventral midbrain infarction (Fig. 3C)</td>
<td></td>
</tr>
<tr>
<td>Park et al. (9)</td>
<td>57/F</td>
<td>None</td>
<td>Right ventral midbrain infarction (Fig. 3B)</td>
<td></td>
</tr>
<tr>
<td>Park et al. (9)</td>
<td>71/F</td>
<td>None</td>
<td>Left ventral midbrain infarction (Fig. 3A)*</td>
<td>Previous midbrain stroke involving inferior rectus and pupil</td>
</tr>
<tr>
<td>Hriso et al. (8)</td>
<td>75/F</td>
<td>Right hemiparesis; dysarthria</td>
<td>Lesion involving cerebral peduncle and portion of midbrain tegmentum (image not shown)</td>
<td></td>
</tr>
<tr>
<td>Current report</td>
<td>75/F</td>
<td>None</td>
<td>Right ventral midbrain infarction (Fig. 3D)</td>
<td></td>
</tr>
</tbody>
</table>

* MRI scan reversed to create overlay schematic diagram (Fig. 3A) and MRI overlay image (Fig. 4). MRI, magnetic resonance imaging; M, male; F, female.
We constructed an overlay image from each MRI scan containing the lesions using MRIcro software version 1.4 (www.mricro.com) (Fig. 4). The lesions of each patient were drawn manually onto transverse slices of the publicly available Montreal Neurological Institute brain, a T1-weighted template MRI scan, which is oriented to match the Talairach space. The template images containing the region of interest of each patient were summed up, and the overlapping area was shown in different colors according to the numbers of intersecting portions: 4 = red, 3 = green, 2 = blue, 1 = purple. One case with additional neurologic deficits due to a large midbrain stroke was excluded (8). The overlapping areas were primarily located in the midbrain between the red nucleus and cerebral peduncle. This area was correlated with previously reported diagram of third nerve fascicular topography (1) (Fig. 5).

**DISCUSSION**

Our case highlights a rare manifestation of partial third nerve palsy characterized by monocular elevation palsy and ipsilateral ptosis due to midbrain infarction. Ischemia of the lateral portion of the fascicle that contains fibers innervating the superior rectus and levator palpebrae were affected in our patient.

Several previous reports (7–10) also support our findings and are summarized in Table 1. Most cases had a focal ischemic lesion of the third nerve fascicle in the anterior portion of the midbrain between the cerebral peduncle and the red nucleus (Fig. 3). A case of lateral midbrain infarct with ptosis and upgaze palsy was documented in a patient with hemiparesis and dysarthria (8). In this patient, autopsy confirmed involvement of the lateral fascicular fibers.

**FIG. 3.** Diagrams of 4 cases of ptosis and ipsilateral monocular elevation palsy due to midbrain infarction. A and B were derived from Ref. (9), C from Ref. (7), and D from the current report.

**FIG. 4.** An overlay image created with MRIcro from MRI lesions of the 4 patients with isolated monocular elevation palsy and ptosis. The area colored in red was most frequently involved (n = 4), followed by those colored in green (n = 3), blue (n = 2), and purple (n = 1). MRI, magnetic resonance imaging.
Most commonly, a superior division palsy of the third nerve is due to a lesion of the cavernous sinus/superior orbital fissure or orbit (3,8). Rarely, the cause may be an extra-axial ischemic neuropathy due to diabetes mellitus (6,11).

In summary, a partial third nerve palsy in the absence of long tract signs can be caused by a fascicular brainstem lesion. Furthermore, midbrain infarction involving the lateral portion of the third nerve fascicle may present with isolated monocular elevation paresis and ipsilateral ptosis.

REFERENCES

**FIG. 5.** Diagram of the topographic fascicular arrangement of the third nerve. The hatched area shows the area of involvement in our patient. IO, inferior oblique; IR, inferior rectus; LP, levator palpebrae; MR, medial rectus; P, constrictor pupillae; SR, superior rectus.
Multiple Concomitant Cranial Nerve Palsies Secondary to Preeclampsia

Marina Gilca, MD, Katie Luneau, MD

Abstract: A 32-year-old primigravid woman developed preeclampsia after delivery of twins along with left fifth, sixth, and seventh cranial neuropathies. She also had evidence of hepatic and renal involvement. Results of patient evaluation were otherwise unremarkable, and the palsies completely resolved over 3 months after treatment with valacyclovir and systemic corticosteroids.

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Cranial nerve palsies during pregnancy require prompt attention. While a wide variety of causes may be implicated, it is of utmost importance to screen for preeclampsia. While often asymptomatic, preeclampsia can have dire consequences if untreated (1). Our report illustrates the need for thorough patient evaluation and careful follow-up in this clinical setting.

CASE REPORT

A previously healthy 32-year-old woman presented to the ophthalmology clinic with a history of recent onset horizontal binocular diplopia. Three days previously she delivered twins. The successful pregnancy required ovarian stimulation with letrozole and artificial insemination. The pregnancy, which was her first, had been uncomplicated until 36 weeks and 6 days of gestation, when she was diagnosed with asymptomatic preeclampsia, associated with hypertension up to 142/96 mm Hg, possible diabetes insipidus, increased liver enzymes (aspartate aminotransferase 122 U/L (normal, 13–39), alanine aminotransferase 89 U/L (normal, 8–31), gamma-glutamyltransferase 63 U/L (normal, 7–33), alkaline phosphatase 247 U/L (normal, 36–110)), acute renal failure with proteinuria (urine albumin 379 mg/L (normal, <30), and increased creatinine (150 μmol/L (normal, 42–89)). She neither fulfilled the diagnostic criteria for HELLP (hemolysis, elevated liver enzymes, and low platelets syndrome) nor the syndrome of acute fatty liver of pregnancy, having a normal renal and liver ultrasound, normal platelet count, and fibrinogen levels.

The patient was hospitalized, and the next day, she underwent pregnancy induction with oxytocin and seizure prevention with magnesium sulfate. She did not need antihypertensive treatment, as her blood pressure remained between 130/70 and 140/100 mm Hg. During labor with uncomplicated epidural anesthesia, she reported numbness on the entire left side of her face. This was confirmed on neurologic examination along with decreased ipsilateral masseter strength. She successfully delivered twins vaginally, with 600 mL of blood loss and the only complication being uterine atony, resolving after uterine massage.

A few hours after delivery, the patient complained of facial asymmetry and was found to have a peripheral left seventh nerve palsy. The remainder of the neurological examination was normal, and review of systems was negative. Treatment was instituted of valacyclovir, 1 gm 3 times a day, and prednisone, 60 mg daily. Both medications were prescribed orally. Two days later, the patient complained of binocular horizontal diplopia, worse on left gaze, and she was found to have a left sixth nerve palsy, while the remainder of her ophthalmic examination was normal. By that time, her blood pressure was within normal range and stable.

A noncontrast brain magnetic resonance imaging study [including a constructive interference steady state sequence] and computed tomographic angiography of the head and neck failed to detect a cause for the cranial neuropathies. Additional testing with normal results included anti-DNA antibodies, extractable nuclear antigen, antinuclear antibodies, treponema pallidum enzyme immunoassay, angiotensin-converting
enzyme, and serum glucose. Given the nonprogression of her symptoms, normalized blood pressure, renal and hepatic function, and negative investigations, it was decided not to do a lumbar puncture but rather to observe the patient. She continued valacyclovir and prednisone for 7 and 10 days, respectively, and her cranial nerve palsies completely resolved over 3 months.

DISCUSSION

A number of cranial neuropathies have been described in pregnancy, most frequently involving the seventh nerve followed by the sixth nerve. Specifically for pregnant patients, the diagnosis of preeclamptic neuropathy must be considered early and the appropriate investigations undertaken. Our case is unusual with simultaneous ipsilateral involvement of 3 cranial nerves.

Seventh Nerve Palsy

Seventh nerve palsy, in addition to being more common in women of reproductive age compared with men of the same age (2, 3), affects pregnant women more often than non-pregnant women (3, 4). It occurs most often in the third trimester or the puerperium (3–6) and seems to have a predilection for preeclamptic women (5, 7). The etiology of seventh palsy in pregnant women is unclear, but a number of etiologies have been proposed, including hypercoagulopathy (3, 5, 8), ovarian hormones (9), hypertension (5, 10), high extracellular fluid content (3, 5), viral infection (3, 11), and immunosuppression (3). Although the presentation is similar in pregnant and nonpregnant patients, the former seem to recover faster (12). According to some reports, corticosteroids can relieve the associated pain but do not improve recovery (4, 8, 11, 13), whereas other authors recommend early treatment with corticosteroids to achieve better outcomes (14). Use of antivirals, such as valacyclovir, may be warranted given the possibility of a viral etiology (3, 11) and, when used in combination with corticosteroids, may improve the clinical outcome (15).

Sixth Nerve Palsy

Sixth nerve palsy in pregnancy seems to be primarily linked to preeclampsia, developing either before (15) or after delivery. It may occur the same day as delivery or up to 11 days later, even with blood pressure under control with antihypertensive medication, similar to our patient (17, 18). There are also reports of sixth nerve palsy associated with pregnancy occurring with transient hypertension (19), without hypertension or preeclampsia (20), and after a febrile illness (21, 22).

During the perinatal period, both unilateral and bilateral sixth nerve palsies have been described within a few days of dural puncture secondary to epidural anesthesia followed by intracranial hypotension (23–27). These patients tend to be symptomatic, usually reporting postural headache (24, 26). Sixth nerve palsy with intracranial hypotension may be due to traction on the nerve by displacement of the brain or compression of the nerve by dura, the petrous apex or branches of the basilar artery (28).

Fifth Nerve Palsy

Trigeminal nerve involvement has been documented primarily in the setting of spinal anesthesia (29–31). It may occur in combination with Horner syndrome or with hypoglossal or facial nerve palsy. Some of the cases had an identifiable dural leak with probable intracranial hypotension. Some of the other etiological hypotheses raised include spread of the anesthetic effect in the subarachnoid space, toxic reaction to the anesthetic, and compromised blood flow to the cranial nerves secondary to sudden change in intracranial pressure (31).

We are unaware of other reported cases of symptomatic multiple cranial neuropathies in a pregnant patient without a dural leak. Multiple mechanisms, alone or in combination, could explain our patient’s clinical findings: hypercoagulopathy, ovarian hormones, microvascular ischemia, increased extracellular fluid content and direct or indirect effects of spinal anesthesia.

REFERENCES

Central Serous Chorioretinopathy in Susac Syndrome

Ozgur Artunay, MD, Alper Sengul, MD, Eda Sonmezay, MD, Emil Gaffarli, MD, Cigdem Kalaycik Ertugay, MD

Abstract: We report central serous chorioretinopathy (CSC) in a patient with Susac syndrome. The diagnosis of Susac syndrome was based on the results of funduscopy, brain magnetic resonance imaging, and audiometric testing. Our case demonstrates that possible choroidal involvement in Susac syndrome may lead to the development of CSC.

CASE REPORT

Susac syndrome is a rare autoimmune endotheliopathy with predilection for brain, retina, and cochlea (1). A presumed autoimmune vasculitic mechanism has been proposed, resulting in microangiopathy affecting the arterioles of the brain, retina, and cochlea (1–4). The syndrome usually affects women in the second decade of life, with female to male ratio being 3:1 (3,4). To date, approximately 80 cases have been reported. Patients typically present with low-frequency hearing loss were detected with audiometry. Headaches are frequently present in addition to tinnitus and often some degree of paranoia (1–4). Partial vision loss is caused by branch retinal artery vasculitis and occlusions (5,6). Abnormalities on brain magnetic resonance imaging (MRI) always show corpus callosum involvement. The mainstay of treatment is systemic corticosteroids and immunosuppressive medications (6–8).

Central serous chorioretinopathy (CSC) is characterized by a serous macular detachment due to a focal disruption in the outer blood–retinal barrier and increased choroidal permeability (9). Although the pathoetiology of CSC is unknown, it is associated with states of hypercortisolism, such as Cushing syndrome, pregnancy, and systemic glucocorticoid therapy.

We report a patient with Susac syndrome who developed CSC.

A 32-year-old woman reported a 1-week history of blurred vision and metamorphopsia in her left eye. For the past 3 weeks, she had experienced decreased hearing with tinnitus and migraine with aura and complained of an unsteady gait, intermittent paresthesias of the face and lower extremities, emotional lability, and forgetfulness. She was previously healthy and had no remarkable medical history other than cold hands and intermittent hypotension. She had never used topical or systemic corticosteroids.

Visual acuity was 20/20, right eye and 20/40 left eye. The anterior segments of both eyes were unremarkable. Fundus examination revealed bilateral multiple peripheral retinal arteriolar occlusions and serous elevation of the left macula. The sites of retinal arterial occlusion were not localized at arterial bifurcation. Fluorescein angiography demonstrated bilateral peripheral arteriolar wall hyperfluorescence distant to areas of arteriolar segmental occlusion (Fig. 1). In the left eye, there was focal dye leakage near the fovea with a neurosensory retinal detachment (Fig. 2). This was confirmed by optical coherence tomography (Fig. 3).

Neurological examination revealed an ataxic gait and cognitive dysfunction with memory loss. Brain MRI disclosed periventricular white matter lesions and punctuate hyperintense foci within the corpus callosum (Fig. 4). Audiometric evaluation revealed bilateral asymmetric sensorineural hearing loss more pronounced for lower frequencies.

The patient was treated with cyclophosphamide and intravenous immunoglobulin. Steroids were not prescribed because of the presence of CSC. The patient improved dramatically with resolution of her neurologic findings except for a mild hearing deficit. In addition, CSC resolved and fluorescein angiography became normal. Treatment was stopped after 6 months.
DISCUSSION

Although the pathophysiology of Susac syndrome is unknown, it is believed to be an immune disorder leading to microangiopathy of the precapillary arterioles of the brain, retina, and inner ear (1–5). Brain biopsies have revealed wall sclerosis of small arteries and multifocal microinfarcts with perivascular inflammatory infiltrates of cerebral arteriolar branches (5–8). Two funduscopic findings in patients with Susac syndrome, Gass plaques and arteriolar wall hyperfluorescence, also point to the endothelium as the site of autoimmune injury (5). 

Fluorescein angiography may reveal arteriolar wall hyperfluorescence distant from affected vessels seen on ophthalmoscopy. This finding has not been demonstrated in other retinal vasculitides. Hyperfluorescence of the retinal arteriolar walls may be found both proximally to the site of occlusion but also in areas remote from occluded arterioles (3,5,6,10).

Although there is no histological evidence of choroidal involvement in Susac syndrome, choroidal endotheliopathy could be present in some patients with this disorder (10). Flammer et al (11,12) postulated that the Susac syndrome is a manifestation of primary vascular dysregulation syndrome (PVDS; formerly vasospastic syndrome), and vascular dysregulation is at least one possible cause of Susac syndrome. The majority of patients with PVDS are female, often have low blood pressure and suffer from cold hands that rarely turn white. The ocular vasospastic syndrome denotes eye involvement in this disorder. Vascular dysregulation can be primary or secondary to an
autoimmune disease. Disorders of many organ systems, particularly the eye, occur with increased frequency in PVDS individuals. These include silent myocardial infarction, altitude sickness, migraine, normal-tension glaucoma, anterior ischemic optic neuropathy, retinal artery, and vein occlusions, Susac syndrome and CSC (11–13).

Abnormalities in the choroidal circulation and retinal pigment epithelium have been hypothesized to cause CSC (9,13,14). We propose that the endotheliopathy in Susac syndrome may alter choroidal vascular permeability as seen in our patient. This resulted in accumulation of submacular fluid. We are unaware of previous reports of CSC associated with Susac syndrome.

REFERENCES
Recent Advances Clarifying the Etiologies of Strabismus

Jason H. Peragallo, MD, Stacy L. Pineles, MD, Joseph L. Demer, MD, PhD

**Background:** Strabismus is commonly encountered in neuro-ophthalmology practice. Adult patients may present with symptoms including disabling diplopia and decreased quality of life. Although presentation to the neuro-ophthalmologist often prompts a thorough workup for a neurologic basis of ocular misalignment, advances in orbital imaging and understanding of orbital mechanics have revealed novel mechanical causes. A goal of this review is to clarify mechanical mechanisms of strabismus that were formerly assumed be neurologic in origin.

**Evidence Acquisition:** The authors combine their own research and clinical experience with a literature review using PubMed.

**Results:** Aberrant paths of the extraocular muscles can lead to strabismus. The extraocular muscles have connective tissue pulleys that control muscle paths and are, in turn, influenced by the extraocular muscle orbital layers. Orbital connective tissues, including the pulleys, constrain extraocular muscle paths. Abnormalities of these tissues may lead to strabismus that is not due to neurologic pathology. Some extraocular muscles are divided into independent neuromuscular compartments, so that partial motor nerve lesions may manifest as selective denervation of only 1 compartment, complicating the presentation of neuropathic strabismus.

**Conclusions:** Strabismus in adults due to nonneurologic causes can result from recently described abnormalities of the orbital connective tissue pulley system. Advances in understanding of compartmental extraocular muscle anatomy and innervation can explain cyclovertical strabismus in partial nerve palsies. Recognition of the underlying pathogenesis of the strabismus can lead to improved treatments.

**ORBITAL ANATOMY**

Histopathologic analysis of all extraocular muscles reveals divisions of the striated muscle fibers into global and orbital layers that share a common origin for each individual muscle (5). The global layer becomes continuous with the sclera as it inserts directly on the globe. The orbital layer of each rectus muscle terminates about 16 mm posterior to the globe, where it inserts into a connective tissue condensation in posterior Tenon's fascia that functions as a pulley (6). The orbital layer of each rectus muscle exerts force on the pulley itself, which actively alters the extraocular muscle's path (6). These pulleys are located posterior to the equator of the globe and are continuous with posterior Tenon’s fascia (Fig. 1).

Extraocular muscles do not follow straight line paths, leading to the notion that each passes through a pulley as first conceived by Miller (7). Pulleys maintain the stability of muscle paths posteriorly in the orbit and prevent slippage of the muscles over the globe in secondary and tertiary gaze positions (8). The muscle pulleys are mechanically coupled to each other and to anchor points on the medial and lateral orbital walls. Smooth muscle is present within the dense collagen rings and elastin that compose the pulley tissue (9,10) (Fig. 2). The smooth muscle within the pulleys has autonomic innervation from sympathectomies in the superior cervical ganglion and likely from...
parasympathetics in the ciliary and pterygopalatine ganglia (4,10). Specific effects of these autonomic pathways on pulley smooth muscles remain uncharacterized and likely depend on the exact orientation of the smooth muscle bundles. Current speculation favors a role for smooth muscle in the region of the medial rectus pulley in reducing the load on the striated medial rectus muscle during convergence, analogous to the manner in which contraction of the ciliary muscle permits relaxation of the fibers of the ciliary zonule during accommodation (11). At present, this is the only plausible explanation for the markedly lower contractility of the medial rectus in convergence than in adduction during horizontal gaze.

High-resolution magnetic resonance imaging (MRI) using orbital surface coils provides important detail of orbital anatomy. Inflections in the paths of the extraocular muscles in secondary and tertiary gaze produced by the orbital pulleys have been demonstrated by MRI for all 4 rectus muscles (12). Although the pulleys themselves cannot always be identified on MRI, inferences about their location can be determined by examining discrete inflection points of extraocular muscle paths in eccentric gaze positions (4,13,14). The inferior oblique muscle also has a pulley, located at the lateral margin of the inferior rectus muscle at the site of the motor nerve entry; the inferior oblique pulley is partially coupled with the inferior rectus pulley, so that the positions of both pulleys depend on the contractile states of the orbital layers of both muscles (Fig. 3). In tertiary gaze positions, the inferior oblique muscle path may be observed to inflect at its pulley adjacent to the inferior rectus muscle’s lateral border. The orbital layer of the inferior oblique muscle inserts on the inferior rectus pulley, on the inferior oblique sheath and on the inferior aspect of the lateral rectus pulley. As a result, inferior oblique contraction displaces the inferior rectus pulley nasally and the lateral rectus pulley inferiorly by a small amount.

The orbital layer of the superior oblique muscle inserts on the superior oblique sheath posterior to the trochlea; the global layer of the superior oblique becomes continuous with the superior oblique tendon. Anterior to where both the superior oblique tendon and sheath are reflected in the trochlea, the superior oblique sheath inserts on the nasal aspect of the superior rectus tendon, whereas the superior oblique global layer tendon inserts on the sclera. Contraction of the superior oblique orbital layer produces nasal displacement of the superior rectus tendon, so that the superior oblique indirectly influences superior rectus pulling direction. Quantitative data on muscle path inflections supports the crucial role of pulleys in regulating muscle pulling directions. The unifying theory explaining the systematic changes in extraocular pulling directions during gaze shifts has been termed the “Active Pulley Hypothesis” to indicate that its kinematic precision is not accidental but rather the result of neutrally regulated forces in the orbital layers of all 6 oculorotary muscles. Nevertheless, because the orbital layers exert their forces against the passive elastic loading of orbital connective tissues, active processes in the orbital layers cannot always compensate when connective tissue pathology becomes sufficiently severe. This is particularly common where connective tissue pathology shifts pulley locations transversely to the long axes of the muscles, altering pulling direction in a way that cannot be compensated by change in orbital layer tension.

