ORIGINAL CONTRIBUTIONS

5 Peripheral Homonymous Hemianopia: Correlation Between Lesion Location and Visual Field Defects by Means of Cytoarchitectonic Probabilistic Maps  
Eleni Papageorgiou, Luca F. Ticini, Ulrich Schiefer

13 Optic Nerve Head Drusen in Black Patients  
Matthew J. Thurtell, Valérie Biousse, Beau B. Bruce, Nancy J. Newman

17 Fluorescein Angiographic Identification of Optic Disc Drusen With and Without Optic Disc Edema  
Stacy L. Pineles, Anthony C. Arnold

23 Clinical Neuro-ophthalmic Findings in Familial Dysautonomia  

27 Visual Sequelae After Consensus-Based Treatment of Ophthalmic Artery Segment Aneurysms: The Johns Hopkins Experience  
Sivashakthi Kanagalingam, Philippe Gailloud, Rafael J. Tamargo, Prem S. Subramanian, Neil R. Miller

33 Sellar and Parasellar Intravascular Lymphoma Mimicking Pituitary Apoplexy  
Philippe Rizk, Maayan Seitibach, Murad Alturkustani, Andrew Leung, J. Alexander Fraser

PHOTO ESSAYS

38 Homonymous Hemianopia From Infarction of the Optic Tract and Lateral Geniculate Nucleus in Deep Cerebral Venous Thrombosis  
Hilary M. Grabe, J. Rajiv Bapuraj, Jeffrey R. Wesolowski, Hemant Parmar, Jonathan D. Trobe

42 Junctional Visual Field Loss in a Case of Wyburn-Mason Syndrome  
Anthony Liu, Yi-Wen Chen, Steven Chang, Yaping Joyce Liao

CLINICAL OBSERVATIONS

45 Acute Optic Neuropathy Associated With an Intracranial Mass in a Patient With POEMS syndrome  
Heather E. Moss, Grant T. Liu

48 Cortical Vision Loss as a Prominent Feature of H1N1 Encephalopathy  
John H. Pula, Ahmad Issawi, Jeffrey R. DeSanto, Jorge C. Kattah

51 Is Intravitreal Bevacizumab an Effective Treatment Option for Nonarteritic Anterior Ischemic Optic Neuropathy?  
Christina Rapp Prescott, Craig A. Sklar, Robert L. Lesser, Ron A. Adelman

54 Is Leber Hereditary Optic Neuropathy Treatable? Encouraging Results With Idebenone in Both Prospective and Retrospective Trials and An Illustrative Case  
Esfandiar J. Sabet-Peyman, Khizer R. Khaderi, Alfredo A. Sadun

STATE-OF-THE-ART REVIEWS

58 Reappraisal of the Optic Nerve Hypoplasia Syndrome  
Mark Borchert

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Supplemental Digital Content  Video
Like the President of the United States, the Editor-in-Chief of the *Journal of Neuro-Ophthalmology* (JNO) is given an initial 4-year term. As we pass the mid-point of this 4-year term, your editorial office wanted to update you on the Journal.

As you know, in 2010, our publisher, Lippincott Williams & Wilkins, moved the JNO to an online submission system. This has streamlined the management of manuscripts as well as the revision process and publication. We have experienced a 17% increase in submissions over the past 2 years, yet have maintained a rapid time to first decision, averaging 21 days. To a large degree, this is due to the outstanding responsiveness and hard work of our reviewers.

In addition to the rapid escalation in peer review management activities, we have implemented several innovations since the start of 2010. One such feature is the availability of “Published Ahead-of-Print.” At the JNO online site, accepted articles are published within 8 weeks of acceptance and immediately become part of the medical literature cited in PubMed. This means our articles now experience a rapid time from acceptance to publication.

Additionally, we have expanded our online repertoire. To date, 4 podcasts have been posted, featuring interviews with authors of State-of-the-Art Reviews and named lecturers (Hoyt, Jacobson). “Virtual issues,” content collections of previously published JNO articles associated with a particular topic, are also available. Current topics include nonarteritic anterior ischemic optic neuropathy and idiopathic intracranial hypertension. Our expanded electronic capabilities also allow us to publish videos of eye movement abnormalities and pupillary disorders as part of an accepted manuscript, enabling you, the reader, to enjoy an enhanced reading experience online.

The readership of the JNO has been surveyed on 2 occasions in recent years. We have responded by maintaining and adding regular sections including State-of-the-Art Reviews, Point-Counterpoint, Photo Essay, Literature Commentary, Basic Science in Neuro-Ophthalmology, and Clinical-Pathological case study. But at the core of the Journal is the original material submitted by our readers and the greater neuro-ophthalmic community. Our reach into that community continues to grow as the JNO now has received submissions from 36 countries in 2011.

We are grateful for the tremendous support given to the Journal by the editorial board, our reviewers, and the North American Neuro-Ophthalmology Society publications committee and board of directors. It is an honor to oversee and direct the JNO. The future looks bright and we look forward to sharing it with you!
Anatomic Correlates of Visual Field Loss: Some Settled, Some Not

Christian J. Lueck, PhD, FRCP(UK), FRACP

Every reader of this Journal knows that a detailed knowledge of anatomy is fundamental to clinical neuro-ophthalmology. The retinotopic organization of the visual pathways provides an example of how an accurate diagnosis relies on a precise understanding of the relevant neural structures. In this issue, 3 articles touch on the neuroanatomy of visual field loss. Two PhotoEssays report highly unusual causes of pathology affecting the visual pathways while an original contribution looks at cytoarchitectonic probabilistic mapping, a new technique which may prove useful in the ongoing quest to define the retinotopic organisation of the primary visual cortex (V1).

Liu et al (1) present the case of a young girl with Wyburn-Mason syndrome. At 6 years of age, the patient was noted to have decreased vision in her right eye associated with a retinal arteriovenous malformation (AVM). Automated perimetry at 11 years of age revealed a defect in the upper temporal visual field of her normal-appearing left eye, and subsequent imaging of her brain showed that her chiasm was compressed by a large AVM. Intracranial AVMs are occasionally documented to interfere with the retrochiasmal visual pathways in Wyburn-Mason syndrome and there have been a few reports of monocular temporal hemifield defects due to chiasmal involvement. However, a junctional scotoma from chiasmal involvement is extremely unusual.

A second patient reported by Grabe et al (2) is a 20-year-old man who developed a very severe illness due to cerebral venous sinus thrombosis while camping at high altitude in Peru. Cerebral venous sinus thrombosis in this situation typically affects superficial veins, such as the superior sagittal sinus, but this patient’s thrombosis involved deep cerebral veins and resulted in infarction of both thalami and surrounding brainstem structures. Following recovery several months later, a residual right homonymous hemianopia was associated with damage to the left optic tract and lateral geniculate nucleus, both of which were clearly demonstrable on MRI. Homonymous hemianopia due to thrombosis of deep cerebral veins is rare.

Though the pathology was unusual in both these cases, it is reassuring that the pattern of visual field loss was entirely consistent with the anatomic sites of the lesions. We have a very clear understanding of the anatomy of visual field loss generated by lesions located between eye and occipital cortex. However, when it comes to understanding the detailed retinotopic arrangement of the primary visual cortex (V1), things are less certain. This is an ongoing area of debate, and the article by Papageorgiou et al (3) offers an interesting new contribution.

It is just over 100 years since Inouye (4) reported his observations on soldiers wounded in the Japanese wars of 1900 and 1904 to 1905. Both his studies and the subsequent work of Holmes (5,6) largely relied on correlating patterns of visual field loss with an estimate of occipital lobe damage derived from the location and superficial appearance of their patients’ gunshot wounds. Apart from Inouye’s erroneous inclusion of 5° of ipsilateral macular representation, both authors generated conceptually similar retinotopic maps of V1, but that published by Holmes (6) in 1945 is much more widely known.

During the past 35 years, there have been dramatic advances in neuroimaging. New techniques have been applied to the question of the retinotopic organization of V1. Early studies of computed tomography (7,8) and positron emission tomography (9) yielded results compatible with the Holmes map, but the spatial resolution of both techniques was low and did not permit examination of the retinotopic map in any detail.

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The author reports no conflicts of interest.
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TABLE 1. Retinotopic maps of visual field projection to area V1

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Methodology</th>
<th>Number of Subjects</th>
<th>Approximate Percentage of Cortex Devoted to Visual Field</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Central 15°</td>
</tr>
<tr>
<td>Inouye (4)</td>
<td>1909</td>
<td>Missile injuries</td>
<td>30</td>
<td>29*</td>
</tr>
<tr>
<td>Holmes and Lister (5)</td>
<td>1919</td>
<td>Missile injuries</td>
<td>23 (+)</td>
<td>23*</td>
</tr>
<tr>
<td>Holmes (6)</td>
<td>1945</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horton and Hoyt (10)</td>
<td>1991</td>
<td>MRI</td>
<td>3</td>
<td>68*</td>
</tr>
<tr>
<td>Wong and Sharpe (12)</td>
<td>1999</td>
<td>MRI</td>
<td>14</td>
<td>37†</td>
</tr>
<tr>
<td>Dumoulin and Winell (15)</td>
<td>2008</td>
<td>Functional MRI</td>
<td>6</td>
<td>53*</td>
</tr>
<tr>
<td>Wandell and Winawer (16)</td>
<td>2011</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Approximate value measured from text figures.
†Stated in text.

The accuracy of the Holmes map was challenged when MRI became available and offered significantly higher spatial resolution. Horton and Hoyt (10) suggested that human V1 was similar to that of old world primates because they found that the representation of the central 30° of vision occupied approximately 80% of V1 compared with previous estimates by Inouye (4) and Holmes (6) of approximately 40% (Table 1). McFadzean et al (11) studied a larger number of patients using both CT and MRI and reported findings that supported Horton and Hoyt (10). A third MRI study by Wong and Sharpe (12) was not so consistent. These authors offered a slightly different map, this time with a somewhat smaller degree of central field magnification.

Emerging techniques continue to be used in an attempt to settle this debate. Several authors have used functional MRI (13–16), and their findings appear to correlate well with Horton and Hoyt’s map. More recently, 7-T MRI (17) and magnetoencephalography (18) have been applied, but precise retinotopic details from these techniques are not yet available.

One factor that undoubtedly contributes to the variation in the findings of the above studies is that no 2 brains are alike. This is hardly surprising. Our faces are not structurally identical, nor are our internal organs, and the differences do not lie just in simple geometric transformations—resizing and rescaling our faces to one standard template would not render us all identical. It therefore seems neither unlikely that resizing and rescaling brains (these transformations generally form an integral part of image analysis) will yield brains whose component areas (such as V1) are identically arranged. Recent studies have attempted to quantify the extent of intersubject variation by detailed examination of postmortem human brains. One study looked at the precise location of Brodmann cytoarchitectonic areas (19), whereas another study used a combination of diffusion tensor imaging and histology (20). Both studies demonstrated a surprisingly large amount of intersubject variability and both produced “probabilistic maps” that offer estimates of the likely spatial locations of given anatomical structures such as Brodmann area 17 (area V1). In fact, it appears that intersubject variability is sufficiently large that only a very small proportion of the area of cortex defined structurally as area V1 in one subject is likely to overlap spatially with the area of cortex defined as area V1 in every other subject. This degree of intersubject variability must have a major impact on any study that tries to generate a “universal template.”

In this issue of the Journal, Papageorgiou et al (3) have used these “probabilistic maps” to study the retinotopic organization of V1 in 2 patients who had cortical lesions responsible for small areas of peripheral visual field loss. They correlated the location of visual field loss with the precise location of the cortical lesions on MRI and concluded that their findings were more supportive of the original Holmes map (5) than either of the more recent maps suggested by MRI studies (10,12). Comparison of probabilistic maps suggested that one patient’s lesion probably involved part of the optic radiation and V1 while the other’s was more likely to have been centered on V1. This demonstrates how difficult it is to know exactly which functional area is being affected by a given lesion in an individual patient.

Despite all the recent advances in neuroimaging, the bottom line is that the appearance of a lesion on an MRI scan still cannot tell us precisely which part of an individual patient’s primary visual cortex has been damaged. To do this we will need an imaging technique that can define the unique anatomic boundaries of V1 in each patient. The debate over the retinotopic organisation of V1 seems set to continue for some time.

REFERENCES


Peripheral Homonymous Hemianopia: Correlation Between Lesion Location and Visual Field Defects by Means of Cytoarchitectonic Probabilistic Maps

Eleni Papageorgiou, MD, Luca F. Ticini, PhD, Ulrich Schiefer, MD

Background: Peripheral homonymous scotomas beyond 30° from fixation are rare. The paucity of publications describing such visual field defects might be attributed to various factors, including the absence of severe symptoms, routine visual field assessment restricted to the central 30° with automated perimetry, and the collateral circulation to the occipital cortex. The aim of this study was to correlate the brain lesions and perimetric findings in 2 unusual cases of peripheral homonymous scotomas, with the anatomic location of the optic radiation and primary visual cortex.

Methods: Two patients with circumscribed homonymous scotomas beyond 30° related to infarcts in the intermediate area of the visual cortex are reported. We describe a new strategy, which relies on modern lesion analysis and stereotaxic probabilistic cytoarchitectonic maps, to accurately correlate the brain lesion site with the location of the peripheral homonymous visual field defects.

Results: In Case 1, the posterior optic radiation was affected in its termination in the upper intermediate visual cortex. In Case 2, the lesion was located in the upper rostral portion of the primary visual cortex. In both, the most anterior part of the visual cortex and the occipital pole were intact, accounting for preservation of the central and most peripheral visual field. Additionally, correlation of the neuroimaging findings with commonly used maps of the representation of the visual field on the striate cortex suggested that our data were most consistent with the Holmes map.

Conclusions: Modern lesion analysis and cytoarchitectonic maps, in combination with the existing retinotopic maps, may provide reliable clues for the localization of cerebral infarction and prognosis of homonymous visual field defects and may lead to a better understanding of the link between neuroanatomical landmarks and functional outcomes.

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Peripheral homonymous visual field defects (HVFDs) sparing more than 10° of the vertical meridian are rare. As a consequence, retinotopic maps depict just a rough estimate of the peripheral visual field representation (Supplemental Fig. 1, Supplemental Digital Content 1, http://links.lww.com/WNO/A20) (1–3). Three documented cases have described homonymous scotomas beyond 25° from fixation. Mejico et al (4) reported a patient with a peripheral HVFD located 40–60° from fixation due to a cavernous angioma. A second patient with a right homonymous hemianopia beyond the central 50° due to an infarction in the ventral portion of the left calcarine fissure was described by Reche-Sainz et al (5). Barton and Benatar (6) reported a patient with a peripheral HVFD extending between 25 and 40° from fixation caused by an ischemic stroke in the midportion of the inferior calcarine cortex. According to the existing retinotopic maps, lesions affecting this portion of the visual field—from 30° to 60°—are located in the intermediate striate cortex (1–3,7). With the introduction of functional magnetic resonance imaging, a significant amount of data about the organization of human visual field maps has been produced and the position, surface area, and visual field representation of various intact human visual areas have been documented (8–12).
FIG. 1. Case 1. (A) 30° threshold-related, slightly supraliminal automated static perimetry. There are defect points (red circles) on the left outer border in both eyes. (B) Semiautomated kinetic perimetry of the binocular 90° visual field for stimulus III4e. A left inferior absolute homonymous peripheral scotoma is present, extending between 30° and 50° along the horizontal meridian.
To gain further understanding of cortical representation of the visual field, we adopted a novel approach making use of lesion analysis techniques in combination with recently developed stereotaxic probabilistic cytoarchitectonic maps (13) of the optic radiation (14,15) and the primary visual cortex (16). We applied this method to investigate 2 new cases of peripheral homonymous scotomas beyond 30°.