Significant abnormalities of the pulley system can produce strabismus. Several kinds of abnormalities of the pulleys have been demonstrated by MRI and computed tomography (CT), including pulley heterotopy that produces a fixed change in muscle pulling direction, instability of a pulley that produces gaze-dependent changes in muscle pulling direction that may cause complex incomitant strabismus, and hindrance to movement of a pulley during muscle contraction, causing restrictive strabismus (4,8).
abduction and supraduction are limited (20,21). It was postulated that the etiology of strabismus in patients with high axial myopia included the erroneous concept that the highly myopic globe was “heavy” and would sink onto the orbital floor or compress the lateral rectus, leading to ischemia of the muscle and mimic a sixth nerve palsy (22,23). The misconception that a large eye is somehow denser than a normal eye is the basis for the misnomer “heavy eye.” Unfortunately time-honored and in widespread use worldwide, the term will be used here. Krzizok and Schroeder (24) proposed that displacement of the lateral rectus muscle inferiorly led to a disturbance in abduction, but this did not explain limitation of elevation of the eye. The highly myopic globe has been demonstrated by MRI to be displaced superotemporally outside of the extraocular muscle cone in these cases (21,25). Yamaguchi et al (21) suggested that the globe itself displaced the extraocular muscles leading to strabismus, although an alternative interpretation is that disruption of the LR-SR band leads to inferior shift of the LR pulley that allows superotemporal globe displacement and subsequent strabismus (21). Because the relative positions of the globe and extraocular muscles are the mechanically relevant considerations, these 2 hypotheses are not mutually exclusive. The alteration of the muscle pulleys leads to abnormal pulling directions. Nasal translocation of the superior rectus pulley converts much of its force to adduction. Inferior displacement of the lateral rectus pulley converts most of its force to infrafraction. There remains no source of abducting force, leading to esotropia.

By recognizing the displacement of the globe superotemporally outside of the rectus pulley array, Yamaguchi et al (21) devised the “Yokoyama” surgical procedure tailored to the orbital anatomic pathology underlying myopic strabismus. This surgery consists of creating a union between the posterior bellies of the superior and lateral rectus muscles, effectively restoring the proper anatomic positions of the extraocular muscles, and so restoring abduction and elevation (21,26) (Fig. 4). Durnian et al (27) demonstrated successful outcomes in 5 patients. However, this operation might be less effective for those patients’ whose eyes are so elongated and misshapen by staphylomata that the globe is physically prevented from rotating due to collision with the orbital walls (28). Coronal plane orbital imaging is critical in establishing the diagnosis of heavy eye syndrome because the mere coexistence of axial myopia with esotropia does not exclude other etiologies such as sixth nerve palsy.

**SAGGING EYE SYNDROME**

Aging leads to widespread degeneration of adnexal connective tissues, including those within the orbit. For example, aponeurotic degeneration of the levator palpebrae superioris leads to ptosis in a significant portion of the elderly population. As the inferior displacement of the lateral rectus...
muscle due to involutional changes of the LR-SR band connective tissue ligament was known to be associated with strabismus, investigation of strabismic elderly patients was performed to determine if this phenomenon was causative (29). High-resolution orbital MRI performed in 3 elderly nonmyopic patients with strabismus demonstrated inferior displacement of the lateral rectus muscle (29). The LR-SR band was qualitatively abnormal on MRI (29). Coronal histologic sections of autopsied human orbits revealed progressive thinning and superotemporal displacement of the LR-SR band with age (29). Healthy older patients were shown to have horizontal rectus muscles more inferiorly displaced than younger subjects (30) (Figs. 5 and 6). Limitation of sursumduction in the elderly may be related to inferior displacement of the horizontal rectus muscle pulleys due to degeneration of the LR-SR band (30). Similar to the heavy eye syndrome, inferior displacement of the lateral rectus muscle converts the action of the lateral rectus muscle from an abductor to an infraductor. Rutar and Demer (29) postulated that when this degeneration is present bilaterally, the primary effect is to create a deficit in abduction bilaterally, along with a symmetrical and, therefore, asymptomatic reduction in the range of sursumduction. These patients present with distance esotropia and bilateral supraduction deficits. The clinical presentation has been described as divergence insufficiency esotropia, also known as age-related distance esotropia, adult-onset age-related distance esotropia, and divergence paralysis esotropia (19,29,32–36). This is one manifestation of the “sagging eye” syndrome. Connective tissue involution in the external adnexa is a clinically useful clue to the sagging eye syndrome. A history of previous surgery for ptosis or high eyelid creases can be considered a marker for degeneration of orbital tissues and may be suggestive of age-related distance esotropia (Fig. 7).

Evaluation of 56 orbits of patients suspected of having age-related degenerative changes as the cause of their diplopia was performed with quantitative high-resolution MRI. For this study, patients with axial high myopia were excluded to avoid confusion with the heavy eye syndrome. In patients who had sagging eye syndrome, a superior orbital sulcus deformity was found in 64% of patients, 29% of these patients had high upper eyelid creases and ptosis. Of the entire patient cohort, 29% had undergone previous facial cosmetic surgery (19). In the orbits of patients with sagging eye syndrome and age-related distance esotropia, orbital anatomy was distorted in comparison with both younger orbits and age-matched controls: the lateral rectus muscle pulley was displaced inferiorly, and the inferior rectus muscle pulley was displaced temporally and inferiorly (19). For patients with sagging eye syndrome and cyclovertical strabismus, the lateral rectus muscle pulley was inferiorly and temporally displaced in the hypotropic eye in comparison with its location in the orbits of younger patients and age-matched controls (19). Interestingly, both lateral rectus muscle pulleys were inferiorly displaced in patients with cyclovertical strabismus, but the hypotropic eye had greater inferior displacement than the hypertropic eye (19). The eye with greater inferior displacement of the lateral rectus pulley also exhibited consistently greater fundus excycloposition than the fellow eye. This excyclo effect is due to the excycloducting torque of the inferiorly

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**FIG. 4.** Intraoperative photograph demonstrating the Yokoyama procedure in which the muscle bellies of the superior and lateral rectus muscles are joined. LR, lateral rectus; SR, superior rectus.

**FIG. 5.** Coronal histology showing LR-SR band as it degenerates over time (van Giesson stain, ×4). IO, inferior oblique; LG, lacrimal gland; LPS, levator palpebrae superioris; LR, lateral rectus; SR, superior rectus.

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displaced lateral rectus path. There was no consistent pattern of horizontal or vertical incomitance of the hypertropia, perhaps related to dynamic instabilities in pulley positions, compensatory vergence mechanisms, or compartmental mechanisms as described below. In both cyclovertical strabismus and age-related distance esotropia, lateral rectus muscle paths were approximately 50% longer than in younger patients or older controls, and the causative bowing of the lateral rectus muscles was evident on axial MRI images (19). The LR-SR band was no longer in older control patients than in young controls. The LR-SR band was thinned, elongated, or ruptured in many patients with sagging eye syndrome.

Because cyclovertical strabismus due to asymmetric lateral rectus pulley sag may mimic some aspects of superior oblique palsy, some discussion of diagnostic criteria for superior oblique palsy is warranted. It is now recognized that the Parks–Bielschowsky 3-step test is not the reliable gold-standard it was once assumed to be. Based on MRI measures of superior oblique muscle function and knowledge that trochlear neurectomy rapidly induces denervation atrophy of the superior oblique muscle, MRI studies have demonstrated that the sensitivity of the 3-step test in the diagnosis of a complete superior oblique palsy is approximately 70% and the specificity is about 50%. Because adaptation to prism-induced vertical heterophoria causes a positive head tilt response even in normal individuals (37), it is no surprise that the amount of change in hypertropia with head tilt is poorly correlated with superior oblique structure or function (38). Nevertheless, the Parks–Bielschowsky 3-step test is still clinically useful in diagnosing unilateral superior oblique palsy in the acute setting.

Patients with sagging eye syndrome may be identified without performing imaging by simple history and clinical examination, given the recognizable external appearance, tendency to have undergone cosmetic surgery, and motility patterns including limited supraduction. On examination, abduction must be full and abducting saccades must be normally brisk, so that sixth nerve weakness can be confidently excluded on clinical grounds. Divergence insufficiency type esotropia in younger patients in suspicious for an underlying neurologic disorder and should be investigated appropriately. Patients who do not meet the clinical profile of age-related distance esotropia or who exhibit associated ocular motor or cranial nerve abnormalities should undergo further neurological investigation regardless of age.

In the treatment of age-related distance esotropia, small-angle distance esotropia can be treated conservatively with prism spectacles. For larger deviations, surgical options include either lateral rectus muscle shortening by resection or plication, or medial rectus muscle recession (39). It should be noted that because of muscle elongation in the sagging eye syndrome, the amount of medial rectus muscle recession must be greater than specified by standard strabismus tables (36). It is suggested that if medial rectus muscle recession is performed for age-related distance esotropia, the angle of deviation used to calculate surgery according to standard tables should be twice the measured angle of distance esotropia (36). For patients with small cyclovertical

FIG. 6. Coronal magnetic resonance imaging demonstrates LR-SR band degeneration in a patient with sagging eye syndrome. Note the progressive displacement of the LR-SR band from its original anatomic position with increasing age. LR, lateral rectus; SR, superior rectus.

FIG. 7. **A**. A patient with sagging eye syndrome has typical connective tissue involutional changes. **B**. Coronal magnetic resonance imaging of the same patient reveals an intact LR-SR band in the right orbit and a ruptured LR-SR band in the left orbit. LR, lateral rectus; SR, superior rectus.
strabismus due to sagging eye syndrome, partial inferior rectus tenotomy under topical anesthesia can address hypertropia while allowing for intraoperative augmentation of the tenotomy up to 90% of the total tendon as necessary.

A clearer relationship between heavy eye syndrome and sagging eye syndrome has recently emerged. The typical findings of sagging eye syndrome may occur in myopes, even axial high myopes, and responds well to conventional strabismus surgery when the globe remains within the general “conical” array of rectus muscles whose elongated paths are centrifugally displaced in the orbit. However, when an axially myopic globe shifts superotemporally, the superior and lateral rectus muscle paths shift towards the cranial midline; the lateral rectus path tends to parallel the inferior rectus path, markedly converting the abducting action of the lateral rectus into infrafduction to produce marked esotropia and hypotropia characteristic of the heavy eye syndrome. These 2 possibilities may be difficult or impossible to distinguish without orbital imaging. We have also encountered a case in which an axially myopic patient exhibited severe esotropia that was presumed to be due to heavy eye syndrome until orbital imaging demonstrated denervation atrophy of the lateral rectus muscle due to a large cavernous sinus meningioma. That patient responded well to conventional vertical rectus transposition because the path of the atrophic lateral rectus muscle had become mechanically irrelevant. These situations illustrate the clinical value of preoperative orbital imaging in management of highly myopic patients.

**EXTRAOCULAR MUSCLE INNERVATION: COMPARTMENTALIZATION**

Individual skeletal muscles may have multiple bellies innervated by different motor neuron populations (40–42). As noted above, the extraocular muscles are each composed of a global layer, that exerts force on the globe itself, and an orbital layer, that translates the connective tissues surrounding extraocular muscles to alter muscle paths. Beyond these 2 compartments, there is evidence of further specialization and innervation of portions of some extraocular muscles.

The sixth nerve has been found to be duplicated in between 8% and 15% of autopsies (43). Histologic sectioning of human and monkey orbits has shown that the sixth nerve divides as it exits from the brainstem or travels peripherally and bifurcates before entering the lateral rectus muscle (44). The bifurcation results in a distribution to 2 distinct zones of muscle fibers, a nonoverlapping superior zone and inferior zone (43). Ocular counterrolling violates Listing Law, and the possibility of compartmental contraction of the lateral rectus muscle during this maneuver was examined using high-resolution MRI imaging. The inferior compartment of the lateral rectus muscle exhibited increased contractility during ocular counterrolling maneuver in normal individuals. This effect was absent in patients with superior oblique palsies, suggesting a complex interaction between the oblique extraocular muscles and the inferior compartment of the lateral rectus muscle (45). There is vestibular input to the sixth nerve nucleus, leading to differential compartmental contraction of the lateral rectus muscle (46).

Evidence for compartmentalization of the superior oblique muscle also has been demonstrated. Two separate nonoverlapping neuromuscular compartments innervated by separate divisions of the trochlear nerve have been identified on histologic sections of 3 adult human cadavers, multiple monkeys, and other mammalian orbits, but not in a preterm fetus. These divisions may implement separate control of torsional and vertical components of the action of the superior oblique muscle, because the more anterior fibers of the superior oblique tendon insert at the equator and have a mainly torsional effect, whereas the more posterior fibers have a mainly vertical effect (A. Le, BS, and J. L. Demer, MD, PhD, unpublished data, October 2014). Selective neuropathy of the torsional or vertical division of the trochlear nerve could produce 2 different patterns of compartmental superior oblique palsy with differences in vertical and torsional manifestations.

Strabismus cases in which the classical cyclovertical muscles are implicated may not involve the cyclovertical muscles at all if differential compartmental activation of horizontal rectus muscles is involved in cycロorotation. This consideration may motivate the clinician to confirm putative cyclovertical muscle paralysis by an imaging method such as MRI to confirm the presence of denervation muscle atrophy.

Imaging can demonstrate changes in morphology of the extraocular muscles. High-resolution MRI of the orbit has identified patients who have developed strabismus from selective compartmental palsies of the lateral rectus muscle. In a study of 18 patients with sixth nerve palsy, 6 exhibited asymmetric atrophy of the lateral rectus muscle, with the superior compartment significantly thinner than the inferior compartment (47). The total volume of the superior and inferior compartments in patients with complete sixth nerve palsies was significantly smaller than the normal contralateral lateral rectus muscle (47) (Fig. 8). Patients with superior compartment lateral rectus palsies retained significantly more abduction function and had less esotropia than those with complete lateral rectus palsies, and the volume of the inferior compartment of the lateral rectus muscle was not smaller than the corresponding contralateral compartment (47).

Clues to the presence of superior division sixth nerve palsy include a smaller angle esotropia in primary position, better abduction, the presence of an ipsilateral hypotropia, and the presence of exocycloversion. Peripheral partial sixth nerve palsies are not the only cause of this pattern of strabismus, as central causes could lead to partial sixth and fourth palsies or skew deviation (48). Finding a selective compartmental sixth nerve palsy raises implications for the treatment of strabismus, as lateral rectus muscle tightening procedures may lead to vertical or torsional strabismus given...
the retained function of the inferior compartment of the lateral rectus muscle. We have recently had surgical success in selectively plicating or resecting only the lateral rectus tendon corresponding to 1 compartment sparing the other.

THE EMERGING CASE AGAINST CLINICAL DIAGNOSIS OF SUPERIOR OBLIQUE PALSY

Diagnosis of superior oblique palsy has classically been established using the Parks–Bielschowsky 3-step test (49). Requirements for diagnosis include ipsilesional hypertropia in primary gaze, increase in the hypertropia with contralateral gaze, and increase in the hypertropia with ipsilateral vs. contralateral head tilt. The increase in hypertropia on head tilt has been proposed to be a result of compensatory superior rectus activation in the presence of deficient incyclotorsion during ocular counterrolling (50).

Previous investigations questioned the validity of the Parks–Bielschowsky 3-step test in diagnosing superior oblique palsy. The 3-step test appears to be nonspecific, as other entities can have positive 3-step tests, such as muscle pulley heterotopy, superior oblique tendon anomalies, and skew deviation (51–54).

Superior oblique atrophy is seen shortly and permanently after experimental denervation of the muscle in macaque monkeys (55). Therefore, atrophy of the superior oblique could be considered a marker of denervation on orbital imaging. In patients with superior oblique muscle atrophy on MRI, the 3-step test was evaluated for sensitivity in diagnosing superior oblique palsy. All 3 steps were satisfied in 70% of patients, leaving a significant number with radiographic evidence of marked superior oblique atrophy who would not have been clinically diagnosed with superior oblique palsy (56). Each individual step had differing sensitivity for superior oblique palsy, with ipsilesional hypertropia in primary gaze and ipsilesional exceeding contralesional head tilt hypertropia being more sensitive (92% each) than contralesional gaze hypertropia exceeding ipsilesional hypertropia (84%).

Therefore, the Parks–Bielschowsky 3-step test for diagnosis of superior oblique palsy may be negative even in the presence of marked atrophy of the superior oblique muscle belly. There is no correlation between superior oblique muscle size in clinically diagnosed superior oblique palsy and head tilt–dependent hypertropia (38).

Using the Parks–Bielschowsky 3-step test may result in erroneous diagnosis of superior oblique palsy in patients who harbor other disorders, while patients with actual neurogenic superior oblique palsy may not satisfy all components of the 3-step test. We recommend that the diagnosis of superior oblique palsy be reserved for situations where there are abnormalities of the superior oblique muscle on orbital imaging. As a provisional alternative, clinicians might consider “incomitant hypertropia” or “head tilt–dependent hypertropia” until or unless an abnormality of the superior oblique muscle or tendon is detected.

Because the lateral rectus muscle path is oblique to the frontoparallel plane, routine coronal MRI or CT will not adequately demonstrate pathology of the LR-SR band or lateral rectus muscle atrophy limited to a single compartment. It will show substantial inferior displacement of the lateral rectus muscle. Optimal imaging requires thin (2 mm) quasicoronal scanning perpendicular to the long orbital axis that is nearly perpendicular to all of the extraocular muscle bellies, except for the inferior oblique muscle. This requires that each orbit be imaged separately. Imaging of the inferior oblique muscle must be performed in a quasisagittal plane parallel to the long orbital axis perpendicular to the path of the inferior oblique muscle. Use of surface coils to maximize signal-to-noise ratio, along with fixation targets to minimize motion artifacts, permits imaging of the motor nerve entry points for most extraocular muscles (57). The T2 fast spin echo pulse sequence reduces scanning time significantly. Repeated imaging in multiple gaze positions is required to demonstrate the changes in muscle cross section and volume indicative of physiologic contractility (11,58–60).
CONCLUSION

Our understanding of orbital anatomy has significantly advanced in the recent decades. Through our knowledge of the orbital structures, their developmental anomalies, and acquired involutional changes, we can explain multiple forms of previously unexplained or incorrectly understood strabismus. By understanding the mechanics and innervation of the orbit, we may be better able to tailor our treatments for specific forms of strabismus.

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State-of-the-Art Review

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Vitamin D in Multiple Sclerosis and Central Nervous System Demyelinating Disease—A Review

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Background: The role of vitamin D as both a risk factor and a disease modifier in multiple sclerosis (MS) has a storied history with ongoing accumulation of supportive convergent evidence from animal data, clinical studies and trials, and biomarkers of disease.

Evidence Acquisition: A detailed review of the published literature ranging from in vivo immune studies to human clinical studies of epidemiology, physiology, immunology, clinical, and radiological markers was undertaken.

Results: There is compelling evidence that vitamin D is not only a risk factor for central nervous system (CNS) demyelinating disease (namely MS) but also seems to modify both the inflammatory and neurodegenerative elements of the disease, with large-scale treatment trials underway. The authors also address questions of interest that remain unanswered.

Conclusions: Vitamin D is an important contributor and modifiable risk factor in CNS demyelinating disease. Further work will determine whether it is also neuroprotective and if such benefits will apply to other inflammatory and degenerative neurological diseases.

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Multiple sclerosis (MS) is an inflammatory and neurodegenerative disorder of the central nervous system (CNS) and the leading cause of nontraumatic neurological disability in young adults (1,2). In 85% of patients, MS is initially heralded by an inflammatory event known as a “clinically isolated syndrome” (CIS), followed by a relapsing course with periods of remission (2,3). After a median disease duration of 20 years, most MS patients transitioned into a secondary progressive phase of the disease (4). Approximately 15% of patients accumulate neurological disability with or without superimposed relapses from the onset of their condition (1,2). Although the realm of therapeutics has evolved dramatically (5,6), neuroprotective treatments remain elusive in MS. Recently, vitamin D has gained attention as a potential adjuvant therapy that seems to reduce MS risk and ameliorate disease severity. A potent immunomodulator, vitamin D, is now routinely recommended to individuals affected by or deemed to be at increased risk of MS (7). Numerous trials are underway to examine the potential benefits of “add-on” vitamin D to approved MS medications. Moreover, vitamin D has been proposed to have neuroprotective effects, a hypothesis, which has been supported by the reduced MS risk associated with sun exposure and the use of vitamin D supplements (8). In this review, we will discuss the epidemiology, immunology, and clinical effects of vitamin D on MS and other demyelinating disorders of the CNS.

EPIDEMIOLOGICAL EVIDENCE SUPPORTING A ROLE FOR VITAMIN D IN MULTIPLE SCLEROSIS

For over a century, MS has been observed to follow a striking geographic pattern. Namely populations living increasing degrees of latitude in both northern and southern hemispheres have increased disease prevalence (9–14). Solar/ultraviolet radiation (UVR) has emerged as the most potent environmental factor, linked to latitude, which inversely correlates with MS prevalence rates (9,15,16) (Fig. 1). Specifically, the risk of MS to individuals who migrate from a “high-risk” MS geographic location to a “low-risk” is reduced (and vice versa) if such a move occurs at a relatively young age (18–22). Reduced UVR exposure has been linked with an increased risk of
developing MS (22,23) and more severe disability (24). Specifically, a meta-analysis of 52 studies showed a highly significant association ($P < 10^{-9}$) between MS prevalence and annual amount of UVR (24).

However, observations in Norway, where more northerly coastal fishing areas of the country have significantly lower rates of MS than the inland regions to the south (25,26), have challenged the north–south gradient-latitude UVR hypothesis. Furthermore, the epidemiological investigation of MS showed that subjects who reported high fatty fish intake had a lower odds ratio (OR) [0.82 (0.68–0.98)] for the presence of MS vs those with low intake, whereas lean fish intake had no such effect (27). The unifying hypothesis is that factors including UVR exposure and fatty fish intake ultimately reflect vitamin D intake and production; a conclusion that has been reached after a multitude of both large and small convergent studies (17).

**Immune Mechanisms of Vitamin D**

Immune regulation is the presumed mechanism by which vitamin D impacts CNS demyelinating disease, supported by the presence of vitamin D receptors on monocytes, activated T cells, and antigen-presenting cells (28–31) (Fig. 2). Activation of the vitamin D receptor is known to alter transcription, proliferation, and differentiation of immune cells (29,33,34). In addition, 1,25-hydroxyvitamin (OH)2D-stimulated B lymphocytes, macrophages, and dendritic cells produce 1α-hydroxylase, whereas 24-hydroxylase is expressed in the presence of 1,25(OH)2D in B lymphocytes and in resting activated monocytes and macrophages (35–37). Other immune effects of 1,25(OH)2D include a reduction in the expression of major histocompatibility complex Class 2 and costimulatory receptors by monocytes (in vitro) (38,39) and reduction in monocyte secretion of proinflammatory cytokines interleukin (IL)-6, IL-12, tumor necrosis factor alpha, and prostaglandin E2 (40–42). Vitamin D receptors also are found on T lymphocytes, which increase with application of 1,25(OH)2D (29), and this in turn, directly impacts T-cell proliferation and associated cytokines. Specifically, IL-2, IL-6, interferon gamma, and granulocyte–macrophage colony-stimulating factor production (proinflammatory effectors that are part of the proinflammatory Th1 “pathway”) are inhibited by 1,25(OH)2D in vitro. Similarly, 1,25(OH)2D promotes an increase in Th2 anti-inflammatory cytokines (43–48). In experimental allergic encephalomyelitis (EAE), the widely accepted model of MS, administration of 1,25(OH)2D before EAE induction has prevented the appearance of MS symptoms, whereas administration after EAE induction has led to disease amelioration, with reduced disability and increased survival time (36,49–52). Studies have shown that the absence of vitamin D receptors negates these effects (31,53). Gender may influence the effect of vitamin D supplementation on EAE outcomes. When EAE animals were supplemented with vitamin D3, the precursor of 1,25(OH)2D, only female mice with functioning ovaries had beneficial neurological outcomes (54,55).

**Vitamin D and Central Nervous System Demyelinating Diseases: Key Questions**

**Does Vitamin D Supplementation Impact Multiple Sclerosis Risk and Prevalence?**

It is not currently known what serum 25(OH)D level the “average” person should aim to attain, or what the amount of UVR exposure and/or vitamin D supplementation is required to achieve this. Normal 25(OH)D values measure between 50 and 80 nmol/L (57), albeit this is somewhat controversial (57,58). To reach a value of ≥75 nmol/L, the average adult requires 1,500 to 2,000 IU/d of supplemental vitamin D, whereas a child requires at least 1,000 IU/d (59). There is evidence to suggest that the degree of vitamin D deficiency impacts MS risk. In a prospectively designed nested case–control study of American servicemen (60), 25 (OH)D levels at enlistment among those who later developed MS showed a striking risk threshold: healthy, non-Hispanic whites with an entry serum 25(OH)D level of ≥100 nmol/L had a 50% reduced risk of developing MS vs those with levels below 75 nmol/L (61). There was a decreased risk of MS (OR = 0.38, 0.19–0.75) in whites with serum 25(OH)D in the highest quintile (99.1–152.9 nmol/L) vs those in the lowest quintile (less than or equal to 63.3 nmol/L). In the Nurses’ Health Study and Nurses’ Health Study II, Munger et al (61) found parallels in dietary vitamin D intake and MS risk. The pooled age-adjusted relative risk comparing women in the highest quintile of total vitamin D intake at baseline with those in the lowest was 0.67 (0.40–1.12). Intake of vitamin D from supplements was also inversely associated with the risk of MS; the relative risk comparing women with intake of greater than or equal to 400 IU/d with women with no vitamin D supplementation was 0.59 (0.38–0.91). A review of cases

**FIG. 1.** Geographic pattern of multiple sclerosis prevalence and latitude and ultraviolet exposure worldwide [modified from reference (17)].
with MS that came out of the Nurses’ Health Study also revealed that predicted 25(OH)D levels in the mothers of incident and prevalent MS cases were inversely associated with MS risk in their daughters (40% lower when comparing the highest to lower quintile [mean intake 350 and 65 IU/d, respectively]) (61). The impact of vitamin D and future risk of MS among CIS patients was addressed by Martinelli and colleagues (62). Cox proportional hazard modeling revealed that hazard ratios of converting to MS for very low (<10th percentile) and low (<25th percentile) 25(OH)D levels were 3.11 (1.25–7.71) and 1.89 (0.96–3.70), respectively. Thus, those in the lowest vitamin D serum level groups had the greatest risk. In a separate analysis of men and women, at 25(OH)D levels measuring <25th percentile, there was a relatively greater increase in the risk for MS in women (63). Vitamin D level and exposure in early life may be associated with future development of MS. Mirzai et al (62) found that vitamin D levels and ingestion during pregnancy affected the risk of MS in female offspring when evaluating the Nurses’ Health Study. A study of UVR and MS in Newfoundland showed that UVR/vitamin D status at a period as early as in utero might contribute to future MS risk (20).

Is There Evidence That Vitamin D Treats the Inflammatory Manifestations of Multiple Sclerosis?

Relapses

Observational studies have shown a relationship between vitamin D, sun exposure, and relapse events. In an Australian longitudinal study (64), 145 relapsing-remitting multiple sclerosis (RRMS) patients were followed for more than 2 years with serial 25(OH)D measurements performed every 6 months. The authors found that for every 10 nmol/L increase in serum 25(OH)D, there was a 9% reduction in relapse risk and that with serum levels of 25(OH)D of roughly 100 nmol/L, there was more than an 80% reduction in the hazard rate of relapse. Mowry et al (65) prospectively followed patients with pediatric onset MS and CIS. Among 110 patients, for every 25 nmol/L increase in adjusted 25(OH)D level, there was a 34% decrease in the rate of subsequent relapse events (65). In an observational study, 156 patients were evaluated with respect to 25(OH)D and relapse rate before and after initiation of disease modifying medications (DMTs) for MS (66). In 76 patients, DMT was started before vitamin D supplementation by 4.2 years (±2.7 years), whereas both treatments were started simultaneously in 80 patients (67). With supplementation, the 25(OH)D level increased from 49 ± 22 nmol/L to 110 ± 26 nmol/L on average. Pooling of data showed a strong impact of the addition of vitamin D on relapse rate: every 10 nmol increase in 25(OH)D level was associated with a reduction in the relapse incidence rate of 13.7%, although there seemed to be no added benefit above a 25(OH)D of 110 nmol/L. In related work, Scott et al (67) showed that among 118 patients using natalizumab, 45 were vitamin D deficient. Sixteen of 26 patients with MS-related relapses in the year before vitamin D testing, and 12 of 17 with relapses after testing were noted among the vitamin D–deficient patients. Patients who were vitamin D sufficient had

FIG. 2. Vitamin D and immune effectors involved in multiple sclerosis [modified from reference (32)].
significantly fewer relapses pretesting and posttesting (67). Notably, studies have shown that 25(OH)D levels are reduced during relapses as compared with periods of remission (68,69) need to be viewed with caution because it is not possible to determine whether sun-avoidant behavior at the time of relapse is a contributing factor.

Early trials of vitamin D supplementation for MS were methodologically flawed either by design or agent choice (70,71), but in more recent years, a small number of more appropriately designed vitamin D treatment trials have been completed. James et al (72) performed a meta-analysis of interventional trials studying the impact of vitamin D on MS relapses, finding a total of 5 studies acceptable for inclusion. Three studies used vitamin D3, 1 used vitamin D2, and 1 used calcitriol. Overall, an impact on relapse events was not found, although the small sample size and heterogeneity of study design and treatment regimen were likely contributors. However, some trials did show a trend toward fewer relapse events in the high-dose vitamin D trial with an OR = 0.31 (0.08–1.21) (73). Using data obtained from the SENTINEL natalizumab trial (in which patients received intramuscular interferon beta-1 alpha with or without natalizumab), Ascherio et al (74) evaluated evidence of MS disability and progression. Serum 25(OH)D values were measured at baseline and 6, 12, and 24 months. A 50-nmol/L increment in mean serum 25(OH)D levels in the first 12 months predicted a 57% lower rate of new active lesions (P < 0.001), 57% lower relapse rate (P = 0.03), 25% lower annual increase in T2 lesion volume (P < 0.001), and 0.41% lower annual loss in brain volume (P = 0.07) between months 12 and 60. Likewise, Ascherio et al (74) studied patients with respect to 25(OH)D measures and MS outcomes within the BENEFIT (The Betaferon/Betaseron in Newly Emerging multiple sclerosis For Initial Treatment) trial, which was designed to assess the impact of interferon beta-1 beta in delaying conversion of CIS to MS. Overall, the relapse rate decreased by 27% for a 50-nmol/L increment in 25(OH)D, but this value did not reach statistical significance. Changes in disability were also found between the groups above or below a 25(OH)D of 50 nmol/L, but this value was not clinically significant (74). Currently, several large-scale, DMT add-on trials of relatively high-dose vitamin D are underway, including a trial of glatiramer acetate ± 5,000 IU/d or 600 IU/d of vitamin D3 (75), the SOLAR trial of interferon beta-1 alpha subcutaneous ± 14,000 IU/d of vitamin D (77), and the CHOLINE trial, also of interferon beta-1 alpha subcutaneous ± twice monthly infusions of 100,000 IU of vitamin D3 (77).

Magnetic Resonance Imaging
In 2000, Auer et al (78) reported a striking, near sinusoidal annual variation in the number of active magnetic resonance imaging (MRI) lesions in 53 MS patients, positioning a variety of potential explanations including infectious agents and/ or UV exposure. Embry et al (79) argued that vitamin D status could explain these observations because 25(OH)D also shows a near sinusoidal annual fluctuation at higher latitudes. These investigators evaluated the published monthly 25(OH)D levels in 415 people in tandem with the data from Auer and found that third-order polynomial curves fit both the 25(OH)D and lesion data significantly. When the 25(OH)D data were lagged by 2 months, there was a close correspondence between the 2 curves with high levels of 25(OH)D correlating with low levels of lesion activity and vice versa. A randomized placebo add-on trial in Finland compared MRI outcomes in 2 groups of patients using interferon beta-1 alpha: one group received 20,000 IU/d of vitamin D3, whereas the second group took placebo more than 12 months (80). Although the primary outcome of T2 lesion burden of disease did not differ between groups, secondary outcomes of total number of T1 gadolinium-enhancing lesions showed a greater degree of decrease in the vitamin D group (P = 0.004). Mowry et al (81) evaluated the relationship between MRI lesion activity and 25(OH)D levels in patients with CIS or RRMS. Annual 25(OH)D levels were evaluated for an association with subsequent new T2-weighted and gadolinium-enhancing T1-weighted lesions on brain MRI, clinical relapses, and disability. A total of 2,362 MRI scans were acquired from 469 subjects. In multivariate analyses, each 25 nmol/L 25(OH)D level was associated with a 15% lower risk of a new T2 lesion (incidence rate ratio = 0.85, P = 0.004) and a 32% lower risk of a gadolinium-enhancing lesion (incidence rate ratio, P = 0.002) (82). In the aforementioned BENEFIT trial (74), the relative decrease in T2 lesion volume for a 50-nmol/L increase in 25(OH)D was 20% per year (P < 0.001). The same 25(OH)D increase was associated with a 0.27% lower rate of brain loss/atrophy in all patients, and the overall 25(OH)D-associated annual difference in brain volume loss for a 50-nmol/L increase in 25(OH)D was 0.41%.

Vitamin D, Demyelinating Disease, and the Visual System
Interrogating the Afferent Visual Pathway Model of Multiple Sclerosis to the Impact of Vitamin D on Central Nervous System Demyelination
As a putative model of MS, the afferent visual pathway (AVP) model, with optic neuritis (ON) as its relapse “prototype,” offers several potential advantages (82). The AVP allows for precise localization and, in the setting of acute ON, provides objective evidence of a symptomatic lesion involving optic nerve, which can be anatomically localized in the CNS. Additionally, the AVP is a functionally eloquent CNS system, and deficits therein can be captured with reproducible measures of visual function including high- and low-contrast visual acuity, automated perimetry, and color vision testing. Furthermore, optical coherence tomography (OCT) provides structural measures of neuronal and axonal integrity in the AVP. By pairing OCT
measures with quantitative visual outcomes, it is feasible to devise a structural–functional paradigm to elucidate the temporal evolution and relative contributions of inflammation, axonal loss, neuronal damage, and cortical compensation to post-ON recovery. The AVP model can be used to monitor tissue specific factors that underlie injury and repair in the CNS of MS patients.

Does Vitamin D Have an Impact in Patients With Optic Neuritis?
Clinical studies suggest that the administration of vitamin D3 supplements to ON patients with low serum vitamin 25 (OH)D levels may delay the onset of a second clinical attack and the subsequent conversion to MS. Malik et al (84) studied adult (n = 253) and pediatric (n = 38) patients presenting with an ON first demyelinating event. Men (adjusted OR = 2.28, P = 0.03) and ON patients with severe attacks (adjusted OR = 5.24, P < 0.001) had poorer recovery post-ON. Recovery was significantly better in the pediatric vs adult group. Season-adjusted vitamin D level was associated with ON attack severity (OR for 10-U increase in vitamin D level = 0.47; 95% confidence interval, 0.32–0.68; P < 0.001), but not recovery.

The authors are currently evaluating the potential neuroprotective effects of vitamin D status on ON recovery, finding that vitamin D deficiency (25(OH)D ≥ 80 nmol/L) at ON onset is associated with less thinning on OCT measures of intereye retinal nerve fiber layer thickness and ganglion cell layer (GCL) values at 6 months (84). Evidence linking vitamin D with disease outcomes in neuromyelitis optica spectrum disorders (NMOSD) is sparse. Kimbrough et al (85) have shown that along with vitamin D deficiency, other features associated with eventual diagnosis of NMOSD included longitudinal extensive transverse myelitis at onset, female gender, African American race, elevated IgG index, an antinuclear antibody titer of 1:160, and antibodies to Ro/SS-A antigen. Similarly, Mealy et al (86) showed that vitamin D levels were significantly lower in patients who developed recurrent spinal cord disease, adjusting for season, age, sex, and race. In this study, vitamin D insufficiency was also linked to disability in NMOSD patients.

Vitamin D and Demyelinating Disease: Unanswered Questions

Is Vitamin D Neuroprotective?
Although the evidence to support an anti-inflammatory role for vitamin D in demyelinating disease is widely accepted, proof of a neuroprotective effect remains elusive. Animal studies have shown at least 2 novel actions of relatively low concentrations of 1,25(OH)2D on neurons, including a direct neuroprotective action against excitotoxic insults and a decrease in both L-type voltage sensitive calcium channels activity and mRNA levels of the corresponding pore-forming subunits of the L-type channel (87). Other mechanisms of vitamin D-associated reduction of calcium levels in the CNS involve stimulation of calcium-binding proteins (parvalbumin and calbindins) and the inhibition of brain gamma glutamyl transpeptidase. Nanomolar concentrations of calcitriol protect neurons from the effects of free radical species such as superoxide and hydrogen peroxide. Furthermore, calcitriol reduces nitrous oxide levels by inhibiting the expression of inducible nitric oxide synthase in the spinal cord and brain and induce neurotrophins (88).

In clinical studies of demyelination, evidence of neuroprotection would typically include long-term clinical monitoring and MRI metrics including brain atrophy measures. Using the AVP model, it has been shown that GCL thinning representing neuronal loss post-ON is worse among patients with a serum 25(OH)D < 80 nmol/L (84).

CONCLUSIONS
There is mounting evidence physiological, experimental, epidemiological, genetic, and immunological arguments supporting a role of hypovitaminosis D in the risk of MS. From a practical standpoint, vitamin D supplementation is relatively simple, inexpensive, and well tolerated. The wealth of evidence in clinical research suggests that vitamin D supplementation is beneficial in early and relapsing–remitting phases of MS. The potential role for vitamin D in promoting neuroprotection and repair in CNS inflammatory disorders awaits further study.

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Bilateral Optic Neuropathy After Erythematous Rash

Sarkis M. Nazarian, MD, Kelli Y. Shaon, OD, John D. Schwankhaus, MD, Joseph G. Chacko, MD, Patricia A. Hudgins, MD, Daniel J. Brat, MD, PhD

Dr. Nazarian:

A 58-year-old farmer with a history of hypertension and hyperlipidemia was evaluated for a 2-day history of sudden painless binocular vision loss. He described “hazy darkness” in both eyes, “like sunglasses,” that had started peripherally and spread centrally. Visual acuity was 20/50 in the right eye and 20/40 in the left eye. There was bilateral optic disc swelling. A few weeks before his vision declined, the patient developed an erythematous rash that had started on his back and spread centrifugally onto his extremities, sparing his palms and soles (Fig. 1). He had experienced a headache, fever, and generalized malaise at the time the rash, which had been diagnosed as a heat rash while working on his farm. He had been treated with a cortisone injection, and the rash began to clear a few days later.

The patient was admitted to a local hospital. A lumbar puncture revealed a normal opening pressure, elevated protein of 100 mg/dL (normal: 15–45 mg/dL), 50 red blood cells (RBC)/high power field (HPF), and 13 white blood cells/HPF (90% lymphocytes). His visual acuity declined to 20/100 in the right eye and 20/100 in the left eye. He was treated with intravenous methylprednisolone for presumed bilateral anterior optic neuritis and, with no improvement in his vision, he was referred to our neuroophthalmology clinic for assessment.

On examination, the patient’s visual acuity was 20/150 in the right eye and 20/200 in the left eye, and color vision was reduced bilaterally. Pupils reacted sluggishly to light without a relative afferent pupillary defect. Extraocular movements were full, and anterior segment examination, including intraocular pressures, was normal. Both optic discs were swollen and the retinal veins somewhat dilated (Fig. 2). Kinetic perimetry showed multiple small pericentral islands of residual vision in both eyes (Fig. 3). Magnetic resonance imaging of the brain was obtained.

Dr. Hudgins:

The entire study was unremarkable. This included the use of intravenous contrast and sequences included T1, T2, fluid-attenuated inversion recovery image, gradient echo, and the use of fat suppression. Projections were obtained in the axial, coronal, and sagittal planes.

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FIG. 1. Appearance of skin rash 2 weeks before onset of visual loss. Note that it is raised and erythematous. It also was pruritic.
Dr. Nazarian:
The patient underwent a variety of serological studies, including tests for syphilis, sarcoidosis, brucellosis, toxoplasmosis, systemic lupus erythematosus, and neuromyelitis optica. All gave negative or normal results. Additional history revealed that the patient had suffered a tick bite about 2 weeks before the onset of his skin rash. Based on this information, Rocky Mountain Spotted Fever (RMSF), antigen titers were ordered. RMSF immunoglobulin G (IgG) was positive by solid-phase enzyme immunoassay, and this result was confirmed using an indirect immunofluorescence assay (IFA) at 1:64 dilution.

Dr. Brat:
Indirect IFAs for both IgM and IgG antibodies are most commonly used to diagnose rickettsial infections, but enzyme-linked immunosorbent assays and dot immunoassays also are available. Complement fixation is less sensitive and less frequently used. Immunostaining of biopsied skin rashes also can be performed with the results being available within a few hours; however, the test is only 70% sensitive. Thus, a negative result does not exclude the diagnosis of RMSF. Polymerase chain reaction assays for Rickettsia rickettsii DNA are considered perhaps the most specific test for RMSF overall but are not widely available.

Final Diagnosis:
Bilateral anterior optic neuropathy due to RMSF.

Dr. Nazarian:
The patient was treated with doxycycline 100 mg orally every 12 hours for 60 days. He had slow incomplete recovery of vision over the next several months with resolution of optic disc swelling and development of optic disc pallor. After 6 months, his visual acuity had improved to 20/60 in the right eye and 20/100 in the left eye with improvement in his visual fields (Fig. 3B).

FIG. 2. Bilateral optic disc edema is present with mild dilation of the retinal veins.
secretion of antidiuretic hormone in response to the hypovolemia.

RMSF manifests after a mean incubation period of 7 days with a triad of high fever, myalgias, and headache (2). A centripetal rash starts in the wrists and ankles by days 3–7 and characteristically spreads centrifugally to the palms and soles. It is eventually seen in about half of all patients with RMSF. Close to 5% of patients develop gangrene or skin necrosis, sometimes requiring amputation of the affected extremities. About 10%–15% of patients with RMSF never develop a rash.

Central nervous system manifestations include lethargy and confusion (in about 25% of cases), ataxia (18%), coma (9%–10%), and seizures (8%) (2). Other neurologic manifestations include meningitis, cranial neuropathies, deafness, paralysis, spasticity, vertigo, aphasia, and photophobia. In addition, RMSF may affect the respiratory, gastrointestinal, and renal systems.

Ophthalmic manifestations of RMSF include conjunctivitis, anterior uveitis, retinal vasculitis, hemorrhages, and arterial occlusions. About 1.5% of reported patients develop optic disc swelling (3), including 1 patient with neuroretinitis (4). With optic nerve involvement, patients are usually left with permanent visual impairment.

RMSF responds to tetracycline, doxycycline, and chloramphenicol. The usual doxycycline dosage is 200 mg/d in 2 divided doses. Treatment generally is continued until patients have been afebrile for at least 3 days; the usual treatment course is 7–10 days (1).

**FIG. 3.** Kinetic perimetry. **A.** At onset, there are multiple, small pericentral islands of visual field. **B.** Six months after antibiotic treatment, visual fields are improved. (Stimulus used: IV4e).
Severe cases may require intravenous administration or longer treatment duration. Pregnant mothers usually are treated with chloramphenicol, 50–75 mg/kg daily.

Before the antibiotic era, RMSF had a mortality rate of up to 30%; however, this has dropped to about 3%–5% (1). Nevertheless, it remains the most common fatal tick-borne disease in the United States, with most of the fatalities occurring in the very young and very old, often due to delayed diagnosis and treatment.

REFERENCES
Should Patients With Acute Central Retinal Artery Occlusion Be Treated With Intra-arterial t-PA?