CASE REPORTS

Case 1
A 39-year-old woman was admitted to the hospital for persistent visual phenomena in her left visual field after a migraine attack. On examination, the patient’s best-corrected visual acuity was 20/20 in both eyes, with normal color vision and normal ocular motility. Pupils were equal in diameter and showed no relative afferent pupillary defect. Visual fields assessed with 30° threshold-related, slightly supraliminal automated static perimetry (Octopus 101 perimeter; HAAG-STREIT Inc., Koeniz, Switzerland) were normal except for 2 single-defect points on the left outer border that were present in both eyes (Fig. 1A). Binocular 90° semi-automated kinetic perimetry using a III4e stimulus revealed an absolute left inferior homonymous peripheral scotoma (Fig. 1B). CT revealed an ischemic infarction in the right occipital region. On further investigation, no cardiovascular risk factors were detected. Neuro-ophthalmological examination 12 months later demonstrated that the left peripheral homonymous defect was unchanged from the initial examination. MRI acquired 12 months post-stroke was used to determine the extent of the lesion (Fig. 2A). The posterior extent of the lesion was located 15 mm from the occipital pole, from which the lesion extended 18 mm anteriorly and spared 12 mm of the most anterior aspect of the right calcarine fissure.

Lesion Analysis
The boundary of the lesion was delineated directly on each transverse slice of the individual MRI using MRicro software (http://www.mricro.com) (17). Both the MRI images and the lesion shapes were then transformed into stereotaxic space using the spatial normalization algorithm provided by SPM5 (http://www.fil.ion.ucl.ac.uk/spm/), using default settings. For determination of the transformation parameters, cost-function masking was employed (18).

The resulting normalized lesion area was plotted onto the stereotaxic cytoarchitectonic probabilistic maps of the optic radiation (Fig. 2B) and the primary visual cortex (Fig. 2C) (14–16). These maps illustrate the relative frequency (from 1 to 10) of appearance of a cytoarchitectonically labeled structure of interest in 10 adult human brains, which were normalized on the reference brain provided by SPM5 (e.g., a value of 5 for a specified structure in a certain voxel indicates that the structure was present in that location in 5 of 10 brains). The probabilistic cytoarchitectonic maps thus served as a measure of inter-subject variability for each voxel in the reference space. By superimposing the lesion area onto the cytoarchitectonic maps, we found that the investigated scotoma was induced by a lesion affecting the posterior part of the optic radiation, at its termination in the upper intermediate visual cortex (Fig. 2B, C, Slice 16). The most anterior part of the visual cortex and the occipital pole were intact.

Case 2
A 54-year-old man with a 25-year history of occipital headaches was admitted to the hospital following acute visual field loss on his right side after a severe episode of headache. His medical history was remarkable only for smoking. On examination, the best-corrected visual acuity was 20/20 in both eyes, pupils were equal in diameter and showed no relative afferent pupillary defect, and slit-lamp examination was normal. Visual field testing with 30° threshold-related, slightly supraliminal automated static perimetry (Octopus 101 perimeter) was normal except for a few defects on the right outer border of both eyes (Fig. 3A). Threshold-related, supraliminal automated static perimetry in the 90° visual field revealed absolute right inferior homonymous peripheral scotomas, extending from 30° to 60° in both eyes (Fig. 3B). The MRI images acquired 1 day after onset of symptoms demonstrated 2 small lesions, one in the left intermediate occipital region (Fig. 4A) and another in the right cerebellar hemisphere. These findings were consistent with a subacute stroke. The posterior extent of the lesion was located 16 mm from the occipital pole, from which the lesion extended 21 mm anteriorly and spared 11 mm of the most anterior aspect of the left calcarine fissure. Transesophageal echocardiography revealed a large persistent foramen ovale (PFO) with atrial septum aneurysm. Due to the cerebral embolic stroke, an intervention PFO closure was planned.

Lesion Analysis
Using similar methodology as in Case 1, we found that the lesion causing the visual field defect was located in the upper rostral portion of the primary visual cortex (Slice 12, Fig. 4C), sparing a small anterior part of the visual cortex as well as the occipital pole. According to the cytoarchitectonic maps, the probability was very low that the optic radiation was also affected (Fig. 4B).

DISCUSSION
HVFDs typically involve the central 10° of vision. To the best of our knowledge, excluding reports of damage to the monocular temporal crescent, there are only 3 documented cases of homonymous scotomas beyond 25° from fixation (4–6). Various reasons may account for the paucity of such reports. First, peripheral HVFDs may remain unnoticed by...
FIG. 2. Neuroimaging findings and stereotaxic probabilistic cytoarchitectonic maps for Case 1. (A) Axial FLAIR MRI 12 months after the cerebral infarct. There is a low-density area in the right occipital cortex that spares the occipital pole and the most anterior part of the visual cortex. Signs of cortical atrophy of the right occipital pole are also observed. (B) Plot of the lesion borders on the stereotaxic probabilistic cytoarchitectonic maps of the optic radiation and the primary visual cortex (C). The color bar indicates the absolute frequency of voxels containing the optic radiation and the primary visual cortex from 1 (dark blue) individual brain to 10 (red, overlap of all 10 brains). The superimposed pink contour represents the lesion borders. The highest relative frequency is observed in Slices 12 and 16 and indicates involvement of both the optic radiation (B) and the intermediate visual cortex (C).
FIG. 3. Case 2. (A) 30° threshold-related, slightly supraliminal automated static perimetry. There are a few defects (red circles) on the right outer border in both eyes. (B) Threshold-related, slightly supraliminal automated static perimetry of the 90° visual field. Right homonymous absolute peripheral scotomas, extending from 30° to 60°, are present in both eyes.
FIG. 4. Neuroimaging findings and stereotaxic probabilistic cytoarchitectonic maps for Case 2. (A) Axial FLAIR MRI shows a lesion in the left occipital cortex with sparing of the occipital pole. (B) Plot of the lesion borders on the probabilistic stereotaxic cytoarchitectonic maps of the optic radiation and the primary visual cortex (C). The color bar indicates the absolute frequency of voxels containing the optic radiation and the primary visual cortex from 1 (dark blue) individual brain to 10 (red, overlap of all 10 brains). The superimposed pink contour represents the lesion border of the patient. The highest relative frequency is observed in Slices 12 and 16 and supports involvement of the intermediate visual cortex (C).
the patient because of low spatial resolution of the peripheral visual field. Second, the rarity of pure peripheral HVFDs may be due to anatomical variations leading to collateral circulation in cases of calcarine artery occlusion (19–22). Third, when a retrochiasmal lesion is suspected, automated static perimetry is usually performed within the central 30° of fixation. In both of our cases, the presence of single-defect points on the outer border of the 30° visual field in both eyes aroused suspicion of a homonymous pattern and led to examination of the peripheral visual field. Such subtle defects may sometimes escape detection or be erroneously interpreted as perimetric artifacts. With semi-automated kinetic perimetry in Case 1 and supraliminal automated static perimetry within 90° of fixation in Case 2, the peripheral homonymous defects were accurately detected.

As to the most appropriate perimetric technique for detecting occipital pole lesions, Wong and Sharpe (23) found that manual kinetic perimetry, either with tangent screen or Goldmann technique, coupled with automated static perimetry (Humphrey Field Analyzer, central 30-2 threshold program) are satisfactory screening tests. Our results confirm this observation.

Three retinotopic maps based on individuals with occipital lobe lesions have been proposed regarding visual field representation in the striate cortex. According to Holmes map, approximately 25% of the surface area of the striate cortex is devoted to the central 15° of vision (1,24,25). This has been corroborated with CT (26–28) and positron emission tomography (29). Horton and Hoyt (2) advocated a revised map based on MRI data of 3 patients with occipital lobe lesions, in which the central 15° of vision are represented by approximately 70% of the total surface area of the human striate cortex. Wong and Sharpe (3) challenged this finding by reviewing MRI data from 14 patients with occipital lobe lesions and concluded that the central 15° of vision occupy 37% of the total surface of the human striate cortex.

To determine the location of homonymous scotomas in our patients, we correlated the MRI findings with the proposed retinotopic maps. The map of Horton and Hoyt predicted that the scotomas would begin around 10° from fixation, the refined map of Wong and Sharpe predicted that the scotomas would be located at 15°, and Holmes map predicted that the scotomas would be located at 25°. Our data are consistent with the Holmes map, and support the hypothesis of Mejico et al (4), suggesting that the Horton–Hoyt and the Wong–Sharpe maps may overestimate the area of the striate cortex devoted to the central visual field. In order to exactly localize the brain lesion onto the visual pathway (optic radiation and primary visual cortex) and to investigate its relation to the functional (perimetric) outcome, we used a lesion analysis that combined established reconstruction techniques (17) with the stereotaxic probabilistic cytoarchitectonic atlas developed by the Jülich group (13–16). This methodical approach has been previously used in studies investigating the anatomy of the pupillary light reflex pathway (30), the functional topography of early periventricular lesions in regard to cerebral palsy and reorganization of language (31), the topography of unilateral tactile agnosia (32), and the involvement of damaged white matter fiber tracts in acute spatial neglect (33). Cytoarchitectonic maps are now available for a variety of brain areas, including primary motor, somatosensory, and visual cortices (34–36). In contrast to plotting the lesion onto the reference brain of the Talairach and Tournoux atlas (37), or the Montreal Neurological Institute (MNI) single-subject or group templates (38), these probabilistic cytoarchitectonic maps are based on the analysis of the cytoarchitecture of a sample of 10 human postmortem brains (http://www.fz-juelich.de/ime/ime_brain_mapping) and provide stereotaxic information on the location and variability of cortical areas in the MNI reference space. The technique used in our study overcomes the considerable intersubject variability of anatomical landmarks that occurs in the striate cortex (39).

The prognosis and recovery of function with visual field defects depends on the localization of occipital lobe infarctions. Celebiosoy et al (40) found that striate cortex involvement was associated with poor prognosis. Similarly, Messing and Ganshirt (41) suggested that the best recovery was recorded after lesions of the occipital pole, while those in the striate area had the poorest prognosis. However, caution is needed when correlating the anatomical imaging data with the functional perimetric findings because the areas of infarct may be surrounded by edema especially in the acute phase. This might confound the delineation of the actual lesion area, where irreversible neuronal death has occurred (3,7). The cytoarchitectonic maps support the localization of brain lesions (optic radiation and striate cortex) but do not provide any detail of retinotopic mapping. They provide a useful adjunct to retinotopic maps and conventional MRI.

ACKNOWLEDGMENT

The authors are indebted to Mrs Elke Krapp and Regina Hofer for their help in preparation of this manuscript.

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Original Contribution

24. Inouye T. Die Sehstörungen bei Schussverletzungen der kortikalen Sehsphäre nach Beobachtungen an Versun...
Optic Nerve Head Drusen in Black Patients
Matthew J. Thurtell, MBBS, FRACP, Valérie Bioussé, MD, Beau B. Bruce, MD, Nancy J. Newman, MD

Background: Several studies have suggested racial differences in the prevalence of optic nerve head drusen (ONHD). We aimed to determine the percentage of patients with ONHD who are black and to describe the clinical, ophthalmoscopic, and perimetric findings in these patients.

Methods: We conducted a retrospective chart review of all patients with ONHD seen at our institution between 1989 and 2010. Only black patients with ONHD confirmed on either funduscopy or B-scan ultrasonography were included. Demographic and clinical findings in these patients were recorded and analyzed.

Results: Of the 196 patients with confirmed ONHD, 10 (5.1%) were black. This included 7 females and 3 males with ages ranging from 8 to 61 years. Six of the 10 patients had bilateral ONHD. The ONHD were buried in 11 of 16 eyes and exposed in 5 of 16 eyes. Fifteen of 16 eyes with ONHD had small cupless optic nerve heads. Visual fields were normal in 4 of 16 eyes with ONHD. In the remainder, visual field defects included an enlarged blind spot (5 eyes), constricted field (5 eyes), nasal defect (2 eyes), central defect (1 eye), and generalized depression (1 eye). Visual field defects were present in 4 of 5 eyes (80%) with exposed ONHD and 8 of 11 eyes (72.7%) with buried ONHD. None of the patients were related, and none of their examined family members had exposed ONHD on funduscopic examination.

Conclusions: ONHD are rare in blacks, possibly due to the presence of a larger cup-to-disc ratio or a lack of predisposing genetic factors. Visual field defects are common in black patients with both exposed and buried ONHD.

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Optic nerve head drusen (ONHD) are laminated acellular concretions that form within the substance of the optic nerve head (1). They often occur in small structurally congested optic nerve heads and are inherited in an autosomal dominant fashion with incomplete penetrance (2). Several studies have suggested racial differences in their prevalence (3–6), such that ONHD are said to occur almost exclusively in whites (4). The prevalence of ONHD in blacks is unknown. An autopsy series of American patients found that the prevalence of buried and exposed ONHD was approximately 2%, but the races of these patients were not specified (7). A series of American patients from Miami, where a significant proportion of the population is black, reported that only 2 of 98 patients with exposed ONHD on fundus examination were black (4). A more recent American series, including patients from Galveston (Texas) and Miami, found that 5 of 85 patients with exposed ONHD were black (5). Since equal proportions of black and white patients are seen at our institution, we performed a retrospective chart review to determine the percentage of patients with exposed or buried ONHD who were black and to describe the clinical, ophthalmoscopic, and perimetric findings in these patients.

METHODS

We retrospectively reviewed the clinic charts of all patients with exposed or buried ONHD seen between 1989 and 2010 at our institution. All patients had received a standardized neuroophthalmic assessment, including perimetry (automated 24-2 or kinetic) and fundus photography, and their relatives were examined whenever possible. The nature of any visual field defect was determined by the clinician at the time of the patient’s evaluation and by the author compiling the database (MJT), who was not blinded to the clinician’s visual field interpretation. In cases where there was a discrepancy in visual field interpretation, the nature of the visual field defect was determined by consensus among the study authors. Race was determined by the clinician, based on the patient’s appearance. When the clinician was not certain of the patient’s race, the patient was asked to report their race. We included only black...
patients who had ONHD confirmed on either fundus examination or B-scan ultrasonography. We excluded nonblack patients and all patients in whom an alternative cause for optic nerve head elevation was identified. The study protocol was approved by the Emory University Institutional Review Board.

RESULTS

Of the 196 patients with ONHD on fundus examination or B-scan ultrasonography, 10 (5.1%) were black. There were 7 females and 3 males with ages ranging from 8 to 61 years (mean, 25 years; median, 15 years). The demographic and clinical characteristics of these patients are summarized in Table 1. No patient with ONHD was excluded from the study due to the presence of an additional cause for optic nerve head elevation. Seven of the 10 patients had no visual symptoms and had been referred for evaluation of abnormal optic nerve heads. Two of the 3 patients with visual symptoms (Cases 3 and 10; Table 1) complained of progressive visual field loss in both eyes, and the third patient (Case 6; Table 1) complained of progressive dyschromatopsia in the right eye only. Of the 10 patients, only 1 (Case 8; Table 1) had another ophthalmic disease; in this case, the patient had keratoconus in an eye without ONHD. None of the patients reported a sudden loss of vision to suggest anterior ischemic optic neuropathy or central retinal artery occlusion, and none of the patients had symptoms or signs of raised intracranial pressure. None of the patients were related, and none of their examined family members had exposed ONHD on fundus examination. Six of the 10 patients had bilateral ONHD. Visual acuity was normal in most eyes with ONHD (range, −0.1 to 0.4; mean, 0.08; median, 0.0; logarithm of the minimum angle of resolution notation). Intraocular pressures were within normal limits in all eyes with ONHD. Fifteen of 16 eyes with ONHD had small cupless optic nerve heads, 13 eyes had elevated optic nerve heads, and 5 eyes had exposed ONHD. Perimetry was normal in 4 of 16 eyes with ONHD, whereas there was an enlarged blind spot in 5 eyes, a constricted field in 5 eyes, a nasal defect in 2 eyes, a central defect in 1 eye, and generalized depression in 1 eye. Visual field defects were present in 4 of 5 eyes (80%) with exposed ONHD and 8 of 11 eyes (72.7%) with buried ONHD. No alternative cause for the visual field defects (e.g., glaucoma, papilledema, or compressive lesion) was identified in any patient.

DISCUSSION

Several prior studies have suggested racial differences in the prevalence of ONHD, but these studies have included only patients with exposed ONHD on clinical examination or fundus photographs (3–6). We included patients with exposed

| Table 1. Demographic and clinical characteristics of black patients with ONHD |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Case Age | Sex | VA | RAPD | Optic Nerve Head Appearance | Perimetry [MD] | B-Scan |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| 1 8 F OD 0.0 — Small, elevated, exposed | EBS, nasal [-15.63] | Calcified ONHD |
| 2 12 M OD 0.0 — Normal | Full [GVF] | Not done |
| 3 14 F OD 0.0 — Small, elevated | Inf>sup arcuate [-16.03] | Calcified ONHD |
| 4 14 M OD 0.2 — Small, elevated | EBS, nasal [-4.48] | Calcified ONHD |
| 5 15 F OD 0.0 — Small, elevated | Full [-1.83] | Calcified ONHD |
| 6 15 F OD 0.1 — Small, elevated | EBS [-1.13] | Calcified ONHD |
| 7 18 M OD 0.0 — Small, elevated | EBS [-4.09] | Calcified ONHD |
| 8 40 F OD 2.3† — Small | EBS, nasal [GVF] | Normal |
| 9 53 F OD 0.2 — Small, elevated | Gen depression [-6.53] | Calcified ONHD |
| 10 61 F OD 0.3 — Small, elevated, exposed | Severe constricted [-30.12] | Not done |
| 11 76 F OD 0.3 — Small, elevated, exposed | Constricted, nasal [GVF] | Not done |

*0.3 log unit RAPD.
†VA was decreased OD due to keratoconus.

Central, central defect; EBS, enlarged blind spot; exposed, exposed ONHD; F, female; full, full field; gen depression, generalized depression; GVF, Goldmann (kinetic) visual field; Inf>sup arcuate, inferior greater that superior arcuate defects; M, male; MD, mean deviation (decibels) from 24-2 automated visual field; nasal, nasal defect; OD, right eye; OS, left eye; RAPD, relative afferent pupillary defect; VA, visual acuity (logarithm of the minimum angle of resolution); —, not detected.


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or buried ONHD, confirmed with either fundus examination or B-scan ultrasonography and found that only a small percentage were black, implying that there is a lower prevalence of ONHD in blacks compared to whites. Since approximately 50% of the patients examined at our institution are black, the disproportion is unlikely to be due to referral bias.

There are several possible explanations for the low prevalence of ONHD in black patients. First, racial differences in optic disc morphology may be relevant. It has been proposed that a small scleral canal size may play a role in the pathogenesis of ONHD, since ONHD usually occur in eyes with small cupless optic nerve heads (8). Indeed, almost all eyes with ONHD in our series had small cupless optic nerve heads. Several studies have demonstrated that, on average, blacks have larger optic disc areas, with larger cups and cup-to-disc ratios, compared with whites (9,10). Thus, ONHD may be less common in blacks than in whites, due to a larger average scleral canal size. Using optical coherence tomography, Floyd et al (11) found that the average scleral canal size in eyes with ONHD was not significantly smaller than in control eyes or fellow eyes without ONHD, calling into question whether scleral canal size has any role in the pathogenesis of ONHD. Although the optic nerve heads of the patients in our series appeared small and structurally congested, optical coherence tomographic measurements of scleral canal size were not available for any of the patients, and we are unable to be certain that scleral canal size was smaller than average in these patients.

A second possibility is that the low prevalence of ONHD in black patients might be due to a lack of predisposing genetic factors. Several previous studies have demonstrated that ONHD are inherited in an autosomal dominant fashion with incomplete penetrance (2,3). Although a candidate gene has not yet been identified, genes have been identified for other autosomal dominant and recessive disorders that are associated with ONHD (12–14). None of the patients in our series had ONHD as a feature of another disorder. Furthermore, none were related, and none of their examined family members had exposed ONHD on fundus examination, suggesting that ONHD may be sporadic rather than an inherited trait in these patients. However, we examined only those relatives who accompanied the patient and we did not systematically arrange for other relatives to be examined. Given the small number of patients and incomplete pedigree information, it remains possible that ONHD might be an inherited trait in these patients.

The clinical and ophthalmoscopic findings in our patients were similar to those reported in other large series of ONHD (2–4). The percentage of our patients with exposed ONHD who had visual field defects (72.7%) was substantially greater than that reported in prior studies (~20%–45%) (15–18). While this could be a consequence of referral bias, it might also indicate that visual field defects are more likely to develop in black than in white patients with ONHD, possibly due to racial differences in the sensitivity of retinal ganglion cells to damage at the optic nerve head.

In summary, we have demonstrated that only a small percentage of patients with ONHD are black, suggesting that there is a low prevalence of ONHD in blacks compared with whites. Although the lower prevalence could be due to a larger average cup-to-disc ratio or a lack of predisposing genetic factors in blacks, a large population-based study, with fundus examination or photography and B-scan ultrasonography, would be required to determine the exact prevalence of ONHD in blacks.

REFERENCES


Fluorescein Angiographic Identification of Optic Disc Drusen With and Without Optic Disc Edema

Stacy L. Pineles, MD, Anthony C. Arnold, MD

Background: The fluorescein angiographic criteria for differentiating optic disc drusen (ODD) from optic disc edema have been unclear. We designed a study to identify distinguishing angiographic features of each and to apply them to cases where both drusen and edema were present.

Methods: A computer search was performed for cases evaluated in a university academic neuro-ophthalmology consultative practice and coded as ODD; all cases were reviewed, and those with fluorescein angiography were selected for further study. Cases were classified as either buried or surface ODD. Ten cases with papilledema were selected for comparison. Eight cases of coexistent drusen and edema were identified. Autofluorescence, early leakage, early blockage, late nodular staining, late peripapillary staining, and late leakage were tabulated.

Results: Two hundred sixteen cases of ODD were identified; 62 (116 eyes) had adequate fluorescein angiography for study. Twenty-three eyes were classified as surface ODD; 90% demonstrated early nodular staining of the disc, with late nodular staining in 90% and late circumferential peripapillary staining in 22%; autofluorescence was visible in 93% with preinjection photography. Eighty-three eyes were classified as buried ODD; 25% demonstrated early nodular staining, with late nodular staining in 29% and late circumferential peripapillary staining in 80%; autofluorescence was visible in 12% of those with preinjection photography. In 9 eyes, buried ODD were present with superimposed true edema. In these eyes, early dye leakage, late nodular hyperfluorescence, and late leakage were present.

Conclusion: Early and late fluorescein angiographic features reliably distinguish ODD from edema and may be particularly useful when the conditions coexist.

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The differentiation of optic disc drusen (ODD) from optic disc edema (ODE) is of critical importance because ODE may be a manifestation of a life-threatening condition requiring urgent patient evaluation, whereas ODD is most often a benign process requiring only observation. In cases of ODD located on the disc surface, diagnosis may be straightforward, but with buried ODD, the optic disc appearance may mimic that of ODE. Furthermore, ODE may develop in cases with preexisting ODD, making the correct diagnosis even more uncertain.

Ancillary testing has been utilized to aid in the identification of ODD, including B-mode ultrasonography (1), CT, and autofluorescence (2–5) Optical coherence tomography (OCT) has been recently used to identify changes in retinal nerve fiber layer thickness associated with ODD (6) and to attempt to differentiate ODD from ODE (7). Each of these techniques has significant limitations. They are used primarily to confirm the presence of ODD, which does not rule out the coexistent ODE. Fluorescein angiography (FA) features in ODD have been reported previously (5), but specific criteria for differentiating ODD from ODE remain unclear, and the distinction in cases of superimposed ODE has not been addressed. In practice, late-phase FA may be useful in differentiation but is often misinterpreted, with specifics of intrapapillary vs peripapillary abnormalities and of dye leakage vs staining of the tissues frequently confused. The early phases of the angiogram, which aid in the differentiation, are rarely integrated into the analysis. We reviewed FA findings in cases of ODD evaluated at the Jules Stein Eye Institute, comparing features to ODE and clarifying those features that allow identification of both when they coexist.

METHODS

This retrospective medical record review was approved by the University of California, Los Angeles, Institutional Review Board. A computer search was performed on all patients evaluated in the consultative neuro-ophthalmology...
practice by 1 investigator (A.C.A.) at the Jules Stein Eye Institute from 1990 to 2009, coded as ODD. All cases were examined, and those with fluorescein angiographic studies, performed by routine technique, were selected for further evaluation.

**Inclusion/Exclusion Criteria**

ODD were diagnosed clinically (based either on visible ODD on the disc surface or on the presence of blurred/scalloped optic disc margin and disc elevation without the presence of optic nerve hyperemia, microvascular abnormalities, or nerve fiber layer edema) or by B-mode ultrasonography (40 eyes) or orbital CT scanning (11 eyes). ODD that were initially diagnosed solely by angiography were excluded.

**Method of Record Review**

Color fundus photographs and FAs were reviewed. FAs were evaluated for the following characteristics: 1) the presence or absence of autofluorescence in those angiograms that included preinjection photographs, 2) the presence or absence of early blockage, 3) the presence and characteristics of early

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**Table 1. Fluorescein angiographic characteristics of 116 eyes harboring ODD**

<table>
<thead>
<tr>
<th></th>
<th>Surface ODD (%)</th>
<th>Buried ODD (%)</th>
<th>Combined ODD/ODE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autofluorescence</td>
<td>93</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Early blockage</td>
<td>35</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Early nodular staining</td>
<td>90</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>Late nodular staining</td>
<td>90</td>
<td>29</td>
<td>100</td>
</tr>
<tr>
<td>Late circumferential peripapillary staining</td>
<td>21</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>Early leakage</td>
<td>0</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Late leakage</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

![Image of ODD](image1)

**FIG. 1.** Surface ODD. **A.** Drusen visible superiorly and nasally (arrows). **B.** Arterial phase of FA revealing early blockage of fluorescence due to the presence of surface drusen (arrows). **C.** Mid-phase angiography revealing early nodular staining of drusen (arrow). **D.** Late-phase angiogram revealing further nodular staining of drusen (arrows).
fluorescence, 4) the presence and characteristics of late fluorescence, and 5) the presence of dye leakage from the optic disc at any point during the angiogram. Clinical features were tabulated, and ancillary testing was recorded. The records and FA of 10 diagnosed with papilledema due to idiopathic intracranial hypertension (IIH) were reviewed for comparison.

RESULTS

Patients

Two hundred sixteen patients with the diagnosis of ODD were identified. Of those patients, 70 had undergone FA. Sixty-two patients (116 eyes) met inclusion criteria of the study with age ranging from 9 to 72 years (mean, 36 years). Thirty-five patients were women, and 27 were men. Seven of the patients had been treated for IIH prior to our consultation due to the presumed presence of papilledema.

Fluorescein Angiographic Findings

Fluorescein angiographic features are summarized in Table 1. Twenty-three eyes (20%) were classified as surface ODD, based on the criteria of visible superficial ODD and no clinical evidence of ODE (Fig. 1A). Early blockage was seen in 8 eyes (35%) (Fig. 1B); twenty eyes (90%) demonstrated early nodular staining of the optic disc (Fig. 1C). Late nodular staining of the disc occurred in 20 eyes (90%) (Fig. 1D). Five eyes (22%) demonstrated late hyperfluorescent staining of the peripapillary area not associated with peripapillary atrophy (Fig. 2). Autofluorescence was visible in 13 (93%) of the 14 eyes with preinjection photographs. None of the eyes demonstrated early or late leakage of the dye from the disc.

Eighty-three eyes (72%) were classified as buried ODD, based on criteria of no visible superficial ODD, elevation and blurred margins of the disc, and no peripapillary retinal vascular obscuration or other clinical evidence of ODE (Fig. 3A). Twenty-one eyes (25%) demonstrated early nodular staining of the optic disc (Fig. 2B); the remaining eyes did...

FIG. 2. Example of buried ODD (A) with circumferential peripapillary staining in late-phase angiogram (B).

FIG. 3. Buried ODD of different patients. A. Blurring of disc margins without blood vessel obscuration or nerve fiber layer opacification. B. Mid-phase angiogram revealing early nodular staining (arrows) of the optic nerve. C. Late-phase angiogram showing late nodular staining (arrow) of the optic nerve.
not demonstrate abnormal early disc staining. Early blockage was seen in 9 eyes (11%). Late nodular staining of the disc occurred in 24 eyes (29%) (Fig. 3C). Sixty-six eyes (80%) demonstrated late circumferential peripapillary staining (Fig. 3D). Autofluorescence was visible in 6 of the 49 eyes (12%) with preinjection photographs. None demonstrated early or late leakage of the dye from the disc.

Nine eyes (8%) were classified as buried ODD with evidence of superimposed ODE, based on the presence of visible buried ODD, ultrasonographic, or CT confirmation, in addition to peripapillary retinal vascular obscuration by nerve fiber layer opacity (Fig. 4A). Etiologies of the ODE included diabetic papillopathy (2 eyes), ischemic optic neuropathy (3 eyes), and IIH (2 eyes). In 2 eyes, no etiology for ODE was detected. Six eyes demonstrated early leakage, 2 of which also showed superimposed early nodular staining (Fig. 4B); 3 eyes showed early nodular staining without leakage. No eyes showed early blocking. All eyes demonstrated late leakage and nodular staining (Fig. 4C). Preinjection photography was not performed in any of these cases. An example of a patient with coexistent ODD and ODE is shown in Figure 4. A second example from this category of patients is depicted also in Figure 4. This patient presented with visible optic disk drusen, but it was unclear if optic nerve edema was present as well (Fig. 5A). FA revealed nodular staining with focal leakage in both the early (Fig. 5B) and late (Fig. 5C) phases of the angiogram. The ODE was felt to be due to nonarteritic anterior ischemic optic neuropathy (NAION).

Ten eyes with ODE secondary to IIH were analyzed for comparison. All demonstrated early and late diffuse leakage from the optic disc without visible nodularity or blocking patterns.

**DISCUSSION**

When ODD are visible on the optic disc surface, identification is straightforward, although it does not rule out the presence of superimposed ODE. The clinical features of buried ODD include optic disc elevation, blurred optic disc margins without obscuration of peripapillary retinal vessels, and nodular border of the optic disc, all in the absence of features of ODE, including retinal nerve fiber opacification with obscuration of retinal vessels, microvascular
abnormalities, such as optic disc surface capillary net dilation, telangiectasia, retinal hemorrhages, and exudates. At times, it may be difficult to distinguish ODD from ODE with certainty.

In our case series, 7 patients were treated for IIH but were later found to have ODE as their sole diagnosis. Of the original 206 ODD patients reviewed, 33 underwent CT scanning, 66 underwent MRI, and 24 underwent lumbar puncture. Given the expense and potential risks of these additional tests, the value of simpler less invasive testing to identify ODD and rule out ODE is essential.

The detection of autofluorescence of the optic disc on preinjection photography is confirmatory for ODD, but the technique is most effective when the ODD are on or near the disc surface. For buried ODD, sensitivity is low; Kurz-Levin and Landau (1) documented autofluorescence in only 15 of 82 cases (18%) of buried ODD. CT is limited not only by 1.5-mm thickness of orbital sections, which may miss ODD, but also by the fact that calcification must be present for their detection. B-mode ultrasonography similarly detects only calcified ODD. While no study has clearly identified the percentage of ODD that are calcified, Kurz-Levin and Landau (1) found positive ultrasonography in only 39 of 82 of eyes (48%) with buried ODD. For this reason, we did not require a positive result on ultrasonography or CT for confirmation of the diagnosis. In our study, 40 eyes with buried ODD underwent B-mode ultrasonography; of which, 24 (60%) were positive for calcified ODD. These data corroborate previous studies confirming the limited role for ultrasonography in detection of buried ODD. Johnson et al (7) have reported on the use of time-domain OCT to differentiate ODD from ODE, based on the internal optic nerve contour and the subretinal hyporeflective space. While this technique shows promise, it seems most effective in cases where surface ODD are clinically apparent; in more subtle cases, the distinguishing OCT features are less clear. Buried ODD can be detected with spectral domain OCT (8), but differentiating ODD from ODE has yet to be established with this technique.