Robert A. Egan, MD, Renee Van Stavern, MD

Pro: t-PA Should Be Given to the Patient With Acute Central Retinal Artery Occlusion: Robert A. Egan, MD

Opening Statement

The management of central retinal artery occlusion (CRAO) is controversial due to lack of large-scale clinical trial data. Currently, patients are treated with conservative measures or with fibrinolysis given intra-arterially or intravenously. This report deals with local intra-arterial fibrinolysis (LIF) only. The goal LIF is to restore vision at a rate greater than conservative therapy currently provides. Because of poor prognosis for visual recovery, I would treat the patient with LIF because I believe that there is a better chance for visual recovery with LIF than without this therapy.

Reasoning

CRAO is the ophthalmic equivalent of a hemispheric stroke and is a medical emergency. The incidence is approximately 1.9/100,000 in the United States (1). Patients typically present with devastating vision loss with little chance for visual recovery. The natural history suggests that 80% of eyes affected by CRAO suffer a final visual acuity of counting fingers or worse (2, 3). Patients who suffer a CRAO also are at increased risk for hemispheric stroke. Anterior chamber paracentesis and carbon dioxide and oxygen (Carbogen) inhalation therapy have been used to help improve the natural course of this disabling ocular condition but are not better than no intervention (4).

Because the pathophysiology of CRAO is akin to that of hemispheric stroke, an assumption can be made that beneficial therapies in 1 disorder may be effective in the other. t-PA, when given intravenously to patients suffering from ischemic cerebral stroke, was found to be efficacious at improving clinical outcomes up to 4.5 hours from onset of symptoms (5, 6). A meta-analysis of 54 studies including 5019 ischemic stroke subjects showed that t-PA given intra-arterially is efficacious and more effective than placebo but seems to offer really no benefit over t-PA when administered intravenously (7).

Both the clinical characteristics and most meta-analyses support the notion that CRAO may respond to LIF. Unfortunately, well-controlled trials regarding the usage of LIF in patients with CRAO are limited. The largest is the European Assessment Group for Lysis in the Eye (EAGLE) study where 84 subjects were recruited from Austria and Germany; 44 received LIF (8). No subject had a symptom duration of longer than 20 hours. Despite the LIF group time interval to therapy being almost 2 hours longer than the conservative treatment group, both arms experienced an improvement in the best-corrected visual acuity. Clinically significant visual improvement was equal between study arms. Adverse reactions occurred in 4.3% of the conservative treatment group and 37.1% in the LIF group. The study was stopped early by the safety monitoring committee. At the time of publication of the results, the authors of the EAGLE study recommended against the routine use of LIF in CRAO.

What most treating physicians agree on is that time is of the essence when treating CRAO. This presents a significant challenge because the percentage of patients with CRAO that do not reach the angiography suite by 8 hours approaches 50% (9). Even in the EAGLE study, the mean treatment time in the LIF group was close to 13 hours after onset of symptoms, an interval, that is, far longer than the time when it is believed that treatment would be effective. Although the exact duration of retinal ganglion cell survival with ischemia is not known, it has been proposed that the limit is between 6 and 6.5 hours (10, 11). Even the EAGLE investigators suggest that the best treatment window lies closer to symptom onset rather than their arbitrary 20-hour treatment window (8). In 1 study, final visual acuity only improved significantly when LIF was administered in less than 6.5 hours after CRAO (11).

Given the lack of efficacy proven in clinical trials, LIF for CRAO should not be routinely administered. The reasoning for this is that interventional centers capable of offering this treatment must be able to demonstrate their ability to catheterize the ophthalmic artery with a low complication rate. Also, centers offering this treatment must also have
a program in place that can deliver patients to the angiography suite in a very timely fashion.

The main argument for continuing for exploring the potential benefits of using LIF in CRAO is that the only “large” randomized trial to date included only 44 patients in the treatment group, a number far too low to draw definite conclusions about benefits and risks (8). My recommendation is for a large multicenter clinical trial to be designed and implemented to study the safety and efficacy of this treatment. A trial of this scope should include a number of treatment centers in North America and Europe that have shown a good track record for the treatment of ischemic cerebral stroke with a low complication rate. Until this time, all patients undergoing LIF for CRAO should be enrolled in a registry to help provide data for planning of this potential treatment trial.

Con: Patients With Acute Central Retinal Artery Occlusion Should Not Be Treated With Intra-arterial tPA: Renee Van Stavern, MD

Opening Statement
The acute management of CRAO is controversial, largely because of the published natural history of a poor visual outcome juxtaposed against the ready availability of intravenous (IV) and endovascular therapies for other vascular disorders affecting the brain. Although thrombolytic and interventional treatments have been studied and are available for acute stroke, there are no large randomized trials in CRAO to help inform practice standards and the evidence available is weak. Current evidence does not support the routine use of intra-arterial tPA for patients with CRAO.

Defense of Position

Timing
The treatment window for intravenous thrombolysis in acute stroke is less than 4.5 hours from the time last known well, and IV tPA trials have consistently demonstrated that time to treatment has an impact on clinical outcome. When intra-arterial therapies are considered, there is an additional delay required to initiate treatment in an angiography suite. Data from the Interventional Management of Stroke pilot trials suggested that patients who achieved angiographic reperfusion less than 7 hours from the time last known well achieved the best clinical outcomes (12). In the EAGLE trial, the only randomized controlled trial examining the use of intra-arterial thrombolysis vs conservative treatment for CRAO, patients were enrolled up to 20 hours from the time last known well, with a mean time from last known well to treatment of 12.78 hours, range 4.75–23.43 hours (13). In addition, patients with CRAO may have additional delays before receiving treatment, as they often present to another health care provider before seeking treatment in an emergency department. In 1 recent retrospective review, fewer than half of the patients with CRAO received an in-hospital evaluation in fewer than 20 hours, with the meantime to emergency department evaluation of 13.1 hours (14). Only 3 of 31 patients presented directly to the emergency department, and there was a mean treatment delay of 5.2 hours when the patient was referred to an in-hospital ophthalmologist from another health care provider.

EAGLE Results and Risk of Harm
The EAGLE study was the first randomized clinical trial to compare the benefit of intra-arterial tPA with conservative treatments in patients with CRAO (8). The treatment groups did not differ in the final analysis of the primary end point of the best-corrected visual acuity. Both treatment groups demonstrated a benefit in the best-corrected visual acuity at 1 month compared with baseline. About 60% of patients in each group had a clinically significant visual improvement, defined as a decrease in logMAR of ≤0.3 at 1 month. Two intracerebral hemorrhages occurred in the intraarterial (IA) treatment group, along with 34.3% experiencing at least 1 minor adverse reaction including 1 ischemic stroke, and 2.1% had minor adverse reactions in the conservatively treated group.

Failure of Interventional Therapies in Acute Ischemic Stroke
More recent interventional treatment trials comparing intra-arterial tPA, clot retrievers, and/or stent retrievers to IV tPA alone have also failed to demonstrate a benefit. The IMS-3, SYNTHESIS, and MR-RESCUE randomized trials each failed to demonstrate superiority of endovascular therapy compared with IV tPA, with a combined total of more than 1000 patients (15–17). IMS-3 and SYNTHESIS included intra-arterial tPA as one of the treatment options in the endovascular arm. Data are not available regarding the number of patients receiving intra-arterial tPA in IMS-3; however, in SYNTHESIS, 109 patients of the 165 randomized to endovascular treatment received intra-arterial tPA alone without the use of other devices. Each of these studies excluded patients with isolated visual loss, as they required NIH stroke scale scores of at least 8.

The benefit of intra-arterial tPA over IV tPA in acute ischemic stroke is suspect, given the available data. However, its use reflects trends supported by other interventional trials in acute stroke using different interventional devices (18, 19). The SWIFT-PRIME, EXTEND-IA, and REVASCAT trials are currently underway and will compare interventional devices directly with IV tPA. Unfortunately, patients with isolated visual loss will not be included in these trials, as enrollment is limited to patients
with moderate-to-severe ischemic strokes and large-vessel intracranial vascular occlusions.

Unknown Benefit of IV tPA in CRAO and Risk of Harm
Given that the basis for using IA tPA is to extend the short treatment window for IV tPA, we would expect to see some demonstrated benefit of IV tPA in patients with CRAO as we have with acute stroke. Part of the purported rationale for using IA tPA in acute stroke is the benefit of IV therapy but with a smaller dose locally delivered to the clot. A phase II, placebo-controlled, randomized trial of IV tPA in CRAO was conducted at multiple hospitals in Australia from 2008 to 2010, enrolling 16 patients (20). The trial found no difference in visual outcomes between the treated and placebo groups at 1 week, 1 month, 3 months, or 6 months. In addition, there was 1 serious adverse event, an intracranial hemorrhage in the tPA-treated group. The average time to treatment delivery was greater than 7 hours in both the groups. Data compiled by Biousse et al (21) in a systematic review of 35 case reports or case series in 2007 revealed a 13% complication rate, including 10 systemic or cerebral hemorrhages, in patients treated with IV tPA. Among those treated with intra-arterial tPA, the overall complication rate was similar, although the adverse outcomes included more ischemic events and fewer hemorrhages. The benefit of both IV and IA tPA in this review seemed to be better than previous natural history studies; however, the outcomes seem to be similar to those reported in the conservative arm of the EAGLE trial.

Rebuttal: Robert A. Egan, MD

I appreciate the cogent arguments put forth by my colleague Dr. Van Stavern. As both of us have stated there is a paucity of data regarding the usage of tPA in CRAO whether it is given intra-arterially or intravenously. I completely agree with her that the benefit of treatment of CRAO is time dependent and that complication rates will likely increase the longer the treatment window.

Another question is whether or not thrombolytics should be given to patients intravenously or intra-arterially. Intravenous therapy can be delivered quickly and safely. Intra-arterial therapy adds time to the treatment window, which is not in favor of clot lysis and beneficial treatment outcomes. Intra-arterial therapy also adds the complication rate associated with catheter manipulation of the extracranial and intracranial arteries.

The restrictions determining patient eligibility for treatment with thrombolytics are also too strict. These include head injury or stroke within 3 months, major surgery within the last 14 days, a history of intracranial hemorrhage, systolic blood pressure over 185 or diastolic blood pressure over 110, rapidly improving symptoms, seizure at onset of stroke, current usage of anticoagulants or prothrombin times greater than 15 seconds, platelet counts less than 100,000 per cubic millimeter, or abnormally high or low blood glucose (6). We must remember that the original criteria establishing the ideal patient to be treated in the NINDS stroke trial published in 1995 were established a priori without any clinical evidence. These likely outdated restrictions may lead to a great reduction in the number of potential patients who could be treated with this drug. This is actually known widely by stroke experts but has not been communicated to treating physicians at large. The most common criterion that is ignored is that of age and many patients are treated safely over the age of 80 now.

The most feared complication of thrombolytic treatment is symptomatic intracerebral hemorrhage (SICH). The criteria of the NINDS trial were established to attempt to reduce this complication. However, as more data are compiled regarding treating these patients, it has been found that patients with NIHSS scores of 7 or less, the equivalent of smaller strokes and smaller areas of potentially affected brain tissue, have a much lower SICH rate than in patients with higher NIHSS scores. In the patient with CRAO, it is presumed that these patients have an NIHSS of 0, which should indicate that they have a very low risk of SICH. Tong et al found that in his series of patients treated with NIHSS scores of \( \leq 7 \), the rate of SICH was 0% and this has been observed before (Tong D, Barzangi N, Rose J, McDermott D, Grosvenor D, Bedenik A, Barakos J. Increasing rt-PA Use using Simplified criteria: the SMART study, personal communication, September 2014) (22–24).

Currently, I would dissuade against common usage of local IA therapy at this time, but believe that it should continue under stringent conditions. This is corroborated by Biousse et al (21). Given the devastating vision loss that occurs, especially in a monocular patient, we have the possibility of restoring vision. My recommendation is that IA therapy in CRAO should only be undertaken in a clinical trial setting or in centers using registries. These centers must have an interventional program that has demonstrated proven expertise with this form of treatment in stroke to help guarantee the lowest complication rates as well as develop a system to attract patients in a very expedited fashion to support intra-arterial therapy within a short time window. All patients should have a stat computed tomography of the head to rule out possible stroke as well as intracerebral hemorrhage. The patients should have a very low NIHSS preferably 0. I believe that dismissing further study of this therapy at this juncture given the poverty of cases reported in the literature would be shortsighted. It is hoped that continued study can determine whether this is a treatment that can benefit patients in the future and that we can also understand why some patients had SICH during treatment, which seems unexpected given data referenced above.
Rebuttal: Renee Van Stavern, MD

Dr. Egan and I agree that intra-arterial tPA should not be used routinely for CRAO, and I also agree with many of his points regarding circumstances when intra-arterial approaches might be considered. My continued concern is patient safety and the risk of intracranial hemorrhage in the trials I originally referenced, which I will emphasize here. Depending on the skill of the examiner, these patients should have National Institutes of Health Stroke Scale (NIHSS) scores of 0-1, 1 perhaps if an inexperienced examiner misinterpreted monocular vision loss to be a hemifield defect. If given IV tPA, patients in this category should have the lowest risk of symptomatic intracranial hemorrhages, about 2% based on a recent pooled analysis that included multiple subgroup studies of those with minor stroke (NIHSS score, 0–5) (22). The symptomatic intracranial hemorrhage rate was 4% in the EAGLE trial and 12.5% in the Australian randomized controlled trial of IV tPA. Although the complication rate in the EAGLE trial is encouraging, a symptomatic hemorrhage rate twice that of patients who have had a completed minor stroke is still troubling, especially considering that there was no difference in the visual outcomes in either trial.

Actively enrolling clinical trials of clot retriever devices may provide an opportunity to investigate this approach in the acute treatment of CRAO in the future. In addition, treating patients with CRAO earlier, less than 6 hours from the time they were last visually and neurologically normal for IA procedures or fewer than 4.5 hours for IV tPA, may demonstrate improved outcomes and minimize harm, as has been seen with IV tPA in acute stroke (23). If intra-arterial thrombolytic or interventional therapies are to be used for CRAO at this point, enrollment in clinical trials, participation in clinical registries, or monitoring outcomes through patient safety and quality improvement initiatives should be encouraged given the weakness of the evidence.

CONCLUSIONS

There is a natural bias toward wanting to treat any patient presenting with acute profound vision loss. There is ample evidence supporting the use of IV tPA for acute cerebral stroke, and it is tempting to try and extrapolate these data and apply them to acute CRAO. Our experts have done an excellent job reviewing the arguments for and against the use of IA tPA in acute CRAO. At this time, the use of IA (as well as possibly IV) tPA for acute CRAO should be considered only on a case-by-case basis (e.g., in a patient presenting with severe visual loss in the fellow eye), or as part of a randomized clinical trial. Including any treated patients in a registry, with assessment of clinical outcomes in part of a randomized clinical trial. Including any treated patients in a registry, with assessment of clinical outcomes might provide further evidence for or against treatment.

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The North American Neuro-Ophthalmology Society, in conjunction with the American Academy of Ophthalmology, established the annual Hoyt Lecture in 2001 in honor of William Fletcher Hoyt, MD, whose contributions to neuro-ophthalmology have spanned seven decades. A fellow of Frank Walsh, MD, the grandfather of clinical neuro-ophthalmology, Dr. Hoyt co-authored the 3rd edition of Clinical Neuro-Ophthalmology, the “bible” of our specialty. A faculty member of the departments of Ophthalmology, Neurology and Neurosurgery at the University of California San Francisco since 1958, Dr. Hoyt is world-renowned as a clinician, scholar and educator. He has published more than 300 scientific contributions and has trained more than 100 fellows, many of whom are senior professors in their own right, training the next generations of neuro-ophthalmologists on six continents.

I must acknowledge two of my mentors, at NYU Medical Center/School of Medicine who shaped my career. The neurosurgeon Dr. Joseph Ransohoff (See Supplemental Digital Content, Figure E1, http://links.lww.com/WNO/A154) understood the complexity of neurosurgical problems and was never reluctant to ask for help and other opinions. Dr. Albert Goodgold (See Supplemental Digital Content, Figure E2, http://links.lww.com/WNO/A155), a brilliant neurologist, who questioned every unsubstantiated neurological concept, pressed to apply new knowledge, and was a master of uncovering iatrogenic-induced disease. From these two individuals, I learned that in order to advance clinical care, we have to read critically and question prevailing concepts if supporting evidence is lacking. Do not be afraid to admit you do not know. Have a “golden rolodex” of individuals you respect and who have knowledge complementary to your own to call for help.

Now, let us turn to the applied science of optical imaging of the pathological changes in the optic nerve. Fortuitously, this topic grew out of findings reported by Dr. Hoyt and one of his fellows, Lars Frisén, MD, demonstrating retinal nerve fiber layer (RNFL) loss in eyes with multiple sclerosis (MS) and, recovered optic neuritis (ON) (1).

For clinical trial design for the Neuro-Ophthalmology Research Disease Investigator Consortium, we researched what type of optical imaging would be the best to study new therapies for 3 optic neuropathies: ON, nonarteritic anterior ischemic optic neuropathy (NAION) and papilledema. When we began our projects, except for evaluating the RNFL in ON, few prospective studies had been done. We also were limited...
because RNFL thickness, the major optical imaging parameter in use to determine axonal loss, may not be normal due to optic nerve head (ONH) swelling and may not have been a suitable baseline to determine future RNFL thinning.

HISTORICAL BACKGROUND OF RETINAL NERVE FIBER LAYER ASSESSMENT

Frisén and Hoyt had photographically demonstrated nerve fiber layer defects in eyes with glaucoma and recovered ON (1,2). This predated by many years the realization that attacks of MS often caused permanent loss of axons even if visual acuity recovered. However, it took the development of optic coherence tomography (OCT) and scanning laser polarimetry (SLP) to provide quantitative measurement of RNFL thinning in a variety of optic nerve disorders. These and other techniques can show injury to peripapillary retinal axons and ganglion cells before RNFL thinning can be demonstrated and assist in clinical decision making. OCT can demonstrate dynamic shape changes in the ONH due to glaucoma, papilledema, and optic disc drusen. Importantly, optic imaging can be used to address pathophysiologic mechanisms affecting the optic nerve.

RETINAL NERVE FIBER LAYER THINNING AFTER ACUTE OPTIC NEURITIS: BASELINE AND THE IMPORTANCE OF 1 MONTH FINDINGS

OCT evaluation performed several months or longer after the onset of ON revealed that reduction in the global mean RNFL thickness was more prevalent in eyes with persistent visual field deficits (3). In order to investigate potential mechanisms of early neural injury or peripapillary change as well as the rate of structural alteration or loss over time, we studied patients with acute ON at presentation, typically within 14 days of vision loss. One month had been reported to be the earliest time point to predict vision outcome from an attack of ON (4). In a study of 40 eyes with acute ON, evaluating the OCT measured RNFL thickness by comparison with the normal fellow eye revealed that axonal swelling was much more common than is seen clinically (5). RNFL swelling was found in 80% of eyes when compared with normal fellow eye and in 33% of when compared with control eyes. Thus, OCT can show swelling in the ONH region at a higher rate than seen on ophthalmoscopy. No RNFL thinning was seen at presentation. By 1 month, using interocular comparison of clock hour sectors, RNFL thickness revealed thinning in 54% of affected eyes. However, RNFL swelling of some amount was detected in 82% of affected eyes at 1 month (Fig. 1). Without the persistent swelling, it is possible that more global or regional axonal loss might have been demonstrated. As a cautionary note, sector analysis, due to variability, must be carefully applied and requires precise alignment of images.

RETINAL NERVE FIBER LAYER CHANGES IN OPTIC NEURITIS OVER 6 MONTHS

We and others suggested that OCT evaluation of the RNFL changes over time to 6 months could provide structural correlates to complement the Optic Neuritis Treatment Trial results, which demonstrated that the 6-month vision performance is an accurate measure of functional outcome for a given episode (6). We also questioned whether
measurement of neuronal structural loss can be used to monitor the effects of therapy, if OCT would be able to show a time when the majority of RNFL thinning occurs, and if there was significant further thinning of the RNFL thickness after 3 months. Additionally, we hypothesized that eyes with significant RNFL thinning at 1 month, a key time point if functional vision recovery does not occur (4), would also be associated with a poor visual outcome (Fig. 2).

Follow-up of the 40 eyes with ON reported above (5) showed RNFL loss by OCT at 3 months occurred in approximately 60% of affected eyes. The thinning occurred in all quadrants and was not selective. Further evaluation of 25 of these eyes showed the 1 month OCT RNFL loss strongly correlated (r = 0.58, P = 0.001) with the amount of OCT thinning at 6 months (7). Furthermore, the amount of average OCT RNFL thinning at 6 months correlated with the 6-month visual field mean deviation (r = 0.48, P = 0.03). No significant further RNFL thinning occurred at 1 year. These data support previous OCT and SLP reports and the results of the Optic Neuritis Treatment Trial that the 6-month functional and structural outcomes are appropriate to use in investigations of acute ON.