FA has been employed to identify ODD and differentiate from ODE, but a comprehensive set of criteria, utilizing the entire angiographic sequence, has not been clearly identified. Sanders and Ffytche (5), and Mustonen and Nieminen (4) reported on FA findings in ODD, describing “early fluorescence” and “nodular well-demarcated late hyperfluorescence” seen without leakage. Cartlidge et al (9) compared the FA findings of eyes diagnosed with “pseudopapilledema” (the percentage with ODD not given) to those of eyes with papilledema, emphasizing the “increased vascularity” seen more often in papilledema. Other FA studies (10–12) have differentiated ODD by noting “disc staining” from ODE characterized by “disc leakage.” But a clear distinction between hyperfluorescence, staining, and leakage, a critical appraisal of intrapapillary vs peripapillary hyperfluorescence, and a comparison of the complete FA sequence in distinguishing between ODD and ODE has not been published.

Our findings demonstrate that careful assessment of the entire FA can reliably differentiate ODD from ODE. Surface ODD do not require FA for diagnosis. In cases of suspected coexistent ODE, the appearance of early or late leakage confirms the presence of ODE. Buried ODD are characterized by either no early staining (75%) or a characteristic early nodular staining (25%), unlike ODE, which will demonstrate early diffuse leakage. Buried ODD also often show late peripapillary staining, either nodular (29%) or circumferential (80%) or both, which is not seen in ODE. On FA, ODE lead to early and late fluorescein leakage from the optic disc (13,14).

The coexistence of ODD and ODE has been described in anecdotal cases of IIH and NAION (15,16), but FA criteria have not been reported. Our data indicate that the presence of fluorescein leakage indicates ODE, and further patient evaluation may be warranted.
We recognize the limitations of our study including its retrospective nature, which may have led to a bias toward obtaining fluorescein angiograms in atypical cases and in those in whom the diagnosis of ODD was more problematic. Nevertheless, our data indicate that in patients with surface or buried ODD suspected of also having ODE, full-sequence FA analysis plays a valuable role in establishing the correct diagnosis.

REFERENCES

Clinical Neuro-ophthalmic Findings in Familial Dysautonomia

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Background: To define the clinical neuro-ophthalmic abnormalities of patients with familial dysautonomia (FD).

Methods: Sixteen patients (32 eyes) with the clinical and molecular diagnoses of FD underwent thorough neuro-ophthalmic clinical evaluation.

Results: Visual acuity ranged from 0.05 to 1.0 decimal units and was reduced in 15 of 16 patients. Mild to moderate corneal opacities were found in most patients but were visually significant in only 2 eyes. Red-green color vision was impaired in almost all cases. Depression of the central visual fields was present on automated visual fields in all patients, even in those with normal visual acuity. Temporal optic nerve pallor was present in all cases and was associated with retinal nerve fiber layer loss in the papillomacular region. Various ocular motility abnormalities also were observed.

Conclusion: Patients with FD have a specific type of optic neuropathy with predominant loss of papillomacular nerve fibers, a pattern similar to other hereditary optic neuropathies caused by mutations either in nuclear or in mitochondrial DNA, affecting mitochondrial protein function. Defects of eye movements, particularly saccades, also appear to be a feature of patients with FD.


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The authors report no conflicts of interest.

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Familial dysautonomia (FD), also known as the Riley-Day syndrome or hereditary sensory and autonomic neuropathy type III, is an autosomal recessive disorder that impairs the development of specific sensory and autonomic neurons during embryogenesis (1–5). The most common mutation, located on the long arm of chromosome 9 (9q31) (6,7), results in a splicing abnormality and a deficiency of the IκB kinase complex–associated protein (IKAP or Elp1) (8–12). The splicing abnormality is tissue specific: neurons produce mostly mutant IKAP messenger RNA (mRNA) and little protein product, whereas other cells produce both normal and mutant mRNAs in different ratios (13). IKAP is widely expressed throughout the body, with its expression being highest in neural tissue and the retina (14).

Patients with FD have a complex neurological phenotype with decreased pain and temperature perception, impaired sense of taste, abnormal swallowing, gait ataxia, decreased/absent myotatic reflexes, and extremely labile blood pressure. Vision deteriorates with age in patients with FD, and by adulthood, most patients have severe visual loss (15–18). Visual impairment has dramatic consequences for these patients as they lack proprioceptive afferents and thus rely heavily on vision for activities of daily living. Dry eye secondary to lacrimal deficiency, myopia, corneal anesthesia, corneal abrasions, and ulcerations were believed to be the main cause of visual deterioration (15,17). However, based on clinical observations, the degree of visual impairment cannot be explained by corneal complications alone, and visual loss occurs in patients without severe corneal damage. Early case reports describe exotropia, pupillary dysfunction, and optic nerve atrophy, but it is not known whether these neuro-ophthalmic features occur in all patients (18–24). Our aim was to define the neuro-ophthalmic phenotype of patients with FD.
METHODS

Subjects
We evaluated 32 eyes in 16 patients with FD, 6 men and 10 women with a mean age of 26.8 years (range, 12–61 years). All patients had typical clinical features, and the diagnosis was confirmed by genetic testing. All patients signed an informed consent and the NYU Institutional Review Board approved the study.

Procedure
Best-corrected visual acuity (BCVA) was assessed independently for each eye using Snellen optotypes with optimum refractive correction, and the results were presented as decimal units. Color vision was estimated using Ishihara plates (Ishihara 16 plates, Tokyo, Japan), and Hardy-Rand-Rittler color vision test (American Optics, Richmond, VA). Pupillary reflexes were assessed using a standard bright light (Halogen illuminator lamp HPX 3.5 V; Welch Allyn, Skaneateles Falls, NY). Ductions, fixation, saccades, pursuit, convergence, vestibulo-ocular reflexes, and optokinetic responses were assessed. Visual fields were obtained using a Humphrey Field Analyzer (HFA 750i; Carl Zeiss, Dublin, CA), with the 30-2 program and SITA Fast strategy using optimal refractive correction. Anterior segments were examined by slit-lamp biomicroscopy. Ocular fundus examination was performed with a binocular indirect ophthalmoscopy (Keeler Vantage, London, United Kingdom) and slit-lamp biomicroscopy (Haag Streit BQ 900; Haag Streit, Koeniz, Switzerland) to evaluate the posterior pole using a noncontact lens of +78 diopters and red-free light with particular attention of the retinal nerve fiber layer. In some patients, mydriatic color and red-free fundus photographs (TRC 50 IX; Topcon, Tokyo, Japan) were acquired.

RESULTS
The main neuro-ophthalmic findings are summarized in Table 1. Myopic refractive defects were present in 27 of 32 eyes. Most patients had a history of corneal lesions. We classified the corneal opacities as absent or mild (17 eyes), moderate (13 eyes), and severe (2 eyes). In none of the eyes was the opacity severe enough to preclude fundus examination through indirect ophthalmoscopy or non–contact lens biomicroscopy, even in the 2 severely affected eyes. Band keratopathy was present in 1 eye.

BCVA ranged from 0.05 to 1.0 decimal units. Most of the patients had acuity less than 0.5 decimal units, which did not appear to be due to corneal opacities or other surface abnormalities except in 2 eyes.

A red-green color vision defect was found bilaterally in all patients examined with variable degrees of severity, and in 4 eyes of 2 patients, blue-yellow color deficiency also was detected.

Central or cecocentral visual field defects were predominant and found in 26 eyes. Four eyes had generalized, deep field depression, and this was associated with poor visual acuity (Table 1). Two eyes had normal visual fields. Retinal nerve fiber layer loss was detected in all eyes, accompanied by temporal pallor of the optic disc. Twenty-five eyes showed only pallor in the temporal region of the optic nerve together with a wedge-shaped loss of fibers in the papillomacular bundle (Table 1). In 7 eyes, there was also generalized optic nerve pallor, but this was always more evident in the temporal portion of the disc (Fig. 1). Retinal vascular tortuosity was present in 6 eyes.

Ocular motility was impaired in various ways (Table 1). While ductions and versions were full in all patients, exophoria was seen in almost all cases (30 eyes). This was

| TABLE 1. Neuro-ophthalmic findings in patients with FD |
|---|---|
| Age, y | No. of Patients |
| 0–20 | 7 |
| 20–40 | 6 |
| 40 | 3 |
| Total | 16 |
| Corneal opacities | No. of Eyes |
| Absent or mild | 17 |
| Moderate | 13 |
| Severe | 2 |
| Total | 32 |
| Visual acuity* | |
| 0.6–1.0 | 2 |
| 0.25–0.5 | 19 |
| 0.05–0.2 | 11 |
| Total | 32 |
| Color vision† | |
| 15/15–11/15 | 6 |
| 10/15–6/15 | 14 |
| 5/15–1/15 | 12 |
| Total | 32 |
| Visual field loss | |
| Mild/nonspecific depression | 2 |
| Generalized depression | 4 |
| Central–ceccocentral | 26 |
| Total | 32 |
| Pupillary reflex | |
| Normal | 4 |
| Hyporeactive | 28 |
| Nonreactive | 0 |
| Total | 32 |
| Optic nerve | |
| Normal | 0 |
| Temporal pallor | 25 |
| Temporal + diffuse pallor | 7 |
| Total | 32 |
| Ocular motility | |
| Exophoria | 30 |
| Saccadic dysmetria | 18 |
| Saccadic intrusion | 24 |

*Decimal notation
†Ishihara color plates (Tokyo, Japan).
associated with limited convergence. There were no limitations of excursions. Saccades tended to be dysmetric; more often they were hypermetric with corrective re-fixation saccades. In some cases, there was adduction slowing, which was confirmed by testing with the optokinetic drum. Pursuit movements were interrupted by repeated saccadic intrusions in almost all cases.

**DISCUSSION**

The main neuro-ophthalmic finding in patients with FD was a characteristic optic neuropathy. Visual acuity was reduced in most patients and appeared to be worse in the older patients. Corneal opacities were present in many eyes, but, in almost all eyes, the central corneas appeared clear enough by slit-lamp biomicroscopy to allow for good vision. The predominant red-green color deficiency that was almost always detected is consistent with optic neuropathy, although some blue color deficits in some eyes may suggest additional retinal dysfunction. The central and cecocentral visual field defects seen in most patients are very similar to those seen in patients with hereditary, toxic, and nutritional deficiency optic neuropathies. In some cases, the central and cecocentral visual field defects were profound and associated with poor visual acuity and color perception. Also, in almost all cases, there was optic nerve head pallor, which was confined to or most prominent in the temporal portion of the optic nerve head and associated with a wedge-shaped area of retinal nerve fiber loss in the papillomacular bundle.

The abnormalities in ocular motility suggest that the disease process in FD can affect ocular motor control mechanisms. The dysmetric saccades, saccadic intrusions, and disrupted pursuit eye movements that we observed might indicate loss of the fine-tuning control of eye movements. Whether these defects are due to abnormalities at the level of the extraocular muscle or due to a supranuclear control deficit cannot be determined by our studies.

There were few retinal findings in our patients. The macular area was always normal with no pigment epithelial changes. In some patients, the fundi showed myopic changes associated with myopic refractive errors greater than −7.00 diopters. Retinal vascular tortuosity was seen in 8 eyes, as previously reported (16,21).

Few authors have described optic neuropathy in FD patients. Rizzo et al (19) studied 3 patients with FD and found optic neuropathy, which they believed was “a rare manifestation of this rare disease.” They did suspect that it appeared later in the lives of affected patients (19). Diamond et al (20) described a group of FD patients who had abnormal visual evoked potentials and optic nerve pallor. Other case reports describing the optic neuropathy in patients with FD have also been published without additional details (21–24). We detected optic nerve damage in all patients, some as young as 11 years old and all with loss of retinal nerve fibers in the papillomacular bundle.

Involvement of central visual field, deficient color perception, and the temporal optic disc pallor that we have observed in patients with FD is strikingly similar to the findings in other hereditary optic neuropathies, such as Leber hereditary optic neuropathy, dominant optic atrophy, and some recessive optic neuropathies. All these optic neuropathies have in common mitochondrial protein dysfunction caused by mutations either in nuclear or mitochondrial DNA (25,26). This suggests that the primary mutation in FD may affect mitochondrial protein synthesis in the nervous system.

**REFERENCES**


Visual Sequelae After Consensus-Based Treatment of Ophthalmic Artery Segment Aneurysms: The Johns Hopkins Experience

Sivashakthi Kanagalingam, MD, Philippe Gailloud, MD, Rafael J. Tamargo, MD, Prem S. Subramanian, MD, PhD, Neil R. Miller, MD

Background: To determine the anatomic and visual outcomes of patients with ophthalmic artery segment aneurysms treated at The Johns Hopkins Hospital using a consensus-based treatment algorithm.

Methods: Retrospective record review of a prospectively accrued case series of 88 patients (101 aneurysms) treated between January 2004 and July 2009. Presenting symptoms and aneurysm parameters were recorded for all subjects. Treatment strategy for all patients was determined by consensus among neurosurgeons, neurointerventionalists, neurologists, and neuroophthalmologists meeting to review the clinical cases on a weekly basis. Final clinical outcomes (aneurysm control, functional status, and vision) were ascertained from in-house examinations, medical records, telephone interviews, or a combination of these methods. Risk factors for visual or other complications were evaluated.

Results: An optic neuropathy was present in at least 30 (34%) of 88 patients after treatment. Presumed new visual loss occurred in 24 (27%) of these patients. The remaining 6 patients had preexisting optic neuropathy–related visual loss that worsened after treatment. No patient with a preexisting optic neuropathy improved following treatment.

Conclusion: Ophthalmic artery segment aneurysms present a treatment challenge because of their anatomic complexity and relationship to critical neural structures, particularly the visual sensory pathway. We have adopted a consensus-based treatment approach in an effort to optimize patient outcomes and aneurysm control. Although our approach resulted in durable treatment of the aneurysm, a sizable proportion of patients experienced new vision loss after treatment, and no patient with preexisting visual loss related to their aneurysm experienced visual improvement after treatment. We recommend that all patients with ophthalmic artery aneurysms receive careful and thorough preprocedural counseling to ensure they are aware of the risks and benefits of treatment regardless of the method used.

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Aneurysms arising from the internal carotid artery (ICA) at the origin of or just distal to the ophthalmic artery are termed “ophthalmic artery segment aneurysms” (1). These aneurysms project dorsally or dorsomedially from the surface of the ICA toward the temporal aspect of the ipsilateral optic nerve (1,2).

The surgical treatment of ophthalmic artery segment aneurysms is both challenging and complex because of their close proximity to the anterior clinoid process and the optic nerves as well as the need to exclude the lesion from the intracranial circulation while maintaining patency of the parent vessel (1–6). Fortunately, refinements in microsurgical techniques and greater understanding of regional anatomy have made surgery of these aneurysms less formidable (7–9). In addition, endovascular therapy has evolved in the last decade to become an effective alternative to microsurgical clipping in the management of these lesions (10–13). Nevertheless, the inherent risk of vision loss remains a significant issue for patients with these aneurysms regardless of the modality of treatment (14,15).

In this report, we present the visual, neurologic, and neuroimaging results in treating patients with ophthalmic artery segment aneurysms treated using our consensus-based strategy at The Johns Hopkins Hospital from January 2004 to July 2009.

PATIENTS AND METHODS

All patients with ophthalmic artery segment aneurysms treated at The Johns Hopkins Hospital between January...
2004 and July 2009 were identified using a database prospectively accrued and maintained by one of the authors (R.J.T.). Further details of the clinical course of the patients were then obtained from the Johns Hopkins electronic patient record and the digital picture archiving and communication system. A total of 88 patients with 101 unruptured and ruptured ophthalmic artery segment aneurysms were identified. We then reviewed the medical records, including operative and procedure notes, as well as all neuroimaging studies on the patients. Age, gender, clinical presentation, and aneurysm characteristics were documented. Aneurysm fundus sizes were taken at the point of maximum width or length. Ophthalmic artery segment aneurysms that measured 1–9 mm in greatest dimension were considered "small"; those measuring 10–24 mm were considered "large," and aneurysms greater than 25 mm were termed "giant." The neck size was regarded as narrow when it was 4 mm or less in largest diameter and wide when it was greater than 4 mm. For patients who presented with ruptured aneurysms, their clinical grade on admission was determined using the Glasgow Coma Scale, and the severity of subarachnoid hemorrhage (SAH) was graded using the Fisher CT Scale. The latter classifies SAH on the basis of the appearance on CT, with no hemorrhage defined as Grade 1, 1 mm thick as Grade 2, more than 1 mm thick as Grade 3, and any thickness associated with intraventricular or parenchymal hemorrhage as Grade 4 (16).