SCANNING LASER POLARIMETRY USE IN ACUTE OPTIC NEUROPATHY WITH OPTIC DISC SWELLING

OCT shows RNFL thickening in eyes with ONH swelling from many causes, but in this setting, it does not provide information on acute axonal disruption or injury. SLP reflects polarization due to intact RNFL axons (8,9) and does not consistently demonstrate ONH swelling in disorders like papilledema or NAION (10). We hypothesized that optical imaging using SLP and OCT together might reveal the status of axon integrity in eyes with acute RNFL swelling. In a prospective study, we evaluated eyes with ONH swelling due to papilledema, ON, and NAION (8). We determined whether regional RNFL values were reduced using criteria of having the OCT or SLP thickness measure of a quadrant be less than the fifth percentile of controls. At presentation, the average RNFL thickness of OCT was similar for eyes with papilledema (213 ± 100 μm) and NAION (214 ± 76 μm, P = 0.97), and less for ON (141 ± 21 μm). In contrast, the average RNFL thickness by SLP was less often increased. It was similar for papilledema (59 ± 7 μm) and ON (55 ± 5 μm) but was reduced for NAION (48 ± 9 μm, P = 0.02) eyes (Fig. 3). The RNFL by SLP was significantly reduced in at least 1 quadrant in 1 of the 24 eyes with papilledema, 1 of the 13 eyes with ON, and in 13 of the 21 eyes with NAION. In NAION eyes, quadrants with reduced SLP had corresponding regional visual field loss that did not recover at 1 or 6 months. By 1 month, eyes with NAION showed RNFL thinning by OCT (41%, mean 111 ± 49 μm) and by SLP (88%, mean 43 ± 9 μm) in contrast to ON (by OCT, 0%, mean 127 ± 16 μm, P = 0.006); and by SLP (9%, mean 52 ± 7 μm, P = 0.0004). The results confirm that OCT and SLP measure different aspects of RNFL changes associated with ONH swelling. OCT reveals thickening, due to edema. SLP reveals a decrease in retardance in eyes with axonal injury associated with visual field loss, which is unlikely to recover. SLP results may be predictive of regions of permanent axon dysfunction and visual field loss in eyes with optic disc edema.

OCT shows anatomical thickening of the peripapillary RNFL no matter what the etiology of the ONH swelling, which is useful for quantifying the degree of edema at presentation and over time. The disadvantage of OCT is that it is relatively insensitive to acute axon damage at the time of presentation and even 1 month later. OCT does not directly measure the dimension of each retinal layer. RNFL birefringence induces delay in 1 of 2 orthogonal beams of polarized light passing through the bundles of nerve fibers. This slowing measured in the reflected light is termed retardance. The retardance is used to calculate RNFL thickness, which is proportional to the birefringence. The SLP retardance is primarily dependent on the integrity of the parallel structural organization of axon plasma membranes, intracellular microtubules, and neurofilaments, which produce birefringence (11,12).

Therefore, SLP would not be expected to reveal an increase in RNFL thickness to the same extent as OCT in conditions of optic disc edema having intact axons with retained intra-axonal cellular organization (5,10). SLP showed a decrease in retardance or birefringence (resulting in a decrease in the derived RNFL thickness) in a large number of the NAION eyes at presentation and at 1 month while optic disc edema was still present. The importance of this finding was that OCT did not show RNFL thinning or loss in any of the affected quadrants for any of the 3 disorders at presentation. The greatest disparity between OCT and SLP

FIG. 2. Optic neuritis eyes with severe vision loss (less than 20/50) at 1 month shows more severe RNFL loss at 6 months than eyes with good vision (20/50 or better) at 1 month. RNFL, retinal nerve fiber layer.

FIG. 3. Examples of OCT and SLP comparisons for eyes with swollen optic nerve head. A. Papilledema eyes have significant thickening of the entire RNFL by OCT (left) and no thickening by SLP (right). B. Optic neuritis with severe visual field loss at presentation in the left eye shows RNFL thickening (right side of plot) by OCT (left) and slight thickening (right side of plot) in comparison with normal right eye by SLP (right). C. NAION in right eye with inferior altitudinal field defect shows RNFL thickening (left side of plot) by OCT (left) and a reduced RNFL thickness in the superior quadrant (left side of plot) by SLP (right). OCT, optical coherence tomography; SLP, scanning laser polarimetry; RNFL, retinal nerve fiber layer; NAION, nonarteritic anterior ischemic optic neuropathy.
values for RNFL at presentation was seen in eyes with NAION, suggesting that in the setting of ischemia, optic disc edema, and visual field loss, SLP may be unique in revealing early disruption of intra-axonal microtubular and neurofilament structure, which may be an early sign of potentially permanent axon loss. Conversely, regional areas that are normal by SLP in acute NAION may not have yet developed the axonal changes associated with inevitable injury and might indicate potential location for recovery from ischemia. This delay in evolution to a more degenerated state might be an explanation for why not all eyes with NAION examined with SLP showed RNFL reduction at presentation. Similarly, since significant permanent vision and axon loss are not as common in papilledema and acute ON, this may explain why SLP-derived RNFL measurements were infrequently thinned on presentation for these 2 disorders.

In a report of 25 eyes with acute NAION, we correlated the SLP findings with visual field threshold and RNFL values organized into Garway–Heath inferior and superior disc sectors and corresponding superior and inferior field regions (9). At presentation, no eyes had reduced RNFL thickness by OCT. Eyes with abnormal field regions had corresponding SLP sectors thinner ($P = 0.003$) than for sectors with normal field regions. During the acute phase, the SLP-derived sector correlated with presentation ($r = 0.59, P = 0.02$) and with at least 3 month post presentation ($r = 0.44, P = 0.02$) corresponding superior and inferior field thresholds (Fig. 4). Since the visual field deficits often show no significant recovery,

GIVEN THE RESULTS IN NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY, WE STUDIED SLP IN ACUTE OPTIC NEURITIS

Using the OCT and SLP RNFL data in 10 eyes with acute ON, we calculated a relative birefringence for each time point. This was derived using a ratio of percent of thickness change using the OCT and the percent retardance change using the SLP. The RNFL relative birefringence was approximately $-17.7\%$ at presentation and gradually rebounded over 6 months (13) (Fig. 5). RNFL swelling due to ON (5) appears to be principally due to increased water content. This is due to intra-axonal edema from axoplasmic flow stasis, which then becomes extracellular as the process progresses. OCT-derived RNFL thickness would be expected to reflect both intracellular and extracellular components. In contrast, SLP does not directly measure the actual dimension of each retinal layer but measures retardance that is primarily dependent on the integrity of the parallel structural organization of axon plasma membranes (11).

The relative birefringence reduction in eyes with ON at presentation could reflect permanent injury, but it is transient in ON. The acute calculated drop in
birefringence may result from reduction in microtubule density due to intra-axonal swelling, which dilates axons or microtubular alterations in response to injury or from extracellular edema (14–16).

**RETNAL GANGLION CELL LAYER MEASUREMENT IN ACUTE OPTIC NEUROPATHY AND/OR PAPILLEDEMA**

Since ONH swelling can prevent accurate OCT evaluation of early structural axonal loss, we sought another region of the optic nerve to study. Measurement of the retinal ganglion cell layer (GCL) in the macula was a potential candidate for demonstrating permanent neuronal injury that would be less susceptible to the effects of ONH swelling. In 38 eyes with acute NAION and 29 eyes with acute ON, we prospectively used spectral domain optical coherence tomography (SD-OCT) to image the macula and applied 2 methods to measure the GCL plus inner plexiform layer (IPL) thickness (17,18). One method, developed by the University of Iowa, used 3 dimensional (3D) layer segmentation (19), and the second method used the OCT machine software, a 2D segmentation algorithm. At presentation, affected eyes did not demonstrate significant thinning of either the RNFL or GCL + IPL thickness by 3D segmentation. The mean macula GCL + IPL values, 80 ± 8.1 μm for NAION and 83 ± 8.9 μm for ON eyes, were not different from unaffected fellow eyes (83 ± 6.4 μm and 82 ± 7.0 μm), using 3D segmentation. In 17 of 57 eyes with NAION (14) or ON (3), the 2D method (46 ± 9 μm) values for GCL + IPL were markedly less than through the 3D method (83 ± 7 μm; \( P = 0.001 \)) values at presentation (See Supplemental Digital Content, Figure E3, http://links.lww.com/WNO/A156). All 17 eyes had 2D method GCL + IPL values ≤20 μm than the values for the 3D method. The initial lower GCL + IPL values from the 2D method rebounded and were thicker by more than 10 μm in these eyes at the next visit (1 month) as the ONH swelling decreased.

At 1 month, GCL + IPL thinning developed in 84% of all affected eyes, and the decrease was greater in NAION eyes. For the 3D segmentation method, the mean change was -17.2 ± 12.3 μm and -9.0 ± 6.2 μm, for NAION and ON eyes, respectively (\( P = 0.001 \)). At 1 month, GCL + IPL thinning correlated with the 1-month LogMar acuity (\( r = 0.36, P = 0.04 \)) and visual field mean deviation (\( r = 0.61, P = 0.001 \)) for NAION but not for ON eyes, due to recovery of function in these latter eyes. In contrast, although there was reduced RNFL swelling and/or thickening, the RNFL thickness was less than controls in only 11% of eyes with both disorders. Reduction of GCL + IPL thickness occurred rapidly in both NAION and ON, but it was more profound in NAION eyes. GCL thickening occurred before RNFL loss, making it a better biomarker of early structural loss in both NAION and ON.

The 2D method for determining GCL thickness frequently fails when the peripapillary RNFL or macula are considerably thickened, presumably due to edema or factors that distort normal retinal layer architecture. This algorithm failure caused the average GCL + IPL thickness at presentation to appear significantly less. The 2D method uses an algorithm that assumes a quantitative relationship between the internal limiting membrane and the other layers of the retina. Thus, this method would be more susceptible to failure with any process, such as edema due to swelling of the peripapillary RNFL and adjacent retina, which disrupts the regular retinal layer position or shape or boundaries. In contrast, the 3D segmentation method uses an algorithm that incorporates 3D contextual information into the optimization process which in general helps to reduce failures due to local distortions in retinal layers. It is clinically important to carefully evaluate algorithm performance in OCT scans, since failures may lead to false interpretations of data and may adversely influence clinical decisions.

**SPECIFICS FOR OPTICAL IMAGING OF PAPILLEDEMA**

Commercially available algorithms, typically using 2D segmentation methodology, also frequently fail to accurately measure the degree of RNFL thickening when ONH swelling due to severe papilledema (20) (Fig. 6). We attempted to improve the imaging to measure the effects of papilledema and enhance the reliability and accuracy of the OCT images to be collected in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT). Our pilot work demonstrated that multiple OCT measures of swelling in the ONH region can be used to follow papilledema and uncovered a dynamic alteration of the ONH shape from factors outside of the globe such as increased pressure in the perioptic subarachnoid space.

**OPTIC NERVE HEAD SHAPE CHANGES**

The deformity of ONH structures, particularly the peripapillary Bruch membrane (BM) and retinal pigment epithelium (RPE) layers, due to papilledema was first noted by Patrick Sibony, MD, as we began applying various programs to reliably image and quantify the effects of papilledema. This observation leads us to conduct studies using SD-OCT to examine the biomechanical deformation of load bearing structures of the ONH resulting from raised intracranial pressure. We postulated that elevated intracranial pressure would create forces in the retrolaminar subarachnoid space that could cause the observed deformity. As a pilot project, we compared ONH shape and RNFL findings in eyes with papilledema (with a wide range of duration and vision loss) due to raised intracranial pressure to findings in eyes with optic disc swelling due to acute ON and NAION, conditions without intracranial hypertension (21,22). The RPE/BM complex at the temporal and nasal borders of the neural canal opening was noted to be deflected...
inward in 20 of 30 eyes (67%) in the 15 patients with papilledema (Fig. 7). In contrast, only 1 of 8 ON eyes (12%) and 1 of 12 NAION eyes (8%) had inward deflection of either border. Of the 22 eyes with papilledema that had less RNFL thickening over time, 17 had less inward deflection of the RPE/BM borders. In papilledema, the inward deflection RPE/BM neural canal border appears to reflect the pressure changes in the retrobulbar subarachnoid space. In subsequent work, we showed that interventions that reduce the elevated intracranial pressure have the effect of reducing a “U” shaped RPE/BM displacement more toward the normal “V” shape (23). This was most significant in patients undergoing ventricular shunt procedures. Further application of shape analysis of the neural canal borders shows that OCT can provide non-invasive information of improved or worse elevation of intracranial hypertension even in eyes with atrophic papilledema that are not capable of showing significant RNFL or ONH swelling (Fig. 8).

Our findings are consistent with experimental studies in dogs. Using confocal scanning laser tomography, Morgan et al (24,25) have shown that intracranial hypertension displaces the optic disc surface and lamina cribosa anteriorly, whereas ocular

**FIG. 6.** When papilledema is severe, the OCT 2D commercial algorithm fails to measure the amount of RNFL thickening. OCT, optical coherence tomography; RNFL, retinal nerve fiber layer.
hypertension displaces the disc surface posteriorly. An increase in cerebrospinal fluid (CSF) pressure resulted in greater anterior displacement than the posterior displacement induced by a corresponding increase in intraocular pressure. The normal lamina cribosa is already slightly bowed backwards (as is the RPE/BM in our controls). This makes it difficult to demonstrate a further increase in the bowing backward until the pressure gradient increases significantly and damages support structures of the ONH as in untreated glaucoma. In the case of raised intracranial pressure, a reversal in the direction of this bowing is seen and may be easier to detect. Additionally, the retrolaminar tissue pressure was shown to be determined by the CSF pressure, and the translaminar pressure gradient was related to the difference between intraocular and cerebrospinal fluid pressures across a wide range of both intraocular pressure and CSF pressures (26,27).

**OPTICAL COHERENCE TOMOGRAPHY MEASURES OF OPTIC NERVE HEAD SWELLING DUE TO PAPILLEDEMA**

OCT has been used to investigate papilledema in single site, mostly retrospective studies. In a prospective multisite clinical trial, we demonstrated that SD-OCT, which provides thickness and volume measurements of the optic nerve and peripapillary retina, can reliably demonstrate structural changes due to papilledema (28,29). At entry, 126 subjects in the IIHTT with mild visual field loss had optic disc and macula region scans collected using a single brand of SD-OCT and software. The images were analyzed using proprietary commercial 2D and custom 3D segmentation algorithms to calculate the RNFL, total retinal thickness (TRT), ONH volume, and GCL + IPL thickness. As expected in papilledema, 90% of eyes had average RNFL thickness greater than 95th percentile of control eyes. The RNFL, TRT, and ONH volume showed strong (r = 0.8) correlations for interocular comparisons. Variability for repeated testing of OCT parameters was low for both 2D and 3D methods, and intraclass correlations were greater than 0.9 except for the 2D method for measuring GCL thickness. In addition, the 2D algorithm derived RNFL, TRT, and GCL + IPL thickness measurements had failure rates of 10%, 16%, and 20% for papilledema eyes, respectively, whereas algorithm failure was uncommon with 3D segmentation–derived measurements (See Supplemental Digital Content, Figure E4, http://links.lww.com/WNO/A157). Only 7% of eyes had GCL + IPL thinning (by 3D segmentation) less than the fifth percentile of normal age-matched control eyes. The RNFL, TRT, and ONH volume strongly correlated (r > 0.67, P = 0.0001) with the Frisén grade of papilledema (30). The results suggest that when 3D segmentation is used, all measurements that reflect ONH swelling, RNFL, TRT, ONH volume (latter 2 measures are not available with commercial algorithms on current OCT machines) can be accurately measured in eyes with papilledema. Furthermore, it is uncommon to detect
a reduction in retinal ganglion cells in eyes with papilledema and mild visual field loss at presentation.

Given the reliability of these OCT measures, we evaluated them all to determine whether they change over time and which might be best at showing the effects of each treatment during the IIHTT. The RNFL, TRT, ONH volume, and GCL + IPL measurements were derived using the 3D segmentation methods. At study entry, OCT values were similar in both treatment groups. At 6 months, the acetazolamide plus weight management group had greater reduction than the placebo plus weight management group for the RNFL (175 vs 89 µm, P = 0.001), TRT (220 vs 113 µm, P = 0.001), and ONH volume (4.9 vs 2.1 mm³, P = 0.001). The RNFL (P = 0.01), TRT (P = 0.003), and ONH volume (P = 0.002) also showed less swelling in subjects in both treatment groups who lost at least 6 percent of the weight at study entry. GCL + IPL thinning was minimal in either the ACZ (3.6 µm) or placebo (2.1 µm) group. The RNFL, TRT, and ONH volume demonstrated moderate correlations (r = 0.48–0.59, P ≤ 0.0001) with Frisén grade. At 6 months, the GCL + IPL thickness was less than the fifth percentile of controls in 14 eyes, and these eyes had worse perimetric mean deviation (P = 0.001) than study eyes without GCL + IPL thinning. Reduced swelling as shown by reduction in the RNFL, TRT, and ONH volume measurements in IIH provides structural data to confirm the effectiveness of acetazolamide and weight loss in patients with mild vision loss at presentation. Retinal ganglion cell atrophy or loss appears to be uncommon in treated patients.

**SUMMARY**

Although we are still early in the evolution of optical imaging of the optic nerve, the available techniques already play an important role in clinical decision making. I would summarize our findings to date as follows:

For acute ON:

Presentation: OCT shows RNFL swelling, normal GCL + IPL by OCT; 1 month: OCT and SLP show RNFL thinning and swelling, GCL + IPL thinning by OCT; 3 months or later: OCT and SLP show RNFL thinning, further mild GCL thinning by OCT; 6 months: RNFL and GCL + IPL thinning finished.

For acute NAION:

Presentation: OCT shows RNFL swelling and SLP shows loss of birefringence, normal GCL + IPL by OCT; 1 month: RNFL swelling and thinning by OCT and thinning by SLP, GCL + IPL thinning by OCT; 3 months or later: RNFL and further mild GCL + IPL thinning; 6 months: RNFL and GCL + IPL thinning finished.
For IIH Papilledema with mild vision loss:
Presentation: OCT shows swelling of RNFL, TRT, and ONH volume;
Presentation: OCT shows normal GCL + IPL;
Presentation: OCT shows neural canal border inward deflection;
6 months: OCT shows structural shape changes reflecting the effectiveness of treatment.

ACKNOWLEDGMENTS
I wish to thank a number of individuals who provided critical support and expertise for the research studies described in this Hoyt Lecture. They include Randy Kardon, MD, PhD, Mary Durbin, PhD, Mona Garvin, PhD, Jui-Kai Wang, MS, Patrick Sibony, MD, and John Keltner, MD.

REFERENCES


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Intracranial aneurysms, especially those of the internal carotid artery (ICA), can present with cranial nerve (CN) palsies. The Pipeline Embolization Device (PED) has demonstrated safety and efficacy in the treatment of cerebral aneurysms by flow diversion, but little data exist reporting the outcomes of cranial neuropathies after treatment with the device.

**Methods:** The prospectively maintained Barrow Neurological Institute’s endovascular database was reviewed for all patients treated with the PED after presenting with 1 or more CN palsies secondary to a cerebral aneurysm since May 2011. Patient charts and digital subtraction angiograms were reviewed to report clinical and angiographic outcomes. Only patients with clinical follow-up were included in the analysis.

**Results:** A total of 127 patients were treated with the PED at the authors’ institution after Food and Drug Administration approval. Twenty-two patients presented with cranial neuropathies, for initial inclusion in this study. Of these patients, 20 had sufficient follow-up for analysis. Cranial neuropathies included those of CN II, III, V, and VI, with presenting symptoms of diplopia, decreased visual acuity, and facial numbness and/or pain. Thirteen lesions were cavernous segment ICA aneurysms, whereas the remainder included supraclinoid and petrous segment ICA, posterior communicating artery, and basilar trunk aneurysms. At an average clinical follow-up of 9.55 months, 15 patients (75%) had resolution or significant improvement of their cranial neuropathies and the remaining 5 had stable symptoms. Of the 18 patients with angiographic follow-up, 12 (66.7%) demonstrated complete obliteration or small neck residual, whereas 6 (33.3%) had residual lesion. Patients with complete or near-complete obliteration of their lesion were significantly more likely to demonstrate symptomatic improvement at follow-up ($P = 0.009$). Two patients with persistent symptoms were eventually treated with microsurgical bypass. Transient complications in this series included 6 extracranial hemorrhagic complications (30%) related to dual-antiplatelet therapy, all of which were managed medically. There was 1 delayed right ICA occlusion after retreatment that led to microsurgical bypass. In 11 patients, 1 delayed right ICA occlusion after retreatment that led to microsurgical bypass.

**Conclusions:** Intracranial aneurysms presenting with 1 or more CN palsies show a high rate of clinical improvement after treatment with the PED. Clinical outcomes must be weighed against the risks and challenges faced with flow diverters. Further research is warranted for patients whose symptoms do not respond optimally to device placement.

Intracranial aneurysms have been traditionally treated with either surgical clipping or endovascular coiling. Both techniques target the outpouching from the parent vessel. Recently, a new technique using flow diverters has been developed. It targets the endoluminal reconstruction of the parent vessel of the aneurysm (see video at http://www.ev3.net/neuro/intl/flow-diversion/embolization-device-product.htm). Currently, there are 3 types of flow diverters: Pipeline embolization device (PED; Covidien, Irvine, CA), Silk flow diverter (SILK; Balt Extrusion, Montmorency, France), and the Surpass flow diverter (SURPASS; Stryker, Fremont, CA) (1).

Twenty patients were retrospectively analyzed to determine the cranial nerve (II, III, IV, V, and VI) outcome after treatment with the PED for an intracranial aneurysm. Portions of the internal carotid artery were involved in 18 patients (cavernous – 13; paraophthalmic/opthalmic – 4; petrous – 1) and 1 patient each had a basilar or posterior communication artery aneurysm. In terms of symptom outcomes, 4 patients (20%) had resolution, 11 patients (55%) had improvement, and 5 patients (25%) were stable at last follow-up (range, 6–28 months with mean of 9.55 months). No patient had worsening of their symptoms with the PED. Angiographic outcome corresponded to the clinical outcome. Eighty-five percent of the patients either resolved or had improvement of their symptoms with complete or near-complete obliteration of the aneurysm compared with only 15% of the patients with angiographic evidence of a residual aneurysm.

Despite the limitations of this study (few patients, short follow-up time period, lack of formal neuro-ophthalmic examination for many of the patients, and no comparator group) and the need for more studies to investigate the clinical success of flow diverters, this early study is encouraging and highlights the necessity of complete to near-complete angiographic obliteration of an aneurysm to achieve a successful clinical outcome (diplopia, visual loss).

—I. Tariq Bhatti, MD

I agree with you, Tariq, that this is an important early study showing the clinical benefit of PED and the ability to perform the PED along with coil embolization. The point
you make about lack of neuro-ophthalmologic examination is important. Most of the patients in the study had improved cranial nerve function: does that mean the abduction deficit is now 30% instead of 50%? Does that really obviate the need for the patient to occlude one eye? My practice has been to follow these patients clinically and not intervene even if there is a cranial neuropathy. I have had a few patients with significant sixth nerve paresis successfully managed with strabismus surgery, which may be less risky, particularly in an elderly patient. Considering the complication rate in this study, including one case of internal carotid artery occlusion, I think we need more support for this procedure before embracing it.

—Mark L. Moster, MD

REFERENCE


Objective: To assess, in a surgical biopsy cohort of active demyelinating lesions, the diagnostic utility of aquaporin-4 (AQP4) immunohistochemistry in identifying neuromyelitis optica (NMO) or NMO spectrum disorder (NMOSD) and describe pathologic features that should prompt AQP4 immunohistochemical analysis and AQP4-immunoglobulin G (IgG) serologic testing.

Methods: This was a neuropathologic cohort study of 20 surgical biopsies (19 patients; 11 cord and 9 brain), performed because of diagnostic uncertainty, interpreted as active demyelinating disease, and containing 2 or more of the following additional features: tissue vacuolation, granulocytic infiltrates, or astrocyte injury.

Results: AQP4 immunoreactivity was lost in 18 biopsies and increased in 2. Immunopathologic features of the AQP4 loss cohort were myelin vacuolation (18), dystrophic astrocytes and granulocytes (17), vascular hyalinization (16), macrophages containing glial fibrillary acid protein (GFAP)-positive debris (14), and Creutzfeldt–Peters cells (0). All 14 cases with available serum tested positive for AQP4-IgG after biopsy. Diagnosis at last follow-up was NMO/NMOSD (15) and longitudinally extensive transverse myelitis (1 each relapsing and single). Immunopathologic features of the AQP4 increased cohort were macrophages containing GFAP-positive debris and granulocytes (2), myelin vacuolation (1), dystrophic astrocytes (1), Creutzfeldt–Peters cells (1), and vascular hyalinization (1). Diagnosis at last follow-up was multiple sclerosis (MS) and both tested AQP4-IgG seronegative after biopsy.

Conclusions: AQP4 immunohistochemistry with subsequent AQP4-IgG testing has diagnostic utility in identifying cases of NMO/NMOSD. This study highlights the importance of considering NMOSD in the differential diagnosis of tumefactive brain or spinal cord lesions. AQP4-IgG testing may avert biopsy and avoid ineffective therapies if these patients are erroneously treated for MS.

Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorder (NMOSD) are a group of diseases that can be a diagnostic challenge. In some situations, a biopsy specimen, of either brain or spinal cord, is needed to include conditions such as a neoplasm or confirm an inflammatory or demyelinating process such as multiple sclerosis (MS).

The authors of this study did something very interesting and unique. They identified 19 patients who underwent a brain or spinal cord biopsy (total of 20 biopsies) because of the uncertainty of the clinical diagnosis and in most to exclude a neoplasm. Despite performing a biopsy, a specific diagnosis still could not be secured. The authors prospectively performed a histopathological and immunohistochemical analysis of these cases that were diagnosed as “active inflammatory demyelination.” Specifically, aquaporin-4 (AQP4) immunoreactivity was assessed to differentiate NMO/NMOSD from MS. The loss of AQP4 immunoreactivity in 18 of the biopsies was indicative of a diagnosis of NMO/NMOSD. When the serum of 14 of these patients was tested for the AQP4-immunoglobulin (AQP4-IgG), all of them were found to be positive consistent with the diagnosis of NMO/NMOSD (amazingly, in 1 patient, the final diagnosis was confirmed 26 years after presentation!). In the final analysis, as a result of re-reviewing the biopsies in a prospective fashion and then retrospectively reviewing the clinical findings and performing AQP4-IgG, the authors were able to confirm the diagnosis of NMO/NMOSD in 15 patients, longitudinally extensive transverse myelitis in 2 patients, and MS in 2 patients.

This study highlights the clinical utility of AQP4 immunohistochemistry analysis in surgical specimens with the following histological findings: active demyelination, myelin and tissue vacuolation, granulocytic inflammatory infiltrates, dystrophic astrocytes, and glial fibrillary acid protein containing macrophages. In addition, this report underscores the need to consider NMO/NMOSD in the differential diagnosis of a patient with a tumefactive brain or spinal cord lesion and to test for AQP4-IgG so as to avoid surgery and refrain from instituting inappropriate treatment.

—M. Tariq Bhatti, MD

For me, the take home message is that patients with mass lesions should have NMO antibody measured before biopsy. If positive, it might obviate the need for invasive surgery in some of these cases. However, I wish the authors would have provided more clinical and neuroimaging information so we would know how these patients presented. For instance,
were these relatively acute deficits suggestive of a demyelinating process with the only suggestion of tumor being the findings on MRI?

—Mark L. Moster, MD


Objective: To evaluate the association between migraine and Bell palsy and to examine the effects of age, sex, migraine subtype, and comorbid risk factors for Bell palsy.

Methods: This nationwide cohort study was conducted using data from the Taiwan National Health Insurance Research Database. Subjects aged 18 years or older with neurologist-diagnosed migraine from 2005 to 2009 were included. A nonheadache age- and propensity score-matched control cohort was selected for comparison. All subjects were followed until the end of 2010, death, or the occurrence of a Bell palsy event. Cox proportional hazards regression was used to calculate the adjusted hazard ratios and 95% confidence intervals (CIs) to compare the risk of Bell palsy between groups.

Results: Both cohorts (n = 136,704 each) were followed for a mean of 3.2 years. During the follow-up period, 671 patients (424,372 person-years) in the migraine cohort and 365 patients in the nonheadache cohort developed Bell palsy. The adjusted hazard ratio was 1.91 (95% confidence interval, 1.68–2.17; P < 0.001). The association between migraine and Bell palsy remained significant in sensitivity analyses, and tests of interaction failed to reach significance in all subgroup analyses.

Conclusions: Migraine is a previously unidentified risk factor for Bell palsy. The association between these 2 conditions suggests a linked disease mechanism, which is worthy of further exploration.

Bell palsy, named after the Scottish Surgeon Charles Bell, is an idiopathic disorder of the facial nerve that was first described by Dr. Nicolaus Friedrich in the 18th century. Eighty percent of facial nerve palsies are due to Bell palsy with an incidence of 10–40 persons per 100,000 per year. The cause of Bell palsy remains somewhat obscure but may be due to reactivation of a latent herpes virus infection. However, many other causes have been associated with Bell palsy including diabetes mellitus, arterial hypertension, and pregnancy.

The investigators of this study tapped into the National Health Research Database, which contains health care information on 99% of the 23 million people of Taiwan, to determine whether there is an association between migraine and Bell palsy. Patients were stratified into 2 groups: migraine group and nonheadache (control) group. There were a total of 136,704 patients in each group after matching for age and propensity score (a method used to reduce the effects of confounding in an observational study). With a mean follow-up of 3.2 years (±1.6 years), 671 patients in the migraine group and 365 patients in the nonheadache group developed Bell palsy. The adjusted hazard ratio was 1.91 (95% confidence interval, 1.68–2.17) with a P value of <0.001. The authors speculate that this nearly 2-fold higher risk of Bell palsy in patients with migraine may be the result of post-viral migraine related demyelination, ischemia due to migraine related vascular disorder, increased clinical awareness due to more frequent doctor visits, or drug-related adverse effect. The authors stated that they cannot be certain that migraine itself or the number of migraine attacks increases the risk of Bell palsy. Finally, given this strong association (as strong as diabetes mellitus and arterial hypertension), the authors suggest a common mechanism is at play between migraine and Bell palsy. The journal NEUROLOGY felt this was such an important article that an accompanying editorial was published (1).

—M. Tariq Bhatti, MD

This study is interesting, even if there is no obvious way of linking a risk for Bell palsy with migraine. However, given that this association was derived from a database raises some issues that were partially addressed in the accompanying editorial. We are not provided any detailed clinical information. The fact that they used a migraine cohort diagnosed by a neurologist might increase the likelihood of a diagnosis of Bell palsy. Additionally, patients with mild migraine may have been excluded because they might not seek attention or have a diagnosis listed in the database.

—Mark L. Moster, MD

REFERENCE


Purpose: We designed a visual field test focused on the field used while driving to examine associations between field impairment and motor vehicle collision involvement in 2,000 drivers aged 70 years or older.

Methods: The “driving visual field test” involved measuring light sensitivity for 20 targets in each eye, extending 158 superiority, 308 inferiorly, 608 temporally, and 308 nasally. The target locations were selected on the basis that they fell within the field region used when viewing through the windshield of a vehicle or viewing the dashboard while driving. Monocular fields were combined into a binocular field based on the more sensitive point from each eye. Severe impairment in the overall field or a region was defined as average sensitivity in the lowest quartile of sensitivity.
At-fault collision involvement for 5 years before enrollment was obtained from state records. Poisson regression was used to calculate crude and adjusted rate ratios (RRs) examining the association between field impairment and at-fault collision involvement.

**Results:** Drivers with severe binocular field impairment in the overall driving visual field had a 40% increased rate of at-fault collision involvement (RR, 1.40; 95% confidence interval [CI], 1.07–1.83). Impairment in the lower and left fields was associated with elevated collision rates (RR, 1.40; 95% CI, 1.07–1.82 and RR, 1.49; 95% CI, 1.15–1.92, respectively), whereas impairment in the upper and right field regions was not.

**Conclusions:** Results suggest that older drivers with severe impairment in the lower or left region of the driving visual field are more likely to have a history of at-fault collision involvement.

Previous studies of visual field (VF) defects in relation to motor vehicle collisions (MVCs) have had varying results. Some of the differences relate to the method of testing (monocular vs binocular, threshold vs screening). Moreover, the vision requirements related to driving vary from state to state in the United States and from country to country. The range in the United States is from no rules related to visual field testing to up to 140 degrees of binocular visual field required.

The current study correlated VF results in 2,000 individuals over the age of 70 years with their past 5-year driving record, looking at MVCs where the person was considered to be at-fault.

The findings were that VF defects were associated with a 40% increased risk of at-fault collision involvement. The locations of VF defect associated with increased risk included the horizontal meridian, lower VF, and left VF but not the upper and right VF.

This study is more useful than many previous studies. First, the authors developed a threshold visual field based on the actual parts of the VF used in driving and eliminated points that were not involved. This improved the validity of the test results. Second, they adjusted for confounding variables, including age, sex, race, visual acuity, contrast sensitivity, mental status (Mini Mental Status Examination), visual processing speed, and the number of comorbidities. Third, it was done in Alabama where drivers do not undergo repeat visual testing after receiving their initial driving license, and despite the requirement for 110 degrees of VF along the horizontal meridian, this is not tested for routinely.

One limitation of this study relates to the issue of comorbidities. For instance, if one patient has hypertension but another has had a stroke with hemiparesis those are not equal in effect and would have an impact on the results. Another limitation pointed out by the authors is that subjects with VF defects may have self-selected not to drive, which would contribute to underestimating the risk of MVCs in this study.

An interesting finding is that the impairment in the left VF was more important than the right VF. One wonders if this is related to oncoming traffic and whether the results might be the opposite in countries where one drives on the left side of the road.

Finally, it is very surprising that 14% of this randomly selected sample at an at-fault MVC in the past 5 years. Whether this is really higher than younger Alabama subjects is not available from this study but raises some very interesting questions.

Studies like this hopefully will lead to improved testing of the VF to assess for driving safety and more useful guidelines.

—Mark L. Moster, MD

I have always had questions in my mind regarding the best visual field test to determine a patient’s ability to safely drive. I am curious to see if and how various states will change their current visual field requirements based on this more “real-world” visual field test and at what collision rate threshold will a visual field defect be acceptable? Will it be 20%, 30%, 40%, etc? Also, based on this study, it seems that it is not just the overall visual field impairment that matters but rather the location of the visual field defect that correlates with the risk of an MVC.

—M. Tariq Bhatti, MD


**Purpose:** To compare the costs of diagnostic workup for optic disc drusen where ophthalmic ultrasound was performed before imaging and invasive studies with those where ophthalmic ultrasound was performed after such studies.

**Methods:** The medical records of patients at the age of 18 years evaluated at a tertiary referral center between 2007 and 2012 for “swollen” optic nerves were retrospectively reviewed. The main outcome measure was cost of diagnostic workup according to Georgia Medicaid global reimbursement rates.

**Results:** A total of 46 children with a B-scan ultrasound–confirmed diagnosis of calcified optic disc drusen were included. Neuroimaging was performed in 23 patients, of whom 20 had the study before ophthalmic ultrasound. The mean cost of evaluations for patients undergoing ancillary testing before ophthalmic ultrasound was $1,173; for those undergoing ancillary testing after, $305.

**Conclusions:** Because optic disc drusen can mimic the appearance of papilledema, it is more cost effective to perform ophthalmic ultrasonography before neuroimaging, especially when the patient is asymptomatic. If ophthalmic ultrasonography confirms the presence of drusen, it is more cost effective to reassess the clinical picture before proceeding with further tests.

This study found that when pediatric patients with calcified optic disc drusen found on ultrasound (US) had the US...
before other studies (e.g., magnetic resonance imaging, lumbar puncture), patient care costs were much lower. Possible reasons the authors provide for why neuroimaging and/or lumbar puncture were ordered before US include lack of access to US, shortage of staff trained to detect drusen, and medicolegal reasons.

The study findings show cost-effectiveness is initially obtaining an US examination, and I believe that the savings are underestimated. First, these investigators used Georgia Medicaid reimbursement rates for the calculations, which are likely lower than private insurers. Additionally, they used an LP cost of $107 which I doubt includes all the costs for analysis of cerebrospinal fluid.

Nevertheless, the results of this report are no surprise, and I think the authors make reasonable recommendations to perform the US first if the suspicion of elevation of intracranial pressure based on clinical history and funduscopic examination is low. One can always proceed with further workup after US if there is still suspicion of elevated intracranial pressure, as was done in 3 patients in this study.

—Mark L. Moster, MD

I agree that the results of this study were predictable and not surprising. No doubt that in some cases, it can be very difficult to differential true papilledema from pseudopapilledema due to buried optic disc drusen based solely on funduscopic examination. My practice has been to obtain B-scan ultrasonography, intravenous fluorescein angiography (looking for disc leakage associated with papilledema), or fundus autofluorescence imaging before ordering neuroimaging. However, I think it is important to remember that there is no reason that a patient cannot have both papilledema and buried disc drusen.

We are not told exactly why the 20 patients underwent B-scan ultrasonography only after other studies were done. As Mark has pointed out and the authors state: “Possible reasons for physicians ordering neuroimaging and other studies before ophthalmic ultrasound include lack of access to ophthalmic ultrasonography, shortage of ancillary staff trained to detect optic nerve head drusen, and a desire to rule out serious intracranial pathology for medicolegal reasons.” I would be interested to assess the thought process of the clinicians who initially evaluated these 20 patients.

The authors discuss the possibility of optical coherence tomography (OCT) as a better test for detecting disc drusen than B-scan ultrasonography. However, I would temper that enthusiasm based on the recent study by Kulkarni et al (1) that showed spectral domain OCT could not reliably differentiate mild papilledema from buried disc drusen.

—M. Tariq Bhatti, MD

REFERENCE


Objective: Varicella-zoster virus (VZV) infection may trigger the inflammatory cascade that characterizes giant cell arteritis (GCA).

Methods: Formalin-fixed, paraffin-embedded GCA-positive temporal artery (TA) biopsies (50 sections/TA) including adjacent skeletal muscle and normal TAs obtained postmortem from subjects >50 years were examined by immunohistochemistry for presence and distribution of VZV antigen and by ultrastructural examination for virions. Adjacent regions were examined by hematoxylin and eosin staining. VZV antigen–positive slides were analyzed by polymerase chain reaction for VZV DNA.

Results: VZV antigen was found in 61 of 82 GCA-positive TAs (74%) compared with 1 of 13 normal TAs (8%) (P < 0.0001; relative risk 9.67; 95% confidence interval, 1.46–63.69). Most GCA-positive TAs contained viral antigen in skip areas. VZV antigen was present mostly in adventitia, followed by media and intima. VZV antigen was found in 12 of 32 skeletal muscles (38%) adjacent to VZV antigen–positive TAs. Despite formalin fixation, VZV DNA was detected in 18 of 45 GCA-positive VZV antigen–positive TAs (40%), in 6 of 10 VZV antigen–positive skeletal muscles (60%), and in 1 VZV antigen–positive normal TA. VZVs were found in a GCA-positive TA. In sections adjacent to those containing VZV, GCA pathology was seen in 89% of GCA-positive TAs but in none of 18 adjacent sections from normal TAs.

Conclusions: Most GCA-positive TAs contained VZV in skip areas that correlated with adjacent GCA pathology, supporting the hypothesis that VZV triggers GCA immunopathology. Antiviral treatment may confer additional benefit to patients with GCA treated with corticosteroids, although the optimal antiviral regimen remains to be determined.

This is a very intriguing article demonstrating evidence that varicella-zoster virus (VZV) triggers giant cell arteritis (GCA). As noted, not all patients had evidence of VZV, suggesting that VZV may be one of numerous causes of GCA. The study was done in specimens that were
deidentified, so no information is available regarding clinical history of zoster, medications, or zoster vaccination. The authors propose that the spread of VZV is transxonal to arteries, infecting the adventitia with subsequent transmural involvement, and primarily affecting the temporal artery. They do not speculate on how the disease spreads to all the other arteries typically involved in GCA. Presumably, there would be a systemic inflammatory response that affects arteries remote from the temporal artery.

The authors advocate addition of antiviral treatment with IV acyclovir to corticosteroids in GCA patients and suggest that it may shorten the length of treatment with steroids. This is likely a premature recommendation but one certainly worth further study.

—Mark L. Moster, MD

I recall several years ago, the theory of VZV as a possible underlying etiology of GCA and whispers of treating patients with antiviral medication. This study certainly resurrects that concept, and no doubt warrants further studies of antiviral therapy in a randomized controlled design. However, until these clinical studies can be performed, corticosteroids remain the standard of care for the treatment of GCA!

—M. Tariq Bhatti, MD
Unilateral Loss of Spontaneous Venous Pulsations in an Astronaut

We previously reported a 57-year-old male astronaut who flew on his first 6-month space mission in 2003 and his most recent flight in 2011–2012 (1). His first premission fundus examination was normal bilaterally, but his postmission examination revealed choroidal folds and a cotton wool spot in his right eye. The left fundus was normal. In 2011, his preflight optical coherence tomography (OCT) documented subtle choroidal folds in the right eye and magnetic resonance imaging (MRI) showed bilateral optic nerve (ON) sheath distention with mild right globe flattening. On ophthalmoscopy, spontaneous venous pulsations (SVPs) were present bilaterally. Five months into the second mission, remotely guided video funduscopy on the International Space Station documented mild disc edema in the right eye without SVPs. The left fundus was normal with prominent SVPs.

Two days postmission there was Frisen Grade 1 disc edema with barely detectable SVPs and choroidal folds in the right eye. The left fundus was normal with prominent SVPs. Six days postflight, MRI documented a moderate increase in both ON sheath diameters (left > right), compared with preflight, and there was bilateral globe flattening. Eight days postmission, the opening pressure was 18 cm H$_2$O on lumbar puncture. Fifty-two days postmission, the right optic disc swelling had resolved, and SVPs remained unchanged from the previous examination. At 21 months after the mission, there was normal peripapillary retinal nerve fiber layer thickness in each eye but persistent right choroidal folds. High resolution Heidelberg spectralis OCT video and 78 D lens assessment revealed SVPs to be absent in the right eye and present in the left eye. Magnetic resonance imaging performed 7 months postflight was unchanged compared with the previous study.

SVPs are pulsatile changes in the diameter of the retinal veins just before their exit from the eye to form the central retinal vein (CRV) (2). The disappearance of previously documented SVPs is a well-known, usually bilateral, clinical sign associated with elevated intracranial pressure. SVPs are generally thought to arise from normal cyclical venous pressure changes that occur in the eye and retrolaminar region. Blood flows from the retinal capillaries into the CRV because there is a relatively high pressure in the retinal capillary bed compared with the low pressure CRV (2). The sudden transient increase in flow at the point of venous outflow during systole temporarily decreases the volume of blood in a small segment of the vein on the optic disc, resulting in venous collapse. During diastole, the flow of venous blood exiting the eye ceases because the retrolaminar venous pressure is higher than the intraocular venous pressure, and the venous blood volume quickly increases in the previously collapsed segment. SVPs are eliminated when the downstream pressure in the CRV at the lamina cribrosa rises above that of the maximum intraocular venous pressure produced during systole. From the lamina cribrosa, the CRV drains within the central portion of the ON but exits the nerve approximately 10 mm posterior to the globe. At this point, the CRV traverses the subarachnoid space, and the stage is set for an elevated subarachnoid space (SAS) pressure to directly impact the pressure within the CRV (3,4).

Before his second space mission, we confirmed that the astronaut had bilateral SVPs suggesting normal SAS pressures within the ON sheaths. However, 5 months into the mission, we documented mild optic disc swelling with absent SVPs in the right eye, despite prominent SVPs and a normal disc in the left eye. The disappearance of right SVPs associated with optic disc swelling and the normal appearance of the left disc during a space mission suggests that microgravity exposure led to increased right periopic SAS pressure. Asymmetric postmission optic disc changes have been documented in other astronauts (1,5). It has been suggested that these findings are due to a microgravity-induced sequestration of CSF within the ON sheath compartment (1,5). This hypothesis is supported by the testing results in our case since the postmission lumbar puncture opening pressure was within normal limits in the presence of asymmetric findings. Absent right SVPs 21 months postmission suggest a continued pressure elevation within the ON sheath long after the mission ended.