Consensus-Based Treatment

Treatment recommendations for all 88 patients were determined by consensus during a conference held weekly and attended by a consistent group of interventional neuroradiologists, neurosurgeons, neurologists, and neuroophthalmologists. All recommendations were based on patient characteristics and a review of all imaging studies, including MRI and angiography, CT and angiography, and catheter angiography. The recommendations were then communicated to the patient. In some cases, the recommendation was for surgical clipping; in others, endovascular treatment was recommended; in still others, the consensus was that both treatment options had equal risks and benefits. In addition, it was assumed that in some patients for whom surgical clipping was recommended, anatomic features of the aneurysm would require wrapping in addition to or instead of clipping.

Microsurgical Technique

Direct surgery was performed via ipsilateral pterional/frontosphenotemporal craniotomy and often involved an anterior clinoidectomy. The carotid artery in the neck was dissected and the ICA exposed for proximal control. The anterior fossa floor, middle fossa floor, and greater and lesser wings of sphenoid were extensively drilled. After the aneurysm was exposed using the surgical microscope, the dural fold overlying the optic nerve was divided, the relationship of the optic nerve to the aneurysm assessed, and the optic nerve mobilized. This often was followed by drilling of the optic canal and anterior clinoid, followed by clipping of the aneurysm neck once it was free of the dura. In cases in which clipping was deemed inappropriate (9%), the aneurysm dome was contracted by coagulation with a bipolar cautery at a low setting (4–6) and then wrapped with coarse or fine cotton (muslin was not used in any case) and reinforced with fibrin sealant (fibrinogen, factor XIII, thrombin, and calcium). Patency of the ophthalmic artery was confirmed via intraoperative micro-Doppler sensors, and an intraoperative angiogram was performed routinely to confirm correct clip placement, obliteration of the aneurysm, and preservation of flow in both the ipsilateral ICA and the ophthalmic artery.

Endovascular Technique

All interventional procedures were performed under general anesthesia. Following femoral arterial access, a 6-French guide catheter was advanced over a 0.035 guidewire into a stable position in the ICA. In 1 case, arterial access had to be obtained from a brachial approach. Preembolization digital subtraction angiography, including 3-dimensional imaging, was then performed. Patients with an unfavorable sac–neck ratio in whom placement of a stent (Enterprise; Cordis Neurovascular, Bridgewater, NJ, or Neuroform; Boston Scientific, Natick, MA) was anticipated were placed on a combined regimen of aspirin and clopidogrel at least 3 days before the procedure. Under road map guidance, a microcatheter was placed within the aneurysmal sac. Aneurysm coiling was performed using various brands of detachable microcoils. All patients were heparinized during treatment and monitored by assessing activated clotting time. Control angiography was obtained at the end of the procedure to ensure obliteration of the aneurysm as well as patency of the parent vessel and the rest of the intracranial circulation. Patients were admitted to the intensive care unit for overnight observation; heparinization was continued for 24 hours.

Angiographic Follow-up

Patients in this series who received endovascular treatment of their aneurysms subsequently underwent cerebral angiography at least 6 months later, with the results being categorized using the classification proposed by Roy et al (17): complete occlusion of the aneurysm without any opacification of the neck or sac of the aneurysm (Class 1), near-complete occlusion with minimal neck remnant in aneurysms (Class 2), and incomplete occlusion with contrast-enhanced opacification in part of the sac (Class 3). Patients who underwent stent-assisted coiling were assessed for presence or absence of stenosis of the parent vessel, stent migration, and coil impaction.

Clinical Evaluation

All patients with visual complaints before or after treatment of their aneurysms were assessed by a complete examination,
including best-corrected or pinhole visual acuity, color vision, visual field testing, pupillary examination, ocular motor assessment, intraocular pressure measurement, and ophthalmoscopy. Other patients were contacted by telephone and asked if they had experienced any visual changes postprocedure. If so, they were asked to return for an ophthalmologic examination, or if they were under the care of an ophthalmologist or optometrist, their records were obtained and reviewed.

General clinical outcomes were reported using the Glasgow Outcome Score (GOS) (18): a score of 5 indicating a neurologically normal result, 4 with disability but independent, 3 with disability, 2 with vegetative survival, and 1 representing death. Clinical outcomes were recorded at the time of discharge and at follow-up.

RESULTS

Patient Demographics
There were 68 women and 20 men ranging in age from 21 to 76 years (mean ± SD, 52.3 ± 12.4 years). Forty-nine patients were white, 30 African American, 5 Hispanic, and 4 of Asian origin. Among the 88 patients, 31 (35.2%) had multiple intracranial aneurysms. Thirteen patients (14.8%) had 2 ophthalmic artery segment aneurysms.

Clinical Presentation
Nine patients presented with SAH from a ruptured ophthalmic artery segment aneurysm. These patients were treated during the acute phase after rupture. Of the 79 patients with unruptured aneurysms, the patient presentations were as follows: 50 (57%) had an incidental finding detected when neuroimaging was performed for an unrelated reason, 17 (19%) experienced headaches, 6 (7%) presented with visual changes, 3 (3.5%) complained of dizziness, and 3 (3.5%) had experienced at least 1 transient ischemic attack.

Of the patients with incidental ophthalmic artery segment aneurysm findings, 8 had experienced previous rupture of another intracranial aneurysm and 7 had visual symptoms unrelated to the aneurysm, including cataract, glaucoma, and a contralateral aneurysm causing optic neuropathy.

Aneurysm Characteristics
Of the 101 aneurysms, 63 were on the left and 38 were on the right. Seventy-seven (76.2%) were small aneurysms, 22 (21.8%) were large, and 2 (2%) were giant.

Aneurysm Treatment and Outcomes
Sixty-nine aneurysms (68.3%) were clipped, 10 (10%) could not be clipped and were wrapped, and 22 (21.7%) were coiled. Seventeen (77%) of the 22 coiled aneurysms also were stented. Three of the 69 aneurysms that were clipped had undergone prior unsuccessful endovascular embolization elsewhere. Of the 22 aneurysms that were coiled, 2 previously had been coiled incompletely and 3 previously wrapped.

Of the 79 aneurysms for which clipping was attempted, 69 (87%) were clipped successfully as confirmed by intraoperative angiography, 3 (4%) were clipped and wrapped, and 7 (9%) could not be clipped but were wrapped. Subsequent imaging was performed in the 8 of the 9 patients with aneurysms that were wrapped (with and without clipping), and none of their aneurysms was determined to require retreatment. In addition, none of the patients whose aneurysms were wrapped experienced an SAH during the follow-up period, which ranged from 6 months to 5 years (mean, 2 years). Of the 22 aneurysms that were coiled or stent coiled, immediate postprocedural angiography demonstrated complete occlusion (Class 1) in 5 (23%), near-complete occlusion with minimal neck remnant (Class 2) in 7 (32%), and incomplete occlusion with opacification of the aneurysmal sac in 10 (45%). At follow-up, complete occlusion (Class 1) was seen in 9 aneurysms (41%), near-complete occlusion (Class 2) in 3 (14%), and incomplete occlusion in 2 (9%). Seven patients with 8 aneurysms (36%) were lost to angiographic follow-up. During the follow-up period, 4 aneurysms initially demonstrating incomplete occlusion (Class 3) spontaneously progressed to complete occlusion (Class 1), 1 aneurysm progressed from incomplete occlusion (Class 3) to near-complete occlusion (Class 2), and 1 aneurysm, initially classified as near-complete occlusion (Class 2), improved to complete occlusion (Class 1). Mild-to-moderate coil compaction (i.e., contraction of the coils within the aneurysm sac) was noted in 5 aneurysms (23%). Recanalization of the aneurysm and subsequent recurrence at the neck were observed in 2 aneurysms (9%). Neither stent migration nor parent artery stenosis was detected in our series.

Visual Outcomes
Prior to treatment, 13 of the 88 patients had visual complaints. All of these patients were examined before treatment by a member of the Neuro-Ophthalmology Division of the Wilmer Eye Institute. Six of these patients (6.9%) were found to have visual deficits from an optic neuropathy related to their aneurysm. The remaining 7 patients had unrelated causes for their visual complaints (e.g., cataract, glaucoma). An additional 5 patients (5.7%) with no visual complaints were evaluated preoperatively and found to have no visual deficits. Posttreatment, 37 (42%) of 88 patients were examined in our institute. Of the remaining 51 patients, we reviewed records of 34 patients (38.6% of total) from outside ophthalmologists, neuro-ophthalmologists, or optometrists. Seventeen patients (19.3%) for whom we were unable to obtain records were contacted by telephone and asked if they had any visual symptoms that had occurred after their surgery. Based on the above assessments, we determined that at least...
30 patients (34.1%) had posttreatment visual dysfunction. Twenty-four of these individuals (80%) definitely or possibly had developed a new visual deficit. Among the 6 patients with preexisting optic neuropathy–related visual loss, 5 (16.6%) experienced further visual loss and 1 (3.4%) maintained stable decreased vision. Thus, none of the patients with preexisting aneurysm-related visual loss experienced improvement in vision posttreatment. In addition, 2 patients developed visual loss in the eye contralateral to the aneurysm following treatment (see below).

Of the 24 patients who apparently or definitely had normal vision preoperatively and who experienced new visual deficits following treatment, 21 had undergone clipping of their aneurysms, 2 had had their aneurysms wrapped, and 1 had had the aneurysm coiled. In 5 of these patients, the aneurysm had ruptured prior to treatment, whereas 19 patients had unruptured aneurysms. Fifteen of the patients (62.5%) had small aneurysms, 7 (29.2%) had large aneurysms, and 2 (8.3%) had giant-sized aneurysms. In 13 patients (54.2%), the new visual deficit consisted of decreased visual acuity, reduced color vision, and a visual field defect. In 12 of these patients, the visual deficit was related to a new optic neuropathy, whereas in 1 patient, pretreatment rupture of the aneurysm produced Terson syndrome with persistent visual loss despite clearing of the intracranial hemorrhage. The degree of visual loss ranged from 20/25 in 1 patient to no perception of light in 2 patients, and 7 of the 13 patients had visual acuity of 2/100 or worse in their affected eye. Of the 11 remaining patients, 3 had normal acuity but reduced color vision and a visual field defect in the affected eye, and 8 patients had only a visual field defect associated with normal acuity and color vision.

Of the 5 patients who experienced progression of their optic neuropathy posttreatment (Table 1), all had unruptured aneurysms: 1 was giant sized, 3 were large, and 1 was small. All patients in this group experienced progressive decreased visual acuity, color vision, and worsening visual field defects. Two of the 5 patients had undergone surgical clipping and 3 had undergone coiling (Table 2). Two of the patients, 1 who underwent clipping and 1 who underwent coiling, had had unsuccessful or incomplete treatment elsewhere before undergoing definitive treatment at our institution. Both experienced both ipsilateral and contralateral visual loss following treatment.

Among the 31 eyes with visual field loss, the defects were purely or primarily inferior in 19 (61.3%). Among the remaining 12 eyes, the defect was nasal in 5 (41.7%), superior in 2 (16.7%), and complete in 2 (16.7%). The remainder of the eyes had mixed defects. The only 2 eyes with purely temporal visual field defects were those contralateral to the aneurysm.

**Complications**

Complications following clipping or wrapping occurred in 19 (27%) of 69 patients, of whom 3 had ruptured aneurysms and 16 had unruptured aneurysms. These complications included stroke (9%), cranial nerve palsies (6%), epidural or subdural hemorrhage (4%), hydrocephalus (1%), myocardial infarction (1%), pulmonary emboli (1%), heparin-induced thrombocytopenia (1%), seizure (1%), cerebral salt wasting (i.e., hyponatremia and dehydration from centrally mediated excessive renal sodium excretion) (1%), vision loss from clipping of contralateral intracranial aneurysm (1%), and diabetes insipidus (1%). Complications following coiling occurred in 4 patients (21%), of whom 1 had a ruptured aneurysm and 3 had unruptured aneurysms. The complications in this group of patients included SAH (5.2%), deep vein thrombosis (5.2%), contralateral occipital hemorrhage and associated vision loss (5.2%), right arm compartment syndrome (5.2%), and transient paresthesias (5.2%).

**Clinical Outcomes**

At discharge, the overall clinical outcomes were excellent (GOS, 5) in 58 patients (65.9%), good (GOS, 4) in 16 (18.2%), and fair (GOS, 3) in 14 (15.9%). At follow-up at least 6 months posttreatment, clinical outcomes were excellent in 66 (75%), good in 13 (14.8%), and fair in 9 (10.2%). As might be expected, patients with unruptured aneurysms were more likely to have an excellent outcome than those with ruptured aneurysms. There were no patient deaths.

**DISCUSSION**

The paraclinoid segment of the ICA is known to be a particularly challenging region to access due to several anatomic complexities, including the adjacent anterior

**TABLE 1.** Progression of preexisting optic neuropathy due to ophthalmic artery segment aneurysm (n = 5 eyes)

<table>
<thead>
<tr>
<th>Pretreatment VA</th>
<th>Posttreatment VA</th>
<th>Treatment Modality</th>
<th>Prior Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light perception</td>
<td>No light perception</td>
<td>Coiling</td>
<td>Wrapped</td>
</tr>
<tr>
<td>4/200</td>
<td>Hand motion</td>
<td>Coiling</td>
<td>None</td>
</tr>
<tr>
<td>4/200</td>
<td>1/200</td>
<td>Clipping</td>
<td>Stent + coiled</td>
</tr>
<tr>
<td>20/40</td>
<td>20/50</td>
<td>Coiling</td>
<td>None</td>
</tr>
<tr>
<td>20/30</td>
<td>20/50–1</td>
<td>Clipping</td>
<td>None</td>
</tr>
</tbody>
</table>

VA, visual acuity.
TABLE 2. Types of visual field defects due to ophthalmic artery segment aneurysm (n = 31 eyes)

<table>
<thead>
<tr>
<th>Visual Field Defects</th>
<th>No. of Eyes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior altitudinal</td>
<td>10 (32.3)</td>
</tr>
<tr>
<td>Nasal</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>Inferior–nasal quadrant</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Complete field loss</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Temporal (contralateral eye)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Superior arcuate</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Inferior–temporal quadrant</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Complete temporal + inferior nasal</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Complete inferior + superior nasal</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Superior–temporal quadrant</td>
<td>1 (3.2)</td>
</tr>
</tbody>
</table>

clinoid process and optic nerves, as well as the potential for aneurysms in this location to be partly extradural (1,3,18).

Previous reports of aneurysms of the entire paraclinoideal segment usually deal with a treatment modality: microsurgical clipping (3,5,14,19–24) or endovascular coiling (10,17,25,26). Few have addressed in detail the risks of visual loss since the availability of endovascular coiling compared to surgical clipping or wrapping (11,13,15,27). Furthermore, inclusion of other ICA aneurysms in some series makes accurate assessment of visual morbidity of ophthalmic artery segment aneurysms difficult (28).

In this series, we have used the classification of ophthalmic artery segment aneurysms proposed by Day (1), that is, those arising in clear relation to the ophthalmic artery. We chose this subset of aneurysms because of their proximity to the optic nerve and the potential for treatment to be associated with damage to the visual apparatus, resulting in visual loss. Using a consensus-based approach, our results demonstrate that regardless of the treatment modality, there is significant risk of vision loss. Twenty-nine patients (33%) had what appeared to be either a new visual deficit or a worse visual deficit after treatment, and no patient with preexisting visual loss experienced visual improvement postoperatively. Factors associated with postoperative vision loss were greater aneurysm size, pre-treatment aneurysm rupture, preexisting visual loss, and aneurysm retreatment. Specifically, 2 giant aneurysms, 7 (32%) of 22 large aneurysms, and 15 (19.5%) of 77 small aneurysms occurred in the group of patients that experienced visual deficits. Five (56%) of 9 ruptured aneurysms were in this group vs 19 (21%) of 92 unruptured aneurysms. Five (83%) of 6 patients with preexisting visual symptoms experienced worsening of their vision posttreatment. In addition, 2 patients in this series, both with large aneurysms, had been treated previously at another institute: one patient had an aneurysm stented and coiled and the other patient had an aneurysm wrapped. Both these patients had bilateral postoperative vision loss.