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The authors report no conflicts of interest.

REFERENCES


Retracting Globe: Enophthalmos and Retraction Due to an Accessory Extraocular Muscle

We read with interest the report of Liao and Hwang of an accessory lateral rectus muscle in a patient with normal ocular motility (1). Accessory extraocular muscles are rare anatomic anomalies. They may represent vestigial structures homologous to the retractor bulbii muscle in amphibians, reptiles, and lower mammals (2) or a disturbance in mesodermal development of extraocular muscles (2–4). We recently evaluated a patient with an accessory extraocular muscle with clinical and radiologic findings differing from the case of Liao and Hwang.

A 26-year-old woman was referred for evaluation of right enophthalmos worse with eye movement present for 3 years and worsening since ptosis surgery 1 year ago. There was associated headache but no other visual or neurologic complaints. Visual acuity was 20/25 right eye and 20/20, left eye. There was limited abduction of the right eye, and the patient reported diplopia in right gaze. The right eye was 4-mm enophthalmic in primary position, and the enophthalmos increased to 7 mm in right superolateral gaze (Fig. 1). The rest of the examination was normal.

Multidetector 2-mm axial noncontrast CT images were obtained with bone and soft tissue technique and coronal isovoxel reformatted images with the patient in primary position and right and left gaze (Fig. 2). Imaging sequences showed a thin elongated structure isodense to normal extraocular muscle, extending from the annulus of Zinn to

![FIG. 1. Extraocular movements demonstrate right enophthalmos that increases with abduction and elevation of the right eye.](image-url)
The authors report no conflicts of interest.

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FIG. 1. Extraocular movements demonstrate right enophthalmos that increases with abduction and elevation of the right eye.
the posterior globe, inferior, and medial to the optic nerve insertion. On right gaze, the eyes were disconjugate with limited abduction of the right eye. On left gaze, the eyes maintained a conjugate position and the accessory extraocular muscle approximated the nasal aspect of the optic sheath. Given the clinical and neuroimaging findings, the patient was diagnosed with an accessory extraocular muscle.

The prevalence of accessory extraocular muscles is unknown, but English-language PubMed search revealed 22 reported cases. Most accessory extraocular muscles arise from the orbital apex (14/22 cases) with others arising from an extraocular muscle. Half of that arise from the apex (7/14) insert onto the sclera of the posterior globe in varied locations: inferomedial (2 cases) (3,5), superolateral (2 cases) (1,6), inferior (1 case) (7), and inferolateral (2 cases) (4,8). Two patients had retraction of the globe (3,7), 3 had enophthalmos (4,6,9), and 1 was asymptomatic (1). In addition, all patients with accessory extraocular muscle attaching to the sclera had some component of restricted ocular motility, except the case reported by Liao and Hwang (1).

There is not always a clear anatomic correlation between clinical and neuroimaging findings, although such was the case in our patient. Her marked enophthalmos was the greatest in right superolateral gaze, opposite to the inferomedial insertion of the accessory extraocular muscle. In comparison, the other 2 cases of inferomedial insertion were associated with restricted elevation on abduction (5) and globe retraction with superior and inferior eye movement (3). In addition, the 2 cases of inferomedial insertion were associated with restricted elevation on abduction (5) and globe retraction with superior and inferior eye movement (3). In addition, the 2 cases of globe retraction associated with an accessory extraocular muscle showed differing radiology findings. One patient experienced globe retraction with adduction and the accessory muscle attached to the posterior sclera inferiorly (7). Retraction of the eye in the second patient occurred with vertical eye movements and the accessory muscle attached to inferomedial posterior sclera (3).

Strabismus is the most common indication for surgery and usually performed in patients with anterior scleral or direct extraocular muscle insertion of the accessory muscle. There are no reports of improvement in enophthalmos with eye muscle surgery.

**FIG. 2.** Noncontrast orbital computed tomography. Axial (A) and coronal (B) scans show the accessory extraocular muscle (arrow) located inferomedial to the optic nerve and extending from the orbital apex attaching to the sclera inferomedially. Axial images in right (C) and left (D) gaze reveal limited abduction of the right eye and increased right enophthalmos in right gaze. In (C) and (D), the white line extends from the medial to lateral orbital rim.

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Letters to the Editor

Bilateral Intracranial Optic Nerve and Chiasmal Involvement in IgG4-Related Disease

We read with great interest the reviews by Yamamoto et al (1) and Kashii (2) on IgG4-related disease (IgG4-RD). We recently evaluated a patient with this disease who experienced bilateral optic nerve involvement.

A 36-year-old man presented with acute painful loss of vision and a droopy lid of the right eye. He had developed a right sixth nerve palsy 2 years earlier and brain magnetic resonance imaging (MRI) at that time showed abnormalities of the right cavernous sinus and sphenoid sinus. This prompted a biopsy of a “polyp” from the right sphenoid sinus, which showed an “inflammatory lesion.” The patient improved over the next 2 months after treatment with systemic corticosteroids. He had a 15-year history of tobacco use, but his medical history was otherwise unremarkable.

Visual acuity was hand motions, right eye and 20/20, left eye. There was a right relative afferent pupillary defect with complete prosis and limitation of right eye movement in all gaze directions. Anterior and posterior segment examinations were normal in both eyes. Automated visual field testing was normal in the left eye. Brain MRI revealed a lesion involving the right cavernous sinus and right prechiasmal optic nerve (Fig. 1A).

FIG. 1. A. Postcontrast T1 coronal magnetic resonance imaging shows enhancement of the right prechiasmal optic nerve (arrow), right cavernous sinus, and dura of the middle cranial fossa (arrowhead). B. Two months later, there is enhancement of the left prechiasmal optic nerve (arrow).
We read with great interest the reviews by Yamamoto et al (1) and Kashii (2) on IgG4-related disease (IgG4-RD). We recently evaluated a patient with this disease who experienced bilateral optic nerve involvement.

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FIG. 1. A. Postcontrast T1 coronal magnetic resonance imaging shows enhancement of the right prechiasmal optic nerve (arrow), right cavernous sinus, and dura of the middle cranial fossa (arrowhead). B. Two months later, there is enhancement of the left prechiasmal optic nerve (arrow).

References

Letters to the Editor

FIG. 2. Sphenoid sinus biopsy specimen. A. There is a plasma cell rich inflammatory infiltrate (hematoxylin & eosin, ×400). B. Areas of focal fibrosis are present (Masson trichrome, ×100). C. IgG4-positive cells are seen with a density of 80 per high power field (IgG4 immunostain, ×400).

Patient evaluation included normal results for purified protein derivative skin testing, serum angiotensin-converting enzyme, anti-proteinase 3, C-ANCA, P-ANCA, antinuclear antibodies, chest x-ray, and whole body gallium 67 scanning.

The patient received intravenous (IV) methylprednisolone 1 g/d for 5 days followed by oral prednisone 1 mg/kg. Over 2 weeks, he showed marked improvement in his ptosis and ocular motility, but visual acuity deteriorated to light perception in the right eye. A dural biopsy was obtained from the right middle cranial fossa, and the neurosurgeon reported that the dura looked “yellow, white, and thickened.” Dural and temporal lobe brain biopsy specimens showed only “patchy lymphocytic infiltration.” The patient received 4-mg dexamethasone with taper over 2 weeks.

Two months later, the patient reported sudden decrease in vision in his left eye. Visual acuity was light perception in the right eye and hand motions in the left eye. Pupillary reflexes were bilaterally sluggish. Lid position and ocular motility were normal with intact corneal reflexes and facial sensation. Ophthalmoscopy showed right optic disc pallor, and the left disc appeared normal. Brain MRI demonstrated a nodular enhancing lesion involving the left intracranial optic nerve and diffuse thickening of the chiasm (Fig. 1B). Venereal disease research laboratory test, treponema pallidum haemagglutination test, and HIV serologies were negative. Cerebrospinal fluid analysis was unremarkable.

The patient was prescribed prednisone 60 mg/d, and the biopsy specimen from the sphenoid sinus was retrospectively reviewed. It had been described as “sphenoidal sinus mass with the stroma being infiltrated by chronic inflammatory cells, mainly plasma cells.” Special IgG4 staining showed a plasma cell rich infiltrate and focal fibrosis with IgG4-positive cells of 80 per high power field (Fig. 2).

Serum amylase, IgG, and IgG4 levels were within normal limits. One month later, the patient received 2 IV infusions of 1000 mg rituximab 2 weeks apart. Two months later, although his serum IgG remained with normal limits, his serum IgG4 was elevated at 1440 mg/L (normal, 39.2–864 mg/L). Three months after IV rituximab, visual acuity had improved to counting fingers, right eye and 20/200, left eye. Spectral domain optical coherence tomography showed severe bilateral reduction in retinal nerve fiber layer thickness. Oral prednisone was tapered over 2 months, and the patient was maintained on azathioprine 50 mg orally twice a day.

Although optic neuropathy has been associated with IgG4-RD (3–6), we could not find previous documentation of intracranial optic nerve involvement. Rather, optic nerve dysfunction has been described with orbital IgG4-RD, including a case with extension into the ipsilateral cavernous sinus and middle cranial fossa (4). In our patient, there was sequential intracranial optic nerve involvement. Features commonly seen in orbital IgG4-RD such as lacrimal gland, extraocular muscle, and infraorbital nerve involvement were absent in our case.

It is not unusual to make the diagnosis of IgG4-RD retrospectively, either because of omission of IgG4 stain or the biopsy site being inaccessible (7,8). In our patient, the first serum IgG4 level was within normal limits, probably because of prolonged steroid treatment. However, subsequent testing did show elevated serum IgG4 titers. Because we could not find other organ involvement and systemic steroids did not resolve all the clinical findings, our patient was classified as “probable IgG4-RD” (9).

Increased IgG4-positive cells may occur in sinonasal or orbital/periorbital biopsies in patients with Wegner granulomatosis (10). In our patient, serum ANCAs were negative, and the biopsy did not show evidence of necrosis, granuloma, or vasculitis.

Systemic steroids are considered the mainstay treatment of IgG4-RD and are usually associated favorable outcome (11). However, efficacy of steroids in cases of optic nerve involvement is uncertain, and in the few cases reported, there was insufficient follow-up data on visual function (4). Our patient had profound loss of vision despite treatment with high-dose systemic steroids. Discontinuation of steroids led to a relapse in the contralateral optic nerve. Rituximab has been used with success in systemic IgG4-RD (12). We could not find previous reports of its use in optic nerve involvement, but it led to visual impairment in our patient.
The authors report no conflicts of interest.

REFERENCES

Robert Malcolm McFadzean, a distinguished Neuro-Ophthalmologist from Glasgow, Scotland, was born in Edinburgh. Following the untimely death of his father in London when he was eight years old, his mother returned to Edinburgh with her two young sons. Subsequently, Robert was enrolled in the prestigious George Heriot’s School, where he excelled. His academic accomplishments continued through the university level to his completion of a medical degree at the University of Edinburgh in 1966. He trained in ophthalmology and neurology in Edinburgh, Aberdeen and Glasgow, and became a Fellow of the Royal College of Surgeons in 1972. His intellectual inquisitiveness steadily drew him toward neuro-ophthalmology during these years, which was greatly fostered by Professor Barry Cullen and later Professor Wallace Foulds. In 1977, he took up a consultant’s post in Glasgow, where he provided a Neuro-Ophthalmology Service to patients in the West of Scotland and beyond at the Institute of Neurological Science, Southern General Hospital. In addition he provided neuro-ophthalmology and general ophthalmology clinical services at the Glasgow Eye Infirmary and Gartnavel General Hospital. As an Honorary Clinical Senior Lecturer in Ophthalmology at the University of Glasgow, he was involved in post-graduate training in neuro-ophthalmology along with participation in undergraduate training in General Ophthalmology. In 1989, he became a Fellow of the Royal College of Ophthalmologists.

Robert’s work in Glasgow led to many publications in the field of Neuro-Ophthalmology with some notable contributions. For example, our understanding of the topographical organization of the visual field representation in the occipital lobe was brought into modern context by his careful analysis. In a comparison study, he showed that non-invasive computed tomography angiography rather than arterial angiography was sufficient to evaluate third nerve palsies for compression by an aneurysm. He had a special interest in pituitary apoplexy and carefully documented the outcomes for the treatment of pituitary adenomas and carotid cavernous fistulas.

In Scotland, Robert chaired the Dr William McKenzie Commemoration Fund and organized the annual meeting in the founder’s memory, this being the major academic event in the Scottish ophthalmic calendar. He also helped to found the British Isles Neuro-Ophthalmology Club in 1984 and participated in the annual meetings. In the mid-1980’s, he attended his first meetings of the International Neuro-Ophthalmology Society (INOS).

In 1990, Robert crossed the Atlantic for the day and a half meeting of the Frank Walsh Society. With his affable manner, distinctive brogue and ready smile, the lively Scot met easily and was soon conversant with many of its members. Encouraged, he attended his first North American Neuro-Ophthalmology Society (NANOS) meeting in 1991. At ease with colleagues from all cultures and nationalities, Robert became the first chair of NANOS’s International Committee in 1998 and expanded his contacts with many colleagues from around the world. His academic and organizational insights were highly regarded as he sought to raise the quality of scientific, medical and educational projects and forums in which he became engaged.

In 2005, Robert became the first president of the European Neuro-Ophthalmology Society (EUNOS), a position which he held with great pride and commitment for 6 years until 2011. As well as participating in annual meetings, he was responsible for formalizing EUNOS by promoting a constitution for the society. During his presidency, he collaborated closely with his Romanian colleagues to help lay the foundations of modern Romanian neuro-ophthalmology. Throughout these years, Robert continued to attend NANOS meetings until his retirement in 2007.

Unfortunately, he soon developed multiple myeloma, which he fought valiantly, maintaining his positive outlook and dignity. His health prevented from further attendance at NANOS but he attended what would be his last EUNOS Update Meeting in Budapest in 2012.

In our estimation two of his biggest disappointments were his forced retirement from the National Health Service simply due to age, and his illness, which stopped him from attending NANOS meetings and continuing further interactions with his colleagues. He felt his career had more to
give. We all knew he had incredible clinical expertise, a vast amount of knowledge, and the desire to share it with patients and colleagues. He was filled with ideas to improve EUNOS and perform clinical research. His battle ended with his passing on January 11, 2015. He was 72 years old. Not surprisingly, news of his death brought condolences from Argentina, Russia, Turkey, Israel, Japan and throughout America and Europe.

Neuro-ophthalmology has lost a wonderful colleague and friend. Bob, as he was known to many in NANOS, was a true Scotsman and gentleman. He wore a kilt on occasion and sampled Scottish whiskeys with the best of them and he frequently exercised his wicked sense of humor. In more formal settings, he noted how “horified” he was with our American habit of carrying cups of coffee or soda cans instead of sitting down and properly consuming them. However, most cherished by him, were the benefits of the intellectual exchanges and the camaraderie of medicine and science of specialties like neuro-ophthalmology.

Robert is survived by his lovely wife and staunch supporter, Rae, and three children Louise, Peter, Paul and a brother, John. NANOS and EUNOS will miss our dear friend, and Scotland will deeply mourn the loss of one of its very patriotic citizens.

John Selhorst, M.D.
Mark Kupersmith, M.D.
Colleagues and Friends

Corresponding Author: John Selhorst Email: selhorjb@slu.edu
Questions and Answers in Neuro-Ophthalmology: A Case-Based Approach


Questions and Answers in Neuro-ophthalmology, A Case-Based Approach written by Andrew G. Lee, MD and colleagues provides 20 classic neuro-ophthalmic topics each presented with a case history followed by a question and answer section.

The topics covered include many of those diagnoses encountered in a neuro-ophthalmic clinic. The first two chapters deal with evaluating the patient with anisocoria including Horner syndrome and an abnormally dilated pupil. The following chapters cover a vast array of optic neuropathies including anterior ischemic optic neuropathy, optic neuritis, papilledema, optic nerve drusen, and toxic/nutritional optic neuropathy. Causes of diplopia are further presented in chapters covering cranial neuropathies, Graves’ disease, orbital apex and cavernous sinus syndromes, carotid-cavernous fistula, and myasthenia gravis. The last topics covered are chiasmal and retrochiasmal disorders, nystagmus and nonorganic visual loss.

The authors do an excellent job presenting each case with external photos, fundus photos, visual fields, optical coherence tomography, or neuro-imaging pertinent to each case. Following each case, there are 6–10 multiple-choice questions with in-depth discussions of the answers as well as a case summary. Pertinent literature references are provided at the end of each chapter.

This case-by-case question and answer book is recommended for medical students, residents, or those who want a reference or review of common neuro-ophthalmic conditions.

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The 41st Annual Meeting of the North American Neuro-Ophthalmology Society

The North American Neuro-Ophthalmology Society held its 41st annual meeting at the Hotel del Coronado in San Diego, California, the site of the classic movie, “Some Like it Hot,” starring Marilyn Monroe, Jack Lemmon, and Tony Curtis. Although the weather was not hot, the symposia, lectures, and interactions were “hot and lively.”

Co-chairs of the Frank Walsh Society meeting were Benjamin Frishberg and Howard Krauss, who carried out the theme of the classic movie by introducing each abstract with a movie theme. Our outstanding guests this year included John Rhee, neuroradiologist, Yuki Takasumi, neuropathologist, Daniel Kelly, neurosurgeon (all from Providence Saint John’s Health Center, Santa Monica, CA), and Chester Griffiths, otolaryngologist from UCLA (Fig. 1). The best Walsh paper was presented by Lulu Burnsztyn from the University of Michigan. The presentation was entitled “Joe and Jerry Flew the Coop” and dealt with the case of H1N1 virus causing bilateral retinal and lateral geniculate nucleus infarctions.

Several symposia featured new treatments and disease pathophysiology. “Journal Club” topics included new therapies for multiple sclerosis, the potential association between phosphodiesterase inhibitors and anterior ischemic optic neuropathy, the use of bariatric surgery in idiopathic intracranial hypertension, and the neuro-ophthalmologic consequences of obstructive sleep apnea. The “Hot Topics” this year featured nonmydriatic fundus photography, imaging of Horner syndrome, and neuro-ophthalmologic consequences of outer space travel. We also learned the outcomes of the recently released Idiopathic Intracranial Hypertension Treatment Trial, and we were treated to a symposium on “Mechanical Causes of Strabismus” with guest Joseph Demer from Jules Stein Eye Institute, UCLA. A unique symposium drew record crowds and standing room only when NANOS partnered with the American Glaucoma Society for a joint symposium on one of the most common optic neuropathies, glaucoma. The Jacobson Lecture was delivered by Thomas Slamovits, who discussed “Neuroendocrine Tumors in Neuro-Ophthalmology.”

This year’s optional symposia also were popular. A number of our colleagues gave us a “tour” of International Neuro-Ophthalmology during a session chaired by Christian Lueck and Klara Landau. Mike Strominger led a hands-on workshop on “Prism Therapeutics in Diplopia.” Betty Kovacs from the St. Luke’s Weight Loss Center in New York City and Shana McCormick from the University of Pennsylvania gave attendees practical ways to assist our obese patients (adult and pediatric) regarding weight loss. Janet Rucker and David Newman-Toker led the sold-out “Eye Movement and Vestibular Skills” session. In addition,

FIG. 1. A southern California team hosted the 2015 Frank Walsh Symposium: Chester Griffiths, Daniel Kelly, Yuki Takasumi, Howard Krauss, Ben Frishberg, John Rhee (left to right).

Section Editor: Kathleen B. Digre, MD

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we learned about many new neuro-ophthalmic research directions in both the scientific platform and poster sessions.

This year’s awardees were:

James A. Sharpe Award for Best Presentation by a Fellow—Enrique Rivera, “Chronic Optic Neuropathy Causes Decreases in both Inner Retinal Blood Flow and Prelaminar Optic Nerve Blood Flow.”

Best Abstract by a Resident—Eric D. Gaier, “Clinical Features of OPA1-Related Optic Neuropathy: A Focus on Genetic Modifiers.”

Best Abstract by a Student—Sui H. Wong, “Natural History of Ocular Myasthenia Gravis in 101 Cases: Towards a Risk of Generalization (‘ROG’) Score.”

2015 Young Investigator Award—Heather Moss, “The Photopic Negative Response in Idiopathic Intracranial Hypertension.”

2015 Pilot Grant Award—Hong Jiang, “Retinal Microvascular Alteration as a Possible Biomarker in Alzheimer’s Disease.”

Hoyt Lecture Award—Mark Kupersmith, “Optical Imaging of the Optic Nerve: Beyond Documenting RNFL Loss.”

Robert Avery, who presented “Hand-Held Optical Coherence Tomography during Sedation Detects Visual Acuity and Visual Field Loss in Young Children with Optic Pathway Gliomas” received the 2013 Young Investigator Award.

The 2015 Thomas Carlow Distinguished Service Award, the highest honor bestowed by NANOS, went to two recipients, Ivy Dreizin (Fig. 2) and Preston Calvert (Fig. 3).

We had 667 attendees at this year’s meeting, which is a record, representing 36 countries. The annual banquet was followed by a marshmallow roast on the beach. Janel Fick and her outstanding staff again hosted a very well-organized meeting. The 42nd meeting will be held in Tucson, Arizona, at the Starr Pass Marriott Resort on February 27–March 3, 2016. Stay tuned!