The most common locations of the visual field defects in the 31 eyes in which defects were present were completely or partly inferior or nasal, presumably reflecting the location of the aneurysm superior and/or temporal to the optic nerve, the surgical approach to the aneurysm, or both. The only 2 eyes with purely temporal visual field defects were those contralateral to the aneurysm, reflecting damage to the nasal region of the contralateral optic nerve, the region most likely to be damaged by the aneurysm or the surgical approach.

Posttreatment optic nerve–related visual loss in patients with ophthalmic artery aneurysms may occur by several mechanisms regardless of the treatment modality used. Intraoperative injury of the optic nerve during clipping may occur from direct vascular compromise (4,29,30), excessive manipulation (6,31), or direct heat from the high-speed drill (12,24,32–34). Wrapping an unclippable or a partially clipped aneurysm may induce a significant inflammatory reaction (35). Suggested strategies to improve visual outcomes postoperatively include minimizing manipulation of the optic nerve during dissection of the surrounding tissue and placement of the clip, preservation of the blood supply to the nerve during these procedures, judicious use of irrigation during drilling of the anterior clinoid process, avoiding the use of muslin for wrapping an aneurysm, and using systemic corticosteroids to reduce the damage caused by muslin-related inflammation (1,3,35,36). Vision loss postcoiling may result from emboli to the optic nerve or retina, an increase in mass effect from coil packing, or coil-related perianeurysmal inflammation that may or may not respond to systemic corticosteroids (11,35,37).

A major limitation of this retrospective study is that not all patients underwent a preoperative or postoperative visual assessment. It is therefore possible that some patients who were visually asymptomatic before and after surgery nevertheless had an unappreciated preoperative deficit that worsened postoperatively and that some patients who had no visual deficit preoperatively had a subclinical postoperative deficit. Thus, the percentage of patients with new or worse visual deficits following treatment of their aneurysms is likely higher than 33%. Although we did not appreciate optic disc pallor in patients with new visual complaints and evidence of an optic neuropathy who were examined within a few days to a week after treatment, we did not perform optical coherence tomography of the peripapillary retinal nerve fiber layer in any of the patients to determine if any had a preexisting subclinical optic neuropathy.

Nevertheless, our findings indicate that regardless of the procedure used to treat an ophthalmic artery aneurysm and even when the treatment used is consensus based, there is a significant risk of visual loss following treatment. There appears to be little chance for improvement of vision in eyes that have already experienced visual loss from the aneurysm following treatment. Finally, patients with giant ophthalmic artery aneurysms may experience not only ipsilateral visual loss following treatment but also contralateral visual loss from damage to the contralateral optic nerve. We recommend that
all patients with ophthalmic artery aneurysms be informed prior to endovascular or surgical treatments that there is a risk of permanent vision loss that may be severe and potentially bilateral and that the likelihood of visual recovery after treatment is low.

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Oriental Contribution
Sellar and Parasellar Intravascular Lymphoma Mimicking Pituitary Apoplexy

Philippe Rizek, MSc, MD, Maayan Seitelbach, MD, Murad Alturkustani, MD, Andrew Leung, MD, J. Alexander Fraser, MD

Background: Intravascular lymphoma (IVL) is a rare subtype of large-cell non-Hodgkin lymphoma, characterized by proliferation of lymphoma cells within the lumina of small vessels. There are no previously reported cases of IVL involving the pituitary gland presenting with neuro-ophthalmic findings.

Methods: A 68-year-old female presented with headache, right third nerve palsy, and Horner syndrome. MRI showed a 1.4-cm sellar mass consistent with a pituitary macroadenoma. Two weeks later, despite treatment with dexamethasone, the patient developed complete bilateral ophthalmoplegia and ptosis. Repeat MRI showed invasion of the clivus and cavernous sinuses, and a transsphenoidal pituitary biopsy was undertaken.

Results: The preliminary histopathology was consistent with bland pituitary apoplexy, but subsequent examination of an incidentally biopsied nasal polyp revealed endovascular malignant lymphoid cells that, on further scrutiny, were also present in the pituitary tissue. The diagnosis of IVL was confirmed, and the patient had an excellent clinical and radiological response to cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab (CHOP-R) chemotherapy.

Conclusion: IVL may involve the pituitary gland, causing sellar mass effect, cavernous sinus infiltration, and pituitary ischemia, mimicking pituitary apoplexy with neuro-ophthalmic features. It can be effectively treated with CHOP-R chemotherapy.

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CASE REPORT

A 68-year-old left-handed female was admitted to the hospital from the emergency room with right ptosis and diplopia. Over the previous month, she developed left cheek pain and severe frontal and retro-orbital headaches. Diagnosed with a sinus infection, the patient failed to improve with decongestants and antibiotics. One week prior to admission, she developed horizontal binocular diplopia associated with nausea and...
presyncope. The onset of complete right ptosis prompted her visit to the emergency room.

Medical history was significant for type 2 diabetes mellitus, hypercholesterolemia, and a hysterectomy for endometrial carcinoma 20 years ago. She was an ex-smoker and rarely used alcohol.

On physical examination, the patient was afebrile with stable vital signs. Systemic examination was unremarkable. Visual acuity was 20/25 bilaterally, color vision was intact, and kinetic visual fields were normal. She had a miotic right pupil, most apparent in dim light without a relative afferent pupillary defect. In primary position, the patient had a 30– prism diopter exotropia. Ocular motility was normal with the exception of diminished adduction of the right eye. There was no slowing of adducting saccades and no nystagmus of the abducting eye to suggest internuclear ophthalmoplegia. Anterior segment and funduscopic examinations were unremarkable. The remainder of the neurological examination, including facial sensation, was normal. Testing with 4% cocaine eyedrops confirmed a right Horner syndrome.

Neuroimaging revealed a sellar mass extending into the right cavernous sinus (Fig. 1A). The patient was placed on dexamethasone to treat edema related to a presumed pituitary macroadenoma and possible apoplexy. Blood work showed deficiency of anterior pituitary hormones: luteinizing hormone and follicle-stimulating hormone were 2.0 IU/L (normal, 16.0–54.0 IU/L) and 3.0 IU/L (normal, 23.0–116.0 IU/L), respectively; TSH was 0.11 mIU/L (normal, 0.27–4.2 mIU/L); and free T3 and T4 were 2.4 pmol/L (normal, 3.0–6.5 pmol/L) and 15 pmol/L (normal, 10–24 pmol/L), respectively. Cortisol was 31 nmol/L (normal, 119.0–618.0 nmol/L); however, this was measured after the patient had received corticosteroids. Her prolactin was normal at 25 mg/L (normal, 2.0–20.0 µg/L).

There was a significant improvement in the patient’s headache and cranial nerve findings with steroids. The neurosurgery service felt there was no urgency for surgical intervention, given the rapid clinical improvement on dexamethasone. She was discharged home with close outpatient follow-up 4 days after admission.

The patient was readmitted 2 days later with worsening headache. Brain CT revealed no pituitary hemorrhage. Over the next several days, she developed complete bilateral ophthalmoplegia, with bilateral ptosis and nonreactive pupils. Brain MRI performed 17 days after the first study revealed increased size of the sellar mass with bilateral cavernous sinus involvement (Fig. 1B). Dural thickening and enhancement and signal change within the marrow of the dorsum sella and clivus were now detected raising the suspicion for an infiltrative or metastatic process. The brainstem was not involved, and careful review of postcontrast MRI showed no evidence of leptomeningeal disease. Systemic metastatic workup, including CT of the thorax, abdomen, and pelvis, mammography, and bone scan, was negative. Cerebrospinal fluid (CSF) analysis was unremarkable. One sample of CSF was sent for cytology and returned negative for malignancy. Flow cytometry could not be performed because of insufficient cell count. Nasopharyngoscopy revealed a polyp in the right nasal cavity. Transsphenoidal biopsies of the nasal polyp and sellar mass were performed.

Preliminary pathology of the sellar tissue was consistent with normal pituitary tissue, with areas of focal necrosis suggestive of “mild pituitary apoplexy”; final pathology was deferred pending immunohistochemical staining. Meanwhile, the nasal polyp pathology returned consistent with sinonasal hemangiopericytoma. Ectatic vascular spaces within the hemangiopericytoma contained large malignant

FIG. 1. Contrast-enhanced T1 coronal MRI. A. At initial presentation, there is a homogeneously enhancing sella mass (arrow) with right cavernous sinus involvement (arrowhead). B. On second hospital admission, there is increased size of the sellar mass (arrow) with bilateral cavernous sinus involvement (arrowheads). C. Tumor regression after 3 cycles of CHOP-R chemotherapy.
lymphoid cells (Fig. 2A) that stained positively with B-cell markers (Fig. 2B–D). Final pathology of the pituitary gland did reveal focal areas of infarction (Fig. 3A), while immunohistochemistry also demonstrated endovascular malignant lymphoid cells (Fig. 3B). The presence of identical endovascular malignant lymphoid cells within both the pituitary gland and the hemangiopericytoma confirmed the final diagnosis of IVL.

The patient was treated with 3 cycles of cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab (CHOP-R) chemotherapy. Repeat MRI after 3 cycles of CHOP-R, approximately 2 months after initial presentation, revealed resolution of the mass (Fig. 1C). At follow-up 6 months later, the patient had a right third nerve palsy, but the remainder of her bilateral ophthalmoplegia had resolved.

DISCUSSION

Our patient demonstrated a rare presentation of IVL with sellar and bilateral cavernous sinus involvement. This precipitated the abrupt onset of bilateral ophthalmoplegia mimicking pituitary apoplexy. Our literature review revealed no previous cases of IVL involving the pituitary gland presenting with neuro-ophthalmic findings.

Arriving at a diagnosis of IVL is challenging since it is established postmortem in 53% of cases (15). Although peripheral blood smear is nondiagnostic, and CSF often does not reveal malignant cells (16), the diagnosis of IVL can sometimes be made antemortem by skin biopsy, provided the disease is suspected. The clinical presentation, laboratory results, and neuroimaging of our patient were initially consistent with apoplectic pituitary macroadenoma. Pituitary biopsy revealed areas of necrosis, consistent with pituitary apoplexy. The key pathological finding in this case, the presence of endovascular malignant lymphoid cells, was almost overlooked on the pituitary biopsy. The detection of these cells within a nasal polyp, incidentally biopsied on the transsphenoidal approach to the pituitary gland, allowed the diagnosis of intravascular large B-cell lymphoma to be made.

Leptomeningeal involvement in IVL is largely confined to areas overlying enhancing parenchymal lesions (17). Pachymeningeal involvement is a more common neuroimaging

![Image](https://example.com/figure2.png)

**FIG. 2.** Histopathology of the sinonasal hemangiopericytoma. **A.** The malignant lymphoid cells (arrowheads) are present in the small blood vessels of the hemangiopericytoma (hematoxylin & eosin, ×100). These malignant cells stain with **B** CD20 (×200), **C** BCL2 (×400), and **D** BCL6 (×400).
and pathological finding in IVL, resulting from lymphomatous infiltration of meningeal blood vessels causing a mix of inflammation and ischemia (18). Cranial nerve involvement, when it occurs in IVL, may be on the basis of mass effect from nearby tumor, as in our patient, or from small vessel ischemia caused by intravascular tumor infiltration (19).

There have been no previous reported cases of parasellar IVL presenting with cranial nerve findings. Schleinitz et al (20) described 2 cases of IVL causing hypopituitarism; one patient diagnosed by skin biopsy had normal-sized pituitary, and the other patient, who was diagnosed by bone marrow biopsy, had an enlarged pituitary on MRI. Kraus et al (12) reported 2 patients with hypopituitarism and a normal MRI of the pituitary. IVL patients have also been reported (14,20) with hypopituitarism and empty sella on MRI of the pituitary (14,20).

Systemic IVL can spread to the pituitary gland without mass formation and cause pituitary dysfunction (12–14). The lack of tissue-specific vascular homing receptors, CD29 and CD54, has been reported in patients with IVL and may contribute to the intravascular and disseminated distribution pattern of the neoplasm (21). In our patient, spread of IVL to the cavernous sinuses would explain her initial right third nerve palsy and Horner syndrome, followed by development of bilateral ophthalmoplegia.

Chemotherapy is the current treatment for IVL. Anthracycline-based regimens have shown clinical benefit, with CHOP being the most commonly used (22–24). A case series by Ferreri et al (1) examined 38 cases of IVL and revealed a response rate of nearly 60% and a 3-year survival of 32% after anthracycline-based chemotherapy. Several studies have demonstrated the benefit of adding rituximab, a CD20 monoclonal antibody, to anthracycline-based regimens in the treatment of IVL (3,25,26). One such study compared rituximab to placebo as an adjuvant to CHOP-based chemotherapy (3). There was no difference in the rate of treatment-related deaths, but at 18 months, the rituximab group showed higher rates of complete response, 2-year progression-free survival, and 2-year overall survival. Thus, the current recommended first-line therapy for IVL is an anthracycline-based regimen, such as CHOP, along with rituximab.

Since 35%–40% of IVL patients present with neurological symptoms, and one third of IVL relapses involve the CNS, some authors argue that first-line chemotherapy should include CNS-penetrating agents, such as methotrexate (MTX), either systemically or intrathecally (23,26–28). Other treatment modalities including autologous stem cell transplantation (1,29–35) and radiotherapy (36,37) have shown limited efficacy to date.

Our patient had a complete MRI response after 3 cycles of CHOP-R chemotherapy, with resolution of the sellar mass and no features of tumor recurrence. At 6-month follow-up, she had a residual partial right third nerve palsy, presumably on the basis of axonal damage, but the remainder of her complete bilateral ophthalmoplegia had resolved. She is to receive 3 more cycles of CHOP-R with intrathecal MTX.

REFERENCES


Abstract: A 20-year-old man developed right homonymous hemianopia, hemiparesis, and hemisensory loss from deep cerebral venous thrombosis in the setting of high altitude. Approximately 3 months later, brain MRI showed encephalomalacia of the left optic tract and lateral geniculate nucleus, as well as signal abnormalities of the internal capsule and posterolateral thalamus. Homonymous hemianopia has previously been described in 1 case after deep cerebral venous thrombosis but without detailed neuroimaging features.

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CASE REPORT

A 20-year-old man began experiencing intermittent headaches while he was camping in Peru at high altitude of 16,000 feet (4,877 m). After he had descended, the headaches persisted and he felt too ill to eat or drink appropriately. He became progressively confused and somnolent and was found unresponsive. In a local emergency room, hemoglobin was 18.0 g/dL and brain CT showed sagittal sinus thrombosis with bilateral thalamic infarcts.

After transfer to the United States 5 days later, brain CT showed high attenuation in the straight sinus and internal cerebral veins and low attenuation in both thalami, internal capsules, and the midbrain, signs consistent with thrombosis of the deep cerebral venous system (Fig. 1A). Magnetic resonance venogram at the time showed absent filling of the internal cerebral vein (Fig. 1B). Right lower extremity popliteal deep venous thrombosis was also found on physical examination.

The patient underwent ventriculostomy for hydrocephalus attributed to intraventricular hemorrhage. He was
given heparin as anticoagulation therapy. Within 2 weeks, he began to regain consciousness and was well enough to undergo rehabilitative therapy. He reported being unable to see objects in his right hemifields. All aspects of an ophthalmologic examination were normal, except for confrontation visual fields, which showed a complete right homonymous hemianopia confirmed by automated perimetry (Fig. 2). Neurological examination demonstrated right hemiparesis and right hemisensory deficit. He was found to be heterozygous for the Factor V Leiden mutation and had an elevated Factor VIII level on coagulation workup. Eight weeks later, a right afferent pupillary defect was detected and ophthalmoscopy disclosed bow-tie optic disc pallor in the right eye and temporal optic disc pallor in the left eye. Neurological examination showed dystonic right hemiparesis that was most striking in the hand. He had a right hemisensory loss to pinprick with hyperesthesia on the face and hypesthesia on the right side of his body. Deep tendon reflexes were slightly increased on the right, especially in the upper extremities. He circumducted with the right leg on ambulation.

Brain MRI performed 84 days after the event showed encephalomalacia of the left optic tract (Fig. 3B), lateral geniculate nucleus (Fig. 3C), internal capsule (Fig. 3D), and thalamus (Fig. 3D). Similar, but less marked, changes were noted of the corresponding structures on the right side. This study also demonstrated that the caliber and flow of the internal cerebral veins was normal, consistent with resolution of the venous thrombosis.

**DISCUSSION**

We have described a patient who sustained homonymous hemianopia in the setting of deep venous sinus thrombosis at high altitude. This report is distinctive in 2 ways: 1) homonymous hemianopia has only been reported once in deep venous sinus thrombosis (1) and 2) deep venous sinus thrombosis has been rarely reported at high altitude (1).

To our knowledge, the only previously published description of homonymous hemianopia in deep venous sinus thrombosis (2) was part of a small case series in which Case 1 involved a 30-year-old woman with progressive headache and associated emesis who noted “a right visual defect that hindered her walking ability.” A “right hemianopia” was found on examination. Subsequent MRI and magnetic resonance venogram demonstrated hemorrhagic infarction of the left thalamus with thrombosis of the deep venous system, including the internal cerebral veins, vein of Galen, and the left transverse and sigmoid sinuses. After 6 months, her “only residual symptoms were fatigue and . . . headache.”

Our patient was unconscious for 2 weeks and with recovery had persistent right hemiparesis, hemisensory loss, and a complete right homonymous hemianopia. The visual field defect was accompanied by a right afferent pupil.
defect, bow-tie pallor of the right optic disc, and temporal pallor of the left optic disc, findings indicative of left optic tract axonal injury.

The spoiled gradient MRI sequence, which provided high-resolution detail, showed encephalomalacia in the region of the left optic tract and lateral geniculate nucleus (Fig. 3B, C), as well as the posterolateral thalamus, responsible for the hemisensory loss, and the medial internal capsule, responsible for the hemiparesis (Fig. 3D). We believe that such clinical–anatomical correlation has not been previously demonstrated in this setting.

The structures affected in our patient are all drained by the deep cerebral venous system. Specifically, the thalamostriate (terminal) vein drains the internal capsule and is usually the largest tributary of the internal cerebral vein (3). The inferior and posterior thalamic veins drain the posterolateral thalamus and lateral geniculate nucleus and empty into the basal vein of Rosenthal (3). The internal cerebral veins then join the basal veins of Rosenthal to become the major contributors to the great cerebral vein of Galen (3).

Our case is also unusual in that it occurred at high altitude. Venous thrombosis at high altitude has traditionally involved the superficial cerebral venous system (4,5). Fujimaki et al (4) reported a 27-year-old man who developed thrombosis of the vein of Labbé due to high-altitude polycythemia. Song et al (5) described 3 mountain climbers in the third and fourth decades of life who developed thrombosis at various sites: subarachnoid veins, superior sagittal sinus, and transverse sinus.

We were only able to find 1 documented case of deep cerebral venous system thrombosis at high altitude (1). It involved a 37-year-old woman who developed dizziness, headache, and vomiting on the fourth day of a mountain-climbing expedition in Nepal reaching a maximum altitude of approximately 4,000 m. Brain CT performed 10 days later demonstrated symmetrical hypodensities of the deep gray nuclei with relative hyperdensity of the internal cerebral veins and straight sinus. She had a right gaze preference but no visual field information was provided.

The contribution of hemococoncentration to cerebral venous thrombosis at high altitude is uncertain. Gradual ascent to an altitude of about 4,500 m does not appear to alter platelet activation, plasma coagulation, or fibrinolysis (6). Hemococoncentration alone is not thought to cause thrombosis. The
slowing of cerebral blood flow secondary to cerebral edema is speculated to play a major pathogenetic role (5).

REFERENCES

Junctional Visual Field Loss in a Case of Wyburn-Mason Syndrome

Anthony Liu, MD, Yi-Wen Chen, Steven Chang, MD, PhD, Yaping Joyce Liao, MD, PhD

Abstract: A previously healthy girl failed a routine eye screening at the age of 6 years. Her visual fields showed generalized depression in the right eye and a supertemporal defect in the left eye, consistent with a junctional scotoma. Funduscopic examination and fluorescein angiography revealed markedly dilated tortuous vascular loops with arteriovenous communications consistent with retinal arteriovenous malformations (AVMs). MRI of the brain and cerebral angiography demonstrated right ophthalmic and right thalamic AVMs, with compression and atrophy of the right optic chiasm. This represents a case of Wyburn-Mason syndrome with a junctional scotoma.

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A previously healthy girl without family history of ocular disease failed a routine vision screening at the age of 6 years, with visual acuities of 20/50, right eye and 20/20, left eye. At 9 years of age, her best-corrected visual acuity in her right eye deteriorated to 20/160 and at 11 years, no light perception. Her visual acuity in the left eye remained at 20/20. Her neuro-ophthalmic examinations also demonstrated a right relative afferent pupillary defect and loss of color vision.

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FIG. 1. Color fundus photographs. A. Large right retinal AVM is present obscuring the optic nerve. B. There is a marked temporal pallor of the left optic nerve without band atrophy.

FIG. 2. Automated visual fields showing generalized field loss in the right eye and a superotemporal defect in the left eye.
appreciation (Hardy-Rand-Rittler color plates) in the right eye. Funduscopic examination revealed a retinal arteriovenous malformation (AVM) with enormous vascular loops in the right eye obscuring the optic disc and optic disc pallor in the left eye (Fig. 1). Her neurologic examination was significant for left hemiparesis and paresthesias.

Automated visual field testing at 11-years of age demonstrated generalized depression in the right eye and a superotemporal defect in the left eye, consistent with a junctional scotoma (Fig. 2). Fluorescein angiography of the right eye demonstrated giant vascular loops with early filling of veins and direct arteriovenous connections with no evidence of leakage (Fig. 3). Brain MRI and cerebral angiography revealed right optic nerve and right chiasmal atrophy. There was an AVM located distal to the origin of the right ophthalmic artery and surrounding the orbital and canalicular portions of the right optic nerve (Fig. 4A, B). There was also a large right thalamic AVM with right chiasmal compression and atrophy (Fig. 4C, D).

Following Cyberknife treatment (25 Gy) of the thalamic and parachiasmal AVM, the ophthalmic artery AVM enlarged, and visual acuity in the right eye declined to 20/400.
Cyberknife treatment (30 Gy) to the right orbital AVM failed to halt progression, and her right visual acuity declined to no light perception over the following 5 months. Vision in the left eye remained stable at 20/20 two years later.

Wyburn-Mason syndrome, also known as Bonnet-Dechaume-Blanc syndrome, is a rare disorder with 3 essential elements: retinal AVM, brain AVM, and vascular changes of the face (1,2). A recent comprehensive review by Schmidt et al (3) identified 52 reported cases. The vascular malformations are not hereditary and are generally unilateral high-flow systems. The ocular complications of Wyburn-Mason syndrome include venous occlusions; intraretinal, macular, and vitreous hemorrhage; optic nerve dysfunction; glaucoma; extraocular motility disorders; nystagmus; and pulsatile proptosis. Forty-eight percent of patients with Wyburn-Mason syndrome have light perception or no light perception vision in the eye with retinal AVM (3). With involvement of the retrochiasmal visual pathways by an AVM (3–5), the most common pattern of visual field loss is homonymous hemianopia. A monocular temporal hemifield defect has also been described (6–8). Other neurologic symptoms, such as hemiparesis and sensory abnormality, depend on the location of the cerebral AVMs (3,9).

These vascular lesions carry a 2%–4% risk of bleeding with a 1% risk for death per year (10,11). Current treatment options for the cerebral AVMs of Wyburn-Mason syndrome include stereotactic radiosurgery, endovascular embolization, and microsurgical resection (12–15). The prognosis is best for lesions less than 3 cm, with complications occurring more frequently for those greater than 6 cm. Although rare, spontaneous involution has been reported (7).

REFERENCES

Acute Optic Neuropathy Associated With an Intracranial Mass in a Patient With POEMS syndrome

Heather E. Moss, MD, PhD, Grant T. Liu, MD

Abstract: A 43-year-old man with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), including long-standing optic disc swelling, had sudden painless vision loss in the left eye. Brain MRI revealed an intracranial mass adjacent to the left optic nerve and enhancement of the optic nerve. The mass decreased in size following chemotherapy for myeloma with some recovery of vision. This represents a unique case of optic neuropathy due to presumed plasmacytoma in osteosclerotic IgA myeloma and POEMS syndrome.

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Observations of multiorgan system involvement associated with plasma cell dyscrasia led to the characterization of POEMS syndrome, with the acronym standing for prominent findings of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. Other common signs include optic disc edema, ascites, pleural effusion, and thrombocytosis. Although optic disc edema occurs in one third to one half of patients with POEMS syndrome (1), vision loss is rare.

CASE REPORT

A 43-year-old man noted sudden painless loss of vision in his left eye following 2–3 days of stuttering visual decline in that eye. Six years earlier, he had been diagnosed with POEMS syndrome on the basis of demyelinating polyneuropathy, hepatosplenomegaly, hypogonadism, hyperprolactinemia, hypothyroidism, vitamin D deficiency, adrenal insufficiency, IgA lambda monoclonal proteinemia, skin darkening, a sclerotic bone lesion in the spine, and extravascular volume overload causing ascites and pleural effusions. He had received a stem cell transplant with clinical improvement for 2 years followed by recurrent symptoms of volume overload. Mild optic disc swelling and high serum vascular endothelial growth factor (VEGF) were found at the time of recurrence and were attributed to POEMS syndrome. He had been chronically managed on 20 mg of dexamethasone weekly. Chemotherapy was planned for treatment of recurrent symptoms and necessitated stopping dexamethasone, 2 weeks prior to vision loss.

Two weeks prior to vision loss, his acuity was 20/40 in each eye with normal color vision, posterior subcapsular cataracts, and bilateral optic disc swelling (Fig. 1). The disc swelling had been present for at least 6 months. Automated visual fields demonstrated general depression in the left eye (mean deviation –5.6 dB, compared with –1.9 dB in the right eye) without focal visual field loss. Because optic disc edema is a common finding in patients with POEMS syndrome, no further testing was performed.

The patient was evaluated 4 days after acute vision loss in the left eye. Visual acuity was 20/40, right eye, and hand motions, left eye. Pupils were equal, round, and reactive to light with a left relative afferent pupillary defect. Color vision was normal on the right, but the patient could not identify any of the color plates with the left eye. The appearance of the optic disc edema was unchanged, and the fundi were otherwise normal.

MRI of the orbits performed 3 days later revealed enlargement and enhancement of the left optic nerve and an adjacent enhancing lesion in the suprasellar cistern (Fig. 2). Lumbar puncture had an opening pressure of 17 cm H₂O. Cerebrospinal fluid analysis demonstrated elevated protein of 131 mg/dL (normal, <45 mg/dL), normal glucose, no pleocytosis, and no malignant cells.

Steroid therapy was immediately reinitiated (single dose of 40 mg of dexamethasone followed by 20 mg weekly) and,
2 weeks later, chemotherapy consisting of cyclophosphamide, bortezomib, and dexamethasone was started. Vision in the left eye declined to no light perception and remained 20/40 in the right eye.

One month later, the patient’s ascites had decreased and his energy level had increased. Vision in the left eye remained no light perception while the right optic nerve remained mildly swollen, and the left optic nerve became flat without pallor. MRI performed 6 weeks after acute vision loss demonstrated persistent enlargement and enhancement of the left optic nerve, with progressive enlargement of the mass lesion (Fig. 3).

Follow-up imaging 5 months after presentation showed some regression of the mass, and biopsy was deferred. Ten months after presentation, the patient could count fingers with his left eye and MRI showed further reduction in the size of the suprasellar mass.

**DISCUSSION**

Screening for and evaluation of vision loss in POEMS syndrome is challenging since optic nerve edema is relatively common in POEMS syndrome occurring in 29% and 55% of patients (1,2). It is a minor criterion for the diagnosis of the syndrome. The etiology of optic nerve edema is not known in most cases. Some cases can be explained on the basis of increased CSF protein or high intracranial pressure (3). Microvascular etiologies have been proposed on the basis of high VEGF levels. Systemic interstitial volume overload may also be a factor in patients associated with cystoid macular edema (4,5). Despite optic nerve edema being common in POEMS syndrome, vision loss is unusual (3). Rare instances of acute visual decline have been attributed to macular edema (4,5) and papilledema related to elevated intracranial pressure due to venous sinus thrombosis (6).

We are unaware of previous reports of an intracranial mass lesion and optic nerve enhancement in POEMS syndrome. The presumed composition of the mass lesion is plasmacytoma. The proposed pathophysiology of vision loss in our patient may be multifactorial. First, there may be compression of the optic nerve similar to reports of POEMS syndrome associated with orbitopathy (7,8). Second, in an analogous fashion to vision loss due to IgG multiple myeloma, tumor infiltration (9,10) and ischemia (9) by IgA osteosclerotic myeloma may have contributed to the optic neuropathy. Finally, nerve conductivity may have been decreased by IgA paraproteins (11).

**FIG. 1.** Bilateral optic disc edema is present 2 weeks prior to acute left vision loss.

**FIG. 2.** Seven days after loss of the vision in the left eye, FLAIR (A), contrast-enhanced T1 axial (B), and coronal (C) MRI demonstrate an enhancing lesion in the suprasellar cistern (arrowhead) with enlargement and enhancement of the adjacent left optic nerve (arrows).
ADDENDUM

A follow-up MRI 14 months after presentation showed complete regression of the suprasellar mass. The abnormal signal within the optic nerve persisted. Vision remained stable at count fingers with the left eye. This complete radiographic resolution following chemotherapy directed at POEMS syndrome supports the presumed pathology of plasmacytoma. Radiation to the area is planned to prevent regrowth.

ACKNOWLEDGMENTS

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REFERENCES


Cortical Vision Loss as a Prominent Feature of H1N1 Encephalopathy

John H. Pula, MD, Ahmad Issawi, MD, Jeffrey R. DeSanto, MD, Jorge C. Kattah, MD

Abstract: A 20-year-old woman infected with the 2009 H1N1 strain of influenza A developed bilateral visual loss. Brain MRI showed restricted diffusion of the parietal and occipital lobes, and her spinal fluid did not contain inflammatory cells. This report describes an unusual case of H1N1 influenza A virus infection primarily affecting the posterior visual pathways.

CASE REPORT

A 20-year-old woman with Type I diabetes mellitus reported 1 week of malaise and fatigue. On initial examination, her blood pressure was 106/66 mm Hg; pulse rate, 114 beats per minute; temperature, 101.9°F; respirations, 51 per minute; and pulse oximeter oxygen saturation, 92%. Arterial blood gas PO₂ was 68 mm Hg (normal, 75–90 mm Hg); PCO₂, 24 mm Hg (normal, 35–45 mm Hg); glucose, 193 mg/dL (normal, 70–99 mg/dL); and creatinine, 2.82 mg/dL (normal, 0.6–1 mg/dL). Chest X-ray showed bilateral patchy infiltrates. Real-time polymerase chain reaction (PCR) sampled from pharyngeal mucosa tested positive for H1N1 influenza virus.

The patient was admitted to hospital and given intravenous fluids, piperacillin/tazobactam, azithromycin, and oseltamivir. Because of respiratory distress, she was intubated, sedated with midazolam and fentanyl, and required an oscillator for 7 days, with traditional ventilation for an additional 10 days. Her creatinine normalized. Blood cultures showed no growth. She developed a hospital-acquired fungal urinary tract infection treated with fluconazole but remained normotensive and hemodynamically stable.