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Highlights From the 2014 Joint Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS)—European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)

The 2014 Joint ACTRIMS-ECTRIMS meeting was held in Boston, Massachusetts, at the John B. Hynes Veterans Memorial Convention Center, September 10–13, 2014. With an impressive 8806 registered participants representing 92 countries in attendance, this was the largest joint meeting of multiple sclerosis (MS) specialists ever held in North America. Notably, NANOS was well represented at the event, with several of our own members included among the 147 faculty representatives. Dr Steve Galetta (New York, USA) delivered a sizzling talk, “Red flags in MS: Zebras or horses?” in the highly popular Differential Diagnoses and Diagnostic Dilemmas teaching course chaired by Dr Patrick Vermersch (Lille, France). Together with Dr Emmanuelle Waubant (San Francisco, USA), Drs Galetta and Vermersch used a case-based format to apply the recently revised McDonald criteria and demonstrate how magnetic resonance imaging (MRI) measures can support, implement, or even replace some clinical parameters in the diagnosis of MS. The course also highlighted the utility of new MRI protocols, including double-inversion recovery sequences, which can be used to detect small cortical lesions in MS patients. High-field MRI studies were also used to illustrate how penetrating veins can be detected in most MS lesions using T2 or susceptibility-weighted MRI.

The Neuro-Ophthalmology Update was chaired by Dr Fiona Costello (Calgary, Canada) and featured Dr Jérôme de Seze (Strasbourg, France), and Dr Laura Balcer (New York, USA) as speakers. Dr Costello kicked off the session with a talk entitled, “Visual Manifestations of CNS Demyelinating Disorders.” This primer outlined the approach to clinical localization of common visual manifestations in MS and related syndromes. Dr Costello also introduced the concept of the afferent visual pathway as a clinical model of MS, which was expanded upon in the talks that followed. Dr. de Seze reviewed new diagnostic criteria that enlarge the spectrum of the neuromyelitis optica spectrum disorders, and proposed therapeutic strategies to help interpret AQP-4 antibody results in a presentation called, “Neuromyelitis Optica: New Diagnostic Criteria Enlarge the Spectrum.” Dr Laura Balcer closed the session with a panoramic summary entitled “The Role of Visual Outcomes in MS Clinical Trials”, with specific emphasis on the role of low-contrast letter acuity, visual evoked potential testing, and optical coherence tomography (OCT). Course participants identified several key learning points, which they planned to implement in their day-to-day clinical practice based on the course content, including the role of OCT testing and the value of more detailed visual assessments for their patients.

The 2014 Joint ACTRIMS-ECTRIMS meeting showcased cutting edge-research in the field of MS. A record-breaking 1724 abstracts were submitted for consideration: 94 were selected for platform presentations, and an additional 981 were selected as posters. There were numerous abstract topics presented that would be of potential interest to neuro-ophthalmologists including diagnosis and differential diagnosis, clinical trials, disease biomarkers, OCT, experimental models, neuromyelitis optica, neurophysiology, neuroprotection, and repair. A novel feature of the 2014 Joint ACTRIMS-ECTRIMS meeting was the effort made to critically examine how factors including the “expert patient”, news media, social media, and health policy affect the relationships between MS patients’ health care providers, and researchers. Certainly, the importance of issues such as patient advocacy and social media-engagement would also resonate with neuro-ophthalmologists.

The potential value of the 2014 Joint ACTRIMS-ECTRIMS meeting was aptly summarized by Dr Steve Galetta: “This provides a large-scale opportunity to view the advances for the treatment of multiple sclerosis and optic neuritis. Vision has become one of the key outcome measures for many of the latest clinical trials and the data is usually presented first in this forum”. The annual ACTRIMS and ECTRIMS meetings, whether held jointly or as separate events, introduce new agents emerging from the therapeutic pipeline and highlight early clinical trial findings related to MS and vision. The next joint meeting has yet to be announced, but future ACTRIMS and ECTRIMS (2015, Barcelona, Spain) meetings could be of considerable interest to neuro-ophthalmologists who...
wish to keep abreast of novel clinical and research developments in MS.

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Neuro-ophthalmology in the United Kingdom

Neuro-ophthalmology in the United Kingdom has a rich and longstanding history with a long list of luminaries that include John Hughlings Jackson (1835–1911), Douglas Argyll Robertson (1837–1909), Harry Moss Traquair (1876–1965), and William John Adie (1886–1935), to name but a few. These historical figures set the foundation for modern neuro-ophthalmology with their seminal work on fundamental concepts ranging from the topographical organization of the visual cortex to the physiological basis of the pupillary light reflex and to the island of vision. More recent notable figures include William Ian McDonald (1933–2006) for his pioneering work on optic neuritis and multiple sclerosis and Anita Harding (1952–1995) who in a short, but stellar, academic career published some of the defining articles on Leber hereditary optic neuropathy and the inherited neuromuscular diseases. The development of neuro-ophthalmology as a distinct subspecialty in the United Kingdom owes a large part to Michael Sanders who spent his fellowship year with William Hot at University of California, San Francisco, CA in 1967 before returning to practice at Queen Square in London (Fig. 1). This important transatlantic link has since flourished with a significant proportion of the current crop of British neuro-ophthalmologists having trained directly under Sanders’ wings.

Training Structure

The majority of neuro-ophthalmologists in the United Kingdom are Fellows of the Royal College of Ophthalmologists (FRCOphth), having initially trained as general ophthalmologists before gaining additional subspecialty experience in neuro-ophthalmology. The minimum period of ophthalmology training is 7 years and, after being awarded a Certificate of Completion of Training, a trainee is eligible to apply for an attending position (known as a Consultant in the United Kingdom). However, an increasing number of neuro-ophthalmologists also come from a neurology background, which further adds to the diversity of skills and expertise. There are a number of

FIG. 1. William Hoyt (center) with Michael Sanders (right) and Robert Daroff (left) during their fellowship year, 1967 (with permission from Kline LB. An interview with William F. Hoyt, MD. J Neuroophthalmol 2002;22:40–50).
well-regarded neuro-ophthalmology fellowships, for example, in Birmingham and in London, which attract both local and overseas trainees. Prospective candidates should keep an eye on the careers section of the British Medical Journal where openings are regularly advertised (http://careers.bmj.com/).

Neuro-Ophthalmology Services

The National Health Service (NHS) in the United Kingdom is a publicly funded system of care that was founded in 1948 at the end of the Second World War. It is the world’s largest healthcare system and despite mounting economic pressures, the NHS remains free at the point of use for UK residents. Although neuro-ophthalmology services are usually concentrated in larger ophthalmology departments based in major cities, many neuro-ophthalmologists will also provide outreach clinics, especially in parts of the country with catchment populations spread over large geographical areas. Patients are referred by a number of sources, but the majority of those are from primary care physicians, casualty departments, and secondary referrals from ophthalmology, and other hospital specialties. Most neuro-ophthalmologists who come from an ophthalmology background will also provide a surgical service, for example, cataract and strabismus surgery, depending on their fellowship training and personal interests. Botulinum toxin injections also are frequently provided by neuro-ophthalmologists for the treatment of a wide range of neurological disorders, in particular facial dystonias, and in the management of more complex strabismus cases.

Clinical and Research Meetings

Neuro-ophthalmology is a relatively small subspecialty, but our members are heavily involved in the training of junior trainees at both local and national levels. Through the Royal College of Ophthalmologists, a number of dedicated neuro-ophthalmology teaching days are organized each year, which are always oversubscribed and highly valued by the attendees (http://www.rcophth.ac.uk/). As a result of popular demand, neuro-ophthalmology sessions have also become a permanent fixture of the main ophthalmology meetings in the United Kingdom such as the Annual RCOphth Congress, the Oxford Ophthalmological Congress (http://www.oxford-ophthalmological-congress.org.uk/), and the Annual Meeting of the Association of British Neurologists (ABN; http://www.theabn.org/). Gordon Plant laid the foundation for a Special Interest Group allied to both the ABN and to the Royal College of Ophthalmologists in 2006. This effort culminated in the creation of the United Kingdom Neuro-Ophthalmology Special Interest Group (UKNOSIG), and the sixth annual meeting took place on March 12, 2014 (Governors’ Hall, St Thomas’ Hospital, London, United Kingdom) with Andrew Lee (Houston, TX) as the keynote speaker (http://www.uknosig.com/). Another important date in the calendar is the annual

### TABLE 1. Some examples of neuro-ophthalmological research in the United Kingdom

<table>
<thead>
<tr>
<th>Region</th>
<th>City</th>
<th>Investigator</th>
<th>Research Interests</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>Birmingham</td>
<td>Mr Michael Burdon</td>
<td>Idiopathic intracranial hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miss Susan Mollan</td>
<td>Idiopathic intracranial hypertension and giant cell arteritis</td>
</tr>
<tr>
<td></td>
<td>Cambridge</td>
<td>Miss Brinda Muthusamy</td>
<td>Pediatric neuro-ophthalmology</td>
</tr>
<tr>
<td></td>
<td>Leicester</td>
<td>Prof. Irene Gottlob</td>
<td>Eye movement disorders, nystagmus, and ocular imaging</td>
</tr>
<tr>
<td></td>
<td>London</td>
<td>Mr James Acheson</td>
<td>Rehabilitation of neuro-visual deficits and vigabatrin toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mr Nadeem Ali</td>
<td>Neuro-motility and functional disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mr Fion Bremer</td>
<td>Pupil abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dr Elizabeth Graham</td>
<td>Uveitis, inflammatory and infectious diseases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dr Gordon Plant</td>
<td>Optic neuropathies and demyelinating disorders</td>
</tr>
<tr>
<td>Newcastle</td>
<td>Mr Patrick Yu-Wai-Man</td>
<td></td>
<td>Mitochondrial disorders, neurogenetics, and clinical trials</td>
</tr>
<tr>
<td>Oxford</td>
<td>Mr John Elston</td>
<td>Prof. Christopher Kennard</td>
<td>Oculomotor control and neurodegenerative diseases</td>
</tr>
<tr>
<td>Sheffield</td>
<td>Dr Simon Hickman</td>
<td></td>
<td>Optic neuritis, idiopathic intracranial hypertension, and clinical trials</td>
</tr>
<tr>
<td>Belfast</td>
<td>Miss Jayne Best</td>
<td></td>
<td>Idiopathic intracranial hypertension</td>
</tr>
<tr>
<td>Scotland</td>
<td>Edinburgh</td>
<td>Dr Stephen Madill</td>
<td>Adult strabismus</td>
</tr>
<tr>
<td>Wales</td>
<td>Bangor</td>
<td>Dr Martyn Bracewell</td>
<td>Higher order visual dysfunction and visuomotor control</td>
</tr>
</tbody>
</table>

For those of you who are somewhat confused by the use of titles such as Mr and Miss in the above table, the explanation is relatively simple. In the United Kingdom, historically, surgical trainees who have successfully completed their Royal College examinations are referred to as Mr or Miss. This rather peculiar British tradition is a throwback to the early 18th century when surgeons (compared with physicians) did not possess a university medical degree (MD) but instead belonged to the “Company of Barber-Surgeons.” However, to confuse matters even further, surgeons in Scotland frequently use the title Dr, and not Mr or Miss, in their clinical practice.
gathering of the British Isles Neuro-ophthalmology Club (BINOC), which brings together a focused group of consultants with a subspecialty interest in neuro-ophthalmology. The BINOC meeting takes place over 2 days, and it provides the ideal forum for colleagues to discuss complex and unusual cases with a neuroradiologist in attendance.

**Research Networks**

The close personal links between neuro-ophthalmologists in the United Kingdom and the comprehensive clinical network provided by the NHS are valuable assets that have contributed to both the breadth and depth of neuro-ophthalmology research in this country. Our members are heavily involved at the cutting edge of both basic and translational research with active collaborations across several specialties (Table 1). The UK neuro-ophthalmology community has also been well represented within major international organizations over the years, such as the North-American Neuro-Ophthalmology Society and the European Neuro-Ophthalmology Society (EUNOS). Christopher Kennard is the current President of EUNOS and the 11th EUNOS meeting (April 10–13, 2013) that took place in the beautiful and historic setting of Oxford was a great success. The future of neuro-ophthalmology is certainly very bright in the United Kingdom, but as a group, we are not resting on our laurels. A central element of our mission statement is the need to foster the next generation of neuro-ophthalmologists, not only to deliver a first class clinical service, but also to lead the way as the teachers, researchers, and leaders of tomorrow.

**Patrick Yu-Wai-Man, BMedSci (Hons), MBBS (Hons), PhD, FRCOphth**

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**ACKNOWLEDGMENTS**

I am grateful to Simon Hickman (Sheffield) for his very useful comments on the historical development of neuro-ophthalmology in the United Kingdom.
Neuro-Ophthalmology in Brazil

Background

With a territory the size of a continent, divided into 26 states and 1 federal district, and with a population of more than 200 million, Brazil currently is the seventh largest economy in the world. It has a large medical community covering most areas of medicine, including all subspecialties of ophthalmology and neurology, particularly in the more developed states located in the southeast and southern regions of the country. Interest in neuro-ophthalmology (NO) has existed in Brazil for more than 50 years, although the subspecialty was until recently practiced by a very small number of physicians. Over the past 15 years, this has changed, with neuro-ophthalmologists practicing in at least half of the states in the country.

The Foundation of Neuro-Ophthalmology in Brazil

Specific interest in NO began in the states of Minas Gerais, Rio de Janeiro, and São Paulo. Professor Henderson C. de Almeida was the first to train in NO when, in the early 1960s, after studying strabismus with Arthur Jampolsky in San Francisco, he underwent a year of training with Frank B. Walsh in Baltimore. On his return to Brazil in 1965, he was given charge of both the strabismus clinic and the NO clinic of the Federal University of Minas Gerais (UFMG), in the city of Belo Horizonte. After a decade, he decided to focus exclusively on strabismus. He was succeeded at the university by Dr Luiz Roberto M. Oliveira who had completed a fellowship in NO with Neil Miller and strabismus with Stewart Wolf. Dr Oliveira was followed by Dr Marco Aurelio Lana Peixoto, a neurologist with residency training in Birmingham, AL, and Saint Louis, MO. Since the late 1980s, Dr Lana Peixoto has primarily focused on NO and is currently in charge of the clinic at UFMG.

Another pioneer of NO in Brazil, Professor Adalmir M. Dantas from Rio de Janeiro, began practicing NO in the early 1970s and taught at the Fluminense Federal University (Niterói, Rio de Janeiro) as the head of the Department of Ophthalmology and at the Federal University of Rio de Janeiro (UFRJ) where he attained the position of head professor. In 1979, Professor Dantas was commissioned by the Brazilian Council of Ophthalmology to deliver a series of keynote lectures on “Propedeutics in Neuro-Ophthalmology” for the Brazilian Congress of Ophthalmology in São Paulo (Fig. 1).

Fig. 1. Left, Photograph of Prof. Adalmir M. Dantas, one of the pioneers of neuro-ophthalmology in Brazil. Middle, Cover page of the “Revista Brasileira de Oftalmologia,” volume 38, 1979, dedicated to the XX Brazilian Congress of Ophthalmology. Right, Introductory page of the same journal indicating the official theme of the congress “Propedeutics in neuro-ophthalmology.”
These lectures encouraged many to consider the field of NO including myself during my last year of medical school.

In the state of São Paulo, interest in NO began at the University of São Paulo Medical School (FMUSP) and Escola Paulista de Medicina (now Federal University of São Paulo, UNIFESP). At FMUSP, the NO clinic began in the 1960s. Initially, patients were seen by professors with interests in other areas of ophthalmology. In 1981, it was transformed into a specialized service under the leadership of Prof. Carlos A. Rodrigues-Alves. After my graduation and residency at FMUSP, I completed an NO fellowship with William Hoyt (San Francisco), and on returning in 1984, developed a busy NO clinic at Hospital das Clinicas (FMUSP), Brazil’s largest university hospital. Since the retirement of Dr Rodrigues-Alves, I have led the NO service, with the invaluable assistance of Dr Maria Kiyoko Oyamada. Over the years, the clinic has played a major role in residency and fellowship training and continuing medical education in NO in Brazil. At UNIFESP, NO was pioneered by Dr Paulo M. Imamura since 1975 after completing his ophthalmology training in São Paulo and the University of Tokyo, Japan. Dr Imamura trained many residents and NO fellows, including Dr Luciana da Cruz Noia who is currently in charge of the service. Dr Carlos F. Chicani, who did fellowship training with Neil Miller, is another member of the UNIFESP NO service.

The Strengthening of Neuro-Ophthalmology as a Subspecialty in Brazil and South America

The development of NO in Brazil and other countries in South America owes much to Dr Hoyt, not only because he personally instructed many fellows but also from his continual support and attendance of important educational events, which significantly fostered interest in the subspecialty. Dr Hoyt lectured at the University of São Paulo in 1990, after which he was a guest of honor at an important meeting in Buenos Aires of the Latin American Club of Neuro-ophthalmology (CLAN) organized in 1988. CLAN is composed of a group of Latin American ophthalmologists and neurologists with special interest in NO and initially led by Cristian Luco (Chile) and Lidia Lopez (Argentina). The 1990 meeting in Buenos Aires, organized by Dr Roberto Ebner and his colleagues, was a landmark in the development of NO in that area of the world. Attendees included A. Dantas, P. Imamura, and myself (Brazil), Ernesto Rios-Montenegro (Peru), Rafael Muci-Mendoza (Venezuela), and many physicians from Argentina and Chile (Figs. 2, 3). Dr Hoyt further strengthened the group by participating in another CLAN meeting in Santiago, Chile, in 1996, organized by Cristian Luco, attended by 2 American CLAN supporters, Rosa Tang and Thomas Hedges III. In 1999, an NO meeting in Belo Horizonte, Minas Gerais, was organized by Dr Lana-Peixoto and attended by approximately 400 Brazilian physicians and CLAN members. American participants included Jack Selhorst, William T. Shults, and Sohan S. Hayreh. The development of NO in Brazil also owes much to other North Americans including Joel Glaser, Norman Schatz, Neil Miller, Alfredo Sadun, Anthony Arnold, Robert Sergott, and Peter Savino who either participated in national or Pan-American meetings that occurred in Brazil or accepted Brazilian physicians as visitors or fellows in their departments.

FIG. 2. Photograph of Dr Hoyt along with the 3 Brazilians who attended the second meeting of the Latin American Club of neuro-ophthalmology held in Buenos Aires in 1990. From left to right: Mário L. R. Monteiro, William F. Hoyt, Adalmir M. Dantas, and Paulo M. Imamura.
Neuro-Ophthalmology in Brazil: Training, Clinical Practice, and Challenges

Since the 1970s, a rotation in NO has been part of the ophthalmology residency programs at UFMG, UFRJ, FMUSP, and UNIFESP. Hundreds of ophthalmologists, and some neurology residents, have been exposed to the subspecialty. Over time, NO residency training has been instituted in a great many Brazilian university hospitals and fellowship/postdoctoral training programs. The subspecialty is currently represented in 13 states, and more physicians (almost all ophthalmology-trained) are specializing in NO (Table 1).

While this may sound promising, the number of practicing neuro-ophthalmologists in the country is actually very small when compared with the total number of ophthalmologists and neurologists. In part, this may be explained by the economics of the Brazilian healthcare systems. Most Brazilians are covered by the Unified Healthcare System (SUS), which provides basic healthcare services free of charge but does not include many of the more complex procedures unless it is practiced in government-supported teaching hospitals. A small portion of the Brazilian population has additional coverage through private or employment-related health insurance plans. Yet, reimbursement from these plans is inadequate for time-consuming consultations and procedures. Therefore, ophthalmologists are not strongly motivated to practice NO when relying on remuneration only from health insurance plans. A minority of specialists can afford to restrict their practice to NO, and when they do, they usually treat only private patients or accept only premier health insurance plans. In most cases, the practice of NO is combined with either general ophthalmology or subspecialties such as retina, orbit and ophthalmic plastic surgery, strabismus, and electrophysiology.

Future Perspectives

Despite these challenges, NO has expanded dramatically in Brazil. The subspecialty is a required subject for the accreditation of ophthalmology residency programs by the Brazilian Council of Ophthalmology, and the subject is included in ophthalmology course curricula and in the programs of all major ophthalmology conferences, such as the annual meetings held by the Brazilian Council of Ophthalmology. The large attendance at lectures on NO is evidence of increasing interest in the subject. In addition, some neurology residency programs offer elective rotations in NO.
Research in NO-related topics has also increased in Brazil. Through CAPES (government program for continuing higher education) and CNPq (National Council for Research and Development), the Brazilian government supports postgraduate research cofunded by universities and local S&T agencies. At least 3 such programs (FMUSP, UNIFESP, and UFMG) have NO-related research projects. The main lines of study in these programs center around structural and functional abnormalities of the optic pathways in chiasmal compression, multiple sclerosis, neuromyelitis optica, papilledema from pseudotumor cerebri, dysthyroid optic neuropathy, and Leber hereditary optic neuropathy.

In conclusion, NO in Brazil is coming of age and is today a subspecialty of which its founding fathers can be proud. As our understanding of disease mechanisms improves and new treatment modalities and diagnostic equipment for visual pathway-related conditions become available, the need for programs offering state-of-the-art training in NO and the number of practicing neuro-ophthalmologists in the country will undoubtedly increase.

Mário L. R. Monteiro, MD, PhD
Department of Ophthalmology and Otorhinolaryngology,
University of São Paulo Medical School,
São Paulo, Brazil

**TABLE 1.** List of Physicians Currently Practicing Neuro-Ophthalmology in Brazil

<table>
<thead>
<tr>
<th>Name</th>
<th>City</th>
<th>State</th>
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<tbody>
<tr>
<td>Adalmir M. Dantas</td>
<td>Niterói</td>
<td>Rio de Janeiro</td>
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<tr>
<td>Alexandre Taleb</td>
<td>Goiânia</td>
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<td>Alexandre Barbosa</td>
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<td>Ana Laura Moura</td>
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<td>Ana Maria Marcondes</td>
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<td>Maria Kiyoko Oyamada</td>
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<td>Tatiana Sakuma</td>
<td>Campo Grande</td>
<td>Mato Grosso do Sul</td>
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<tr>
<td>Wander I. S. Borges</td>
<td>Rio de Janeiro</td>
<td>Rio de Janeiro</td>
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