On Hospital Day 17, she was extubated and stated that she could not see. On neurologic examination, the patient was mildly agitated and irritable. Visual acuity was hand motions in each eye. External, pupillary, and funduscopic examinations were normal.

The following day, brain MRI demonstrated signal abnormalities involving the posterior parietal and occipital cortex bilaterally (Fig. 1). There was mild patchy enhancement in regions of signal abnormality without evidence of hemorrhage on gradient echo, nor evidence of cerebral venous thrombosis on T1-weighted imaging. Electroencephalography showed periodic lateralizing epileptiform discharges from the right hemisphere. Cerebrospinal fluid (CSF) analysis showed no white or red blood cells, glucose was 78 mg/dL (normal, 40–70 mg/dL), and protein was 110 mg/dL (normal, 12–60 mg/dL). CSF HSV PCR, cryptococcal screen, Gram stain, and bacterial culture were negative.

On Hospital Day 20, the patient became drowsy and agitated and required reintubation for worsening respiratory function. One week later, she was extubated, and on the following day, she was alert with visual acuity of J5 in both eyes with normal pupillary testing and funduscopy. Brain MRI with FLAIR sequences showed signal abnormalities in the occipital lobes bilaterally (Fig. 2).

The patient had no further respiratory decompensation but maintained a persistently flat affect. Neuropsychologic examination showed moderately reduced cognitive function. Simple auditory attention was preserved. However, on tasks requiring visual attention and speed, her performance was moderately to severely impaired. Abstract visual construction was also decreased.
DISCUSSION

There are 3 types of influenza virus: A, B, and C. Influenza A is an enveloped RNA virus of multiple strains and is named for which subtypes of hemagglutinin and neuraminidase antigen are on its surface. These subtypes include H1N1, H1N2, H3N1, H3N2, and H2N3 (1). Episodically, influenza A H1N1 strains have caused outbreaks of human disease. For example, the 1918 Spanish flu epidemic implicated in encephalitis lethargica was triggered by an H1N1 strain (1).

In 2009, a genetically distinct strain of H1N1 influenza A became pandemic. This strain clinically manifested mainly with respiratory problems, especially in young people. Neurologic complications of the 2009 H1N1 strain occurred primarily in children, resulting in seizures and encephalopathy (2,3). Focal neurologic problems such as hemisensory loss caused from H1N1 were less commonly reported (4,5). Despite neurologic involvement, CSF analysis in these patients was often normal (6–9). In our patient, the elevated protein but otherwise unremarkable CSF is consistent with the CSF profile from other H1N1 encephalopathy patients (6,10).

Neuroimaging abnormalities from influenza A encephalitis may be due to several mechanisms. Hypoxic or anoxic damage as a result of respiratory dysfunction can lead to CNS ischemia or infarction (10). Alternatively, CNS damage may be due to a direct infectious or parainfectious process related to the H1N1 virus. Mainly described in children, these parainfectious syndromes range from acute demyelinating encephalomyelitis to more hyperacute states, such as acute hemorrhagic leukoencephalopathy (4).

Probably related, acute necrotizing encephalopathy is a syndrome mainly described in East Asian children, resulting in seizures, fever, and coma (11). Brain imaging typically demonstrates bilateral symmetric lesions of the thalami, white matter, and brainstem (7,12). In such a case,
autopsy findings showed vasculopathy and necrotizing lesions of white matter, basal ganglia, thalami, and brainstem (13).

Neuroimaging abnormalities associated with the pandemic 2009 H1N1 strain have been reported infrequently, usually in children (4,10,14,15). Not all neurologic symptoms occurring in H1N1 patients produce MRI changes (5). In a series of 8 children with H1N1 encephalopathy, only 3 showed bilateral lesions of the thalami and white matter on MRI (16). Lyon et al (17) described the case of a 12-year-old girl with H1N1 encephalopathy who developed seizures and lethargy and had bilateral thalamic and brainstem MRI lesions. Haktanir (15) reported a 3-year-old girl with bilateral thalamic and brainstem T2 hyperintensities, which showed restricted diffusion on diffusion-weighted imaging (DWI). Occipital lobe involvement due to H1N1 has been documented in 2 previously reported cases, but the young age of both patients precluded accurate assessment of visual function (18,19).

The neuroimaging abnormalities in our patient raised the possibility of posterior reversible encephalopathy syndrome. Yet the lack of clinical improvement and cytotoxic edema found on DWI are both inconsistent with this diagnosis. Hypoxia also could result in restricted diffusion but would produce imaging findings of cortical laminar necrosis, which were not present in our patient. Finally, cerebral ischemia was considered, but the vascular territories involved are not representative of hypotension or arterial thromboembolism, and there was no evidence of venous thrombosis. Thus, the pattern of symmetrical MRI abnormalities with restricted diffusion in our case most likely represents a parainfectious encephalopathy.

REFERENCES
Is Intravitreal Bevacizumab an Effective Treatment Option for Nonarteritic Anterior Ischemic Optic Neuropathy?

Christina Rapp Prescott, MD, PhD, Craig A. Sklar, MD, Robert L. Lesser, MD, Ron A. Adelman, MD, MPH

Abstract: Nonarteritic anterior ischemic optic neuropathy (NAION) causes sudden profound loss of vision with no known cause or cure. Various treatment modalities, both surgical and pharmacologic, have been tried without success. The purpose of our retrospective study was to evaluate the effect of intravitreal bevacizumab (Avastin) as a treatment option for NAION. We evaluated demographics of 5 patients and compared visual acuity and automated visual fields prior to and following intravitreal bevacizumab injection. Visual acuity at presentation was 20/20 in 4 of 5 patients and 20/150 in 1. Visual acuity improved to 20/40 in the patient who presented with decreased acuity and decreased slowly in 3 patients and rapidly in 1. All patients presented with variable visual field defects: 1 improved slightly, 3 progressed, and 1 remained stable. These results are consistent with the natural course of the disease, and bevacizumab did not appear to have a dramatic effect on the clinical outcome in this small series of patients with NAION.

METHODS

We performed a retrospective study of patients seen at the Yale Eye Center and The Eye Care Group between July 1, 2007 and July 30, 2010. We searched our patient databases using NAION and bevacizumab as keywords. Eleven patients were identified in the initial screen. These patients’ charts were reviewed, and 5 were identified who received bevacizumab within 3 months of onset of NAION. Each patient was examined independently by at least 2 ophthalmologists. Visual acuity and automated visual fields were compared between visits, including prior
to and following intravitreal injection of bevacizumab (1.25 mg/0.05 mL). The appearance of the optic disc was monitored with serial photographs. The Human Investigation Committee at the Yale University School of Medicine exempted this study from the Institutional Review Board approval.

**Case 1**
A 49-year-old man with a history of tadalafl (Cialis; Eli Lilly, Indianapolis, IN) use presented with visual acuity of 20/20 and an inferior altitudinal defect in the left eye (Fig. 1). Five days later, he received an intravitreal injection of bevacizumab. Seven days following injection, his acuity remained 20/20, but his field loss increased in the left eye (Fig. 1). Vision in the left eye decreased to 20/30 over 3 years, but visual field remained stable (mean deviation, −23.70 dB). However, 2.5 years after his initial presentation, he developed a dense superior altitudinal defect in his right eye (mean deviation, −14.49 dB), which progressed to near-total field loss (mean deviation, −30.18 dB) 2 weeks later.

**Case 2**
A 56-year-old man noted loss of visual field in his right eye 2 weeks previously. His vision was 20/20 bilaterally. Three weeks later, his vision remained 20/20 in the right eye, but field loss progressed (Fig. 1). Four days later, he received an intravitreal injection of bevacizumab. His visual field stabilized (mean deviation, −25.46 dB) (Fig. 1), but vision has gradually decreased to 20/50 in the right eye. The patient’s visual function has remained unchanged over 3 years of follow-up.

**Case 3**
A 40-year-old man was evaluated 1 week after noticing inferior visual field loss in the right eye (Fig. 1). His vision was 20/20 in each eye. Three weeks later, his vision remained 20/20 in the right eye, but field loss progressed (Fig. 1). Four days later, he received an intravitreal bevacizumab injection. His visual field stabilized (mean deviation, −25.46 dB) (Fig. 1), but vision has gradually decreased to 20/50 in the right eye. The patient’s visual function has remained unchanged over 3 years of follow-up.

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**Table 1**

<table>
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<th>Patient No. / Age / Sex</th>
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**FIG. 1.** Visual field results in 5 patients with NAION prior to and following intravitreal bevacizumab.
Case 4
A 69-year-old woman with a history of NAION in the right eye developed NAION in the left eye 4 months later. Her vision was 20/150 in the left eye, and left visual field showed diffuse loss (Fig. 1). The next day, she received an intravitreal bevacizumab injection in the left eye and subjectively noticed an improvement within 12 hours. Four days later, her vision improved to 20/40, with improvement in her visual field (Fig. 1). Over the ensuing 10 months, visual acuity and visual field in the left eye remained stable (Fig. 1).

Case 5
A 62-year-old man with a 2-year history of NAION, left eye, developed NAION in the right eye. His vision was 20/20 on presentation with right visual field loss (Fig. 1). He received an intravitreal bevacizumab injection 9 days later. One week following injection, visual acuity decreased to 20/400 with slightly increased field loss (Fig. 1) (mean deviation, -24.02 dB). Two months after his bevacizumab injection, his vision in the right eye was counting fingers at 1 ft with further decline in visual field (mean deviation, -28.97 dB).

RESULTS
All 5 patients presented with optic disc edema in the affected eye and subsequently developed varying degrees of optic atrophy. The only patient (Case 4) who presented with decreased visual acuity showed improvement, while 3 of the 4 patients who presented with 20/20 experienced a decline in acuity. Case 1 presented with an inferior altitudinal defect and developed field loss in the superior visual field after receiving treatment. In Case 2, the field defect progressed prior to receiving bevacizumab. Case 3 presented with a macular sparing inferior altitudinal defect that progressed to involve the macula. Only Case 4 demonstrated improvement in visual acuity and visual field following treatment. Case 5 also suffered progressive decline in acuity and field following intravitreal bevacizumab injections.

DISCUSSION
In our small retrospective case series, only 1 patient (Case 4) who presented with decreased visual acuity improved. Of the 4 with 20/20 acuity initially, all experienced a decline in vision, and 1 developed NAION in the fellow eye.

Each of our patients received a single injection of bevacizumab, between 1 day and 5.5 weeks after the onset of symptoms. The only patient whose vision improved was treated within 1 day of reporting symptoms, while the others were treated between 5 days and 5.5 weeks. Perhaps earlier treatment would have had a more beneficial effect. Bennett et al (6) reported improvement in both visual acuity and visual field in a patient treated with a single dose of bevacizumab (1.25 mg/0.05 mL) 3 weeks after the onset of visual loss.

For any treatment to be considered effective, it must be significantly better than observation. In the IONDT (5), 42.7% of patients in the control group improved visual acuity by 3 or more lines and 12.4% lost 3 or more lines at their 6-month follow-up visit. However, the patients in the trial began with vision worse than 20/40, so the only patient in our small study who would have qualified for the trial based on visual acuity was the patient whose vision improved. Similarly, the control group in the study by Hayreh and Zimmerman (4) had similar results to the IONDT but also started with worse vision (worse than 20/70) than our patients. We do not know whether our patient (Case 4) experienced improvement in vision due to the natural course of NAION or whether she responded to bevacizumab.

There are many limitations of this study. It was retrospective with a small sample size and no controls. Patients were not excluded based on ocular history; specifically, 2 of the patients had a history of NAION in the other eye. Bevacizumab was given at variable time points following vision loss, with no masking of who received treatment. Additionally, 4 of our 5 patients presented with isolated visual field defects and 20/20 visual acuity, so our sample is not representative of typical NAION. Bevacizumab did not appear to have a beneficial effect in our small case series and will remain a controversial treatment until a prospective randomized clinical trial is conducted.

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Is Leber Hereditary Optic Neuropathy Treatable? Encouraging Results With Idebenone in Both Prospective and Retrospective Trials and An Illustrative Case

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Abstract: A 31-year-old woman developed subacute bilateral visual loss over a 2-week period. Two months later, the diagnosis of Leber hereditary optic neuropathy (LHON) 11778/ND4 was established and the patient was treated with 900 mg of idebenone daily. Over the ensuing 9 months, visual acuity improved from 20/200 to 20/25 in each eye with near-total resolution in visual field abnormalities. Our case report is in agreement with 2 large published series of patients with LHON treated with idebenone, raising hope for treatment of this visually devastating mitochondrial disorder.

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Leber hereditary optic neuropathy (LHON) is untreatable. Or so we have been told for many decades. We present a case that challenges this notion and supports the possibility that idebenone may indeed be therapeutic in patients with LHON 11778/ND4, as suggested by the recent prospective study by Klopstock et al (1) and the accompanying retrospective study by Carelli et al (2) recently published in the journal Brain. There have been reports of spontaneous improvement of visual acuity in some patients with LHON, particularly in those with the 14484/ND6 mutation; however, 11778/ND4 cases rarely recover and even so, such recovery is very incomplete and generally occurs 1–6 years following the onset of disease (3). We present a patient with LHON 11778/ND4 treated with long-term (9 months) high-dose idebenone, in whom improvement of several visual parameters was documented.

CASE REPORT

Over a 2-week period, a 31-year-old woman noted bilaterally decreased vision first in the left eye and then in the right. She had an aunt diagnosed with LHON, and the patient was soon diagnosed as well with the 11778/ND4 (homoplasmic) mitochondrial mutation. She was started on 900 mg of oral idebenone daily as well as a 3-day course of coenzyme Q10 (200 mg by mouth daily) and intravenous methylprednisolone (250 mg every 6 hours) within 2 weeks of her blood draw and 2 months after her initial symptoms of visual loss. At that time, visual acuity was 20/200 in both eyes without a relative afferent pupillary defect. The patient showed continued improvement, and 9 months after initiation of treatment, vision was 20/25 in each eye with intact color vision and marked improvements in her visual fields (Fig. 1C).

Two months later, her vision was 20/70 in right eye and 20/200 in left eye, with improvement in visual fields (Fig. 1B). The patient showed continued improvement, and 9 months after initiation of treatment, vision was 20/25 in each eye with intact color vision and marked improvements in her visual fields (Fig. 1C).

Initially, OCT of the retinal nerve fiber layer (RNFL) demonstrated diffuse RNFL thickening in all quadrants (Fig. 2A). Over a 7-month period of follow-up, RNFL thickness returned to normal (Fig. 2B, C).

DISCUSSION

This case report illustrates dramatic recovery of visual acuity, prevention of diffuse RNFL thinning (4), and near-complete resolution of central/paracentral scotomas in a patient with...
LHON 11778/ND4 treated early with high-dose idebenone. Although it is impossible to tell how the limited treatment with solumedrol and coenzyme Q10 affected the patient, we do not believe they had a significant impact on the patient’s long-term visual recovery.

LHON is caused by a mitochondrial DNA mutation affecting respiratory complex I of the electron transport chain (3,5) most frequently at positions 11778/ND4, 14484/ND6, and 3460/ND1 (3,6,7). These mutations interfere with the interaction of complex I with coenzyme

FIG. 1. Sequential pattern deviation plots of automated visual fields. Right eye is represented in right column and left eye in left column. A. At baseline, visual fields show a small central scotoma in the right eye (9/14 fixation losses, 33% false positives, 20% false negatives) and an inferiorly displaced (by eccentric fixation) larger paracentral scotoma in the left eye (12/13 fixation losses, 46% false positives, 20% false negatives). B. Two months after starting treatment, there is improvement in the central scotoma on the right (3/13 fixation losses, 25% false positives, 12% false negatives) and the paracentral scotoma on the left (4/13 fixation losses, 21% false positives, 1% false negatives). C. Five months after starting treatment, there is near total resolution of central scotoma in the right eye (6/11 fixation losses, 16% false positives, 0% false negatives) and mild improvement of paracentral scotoma in the left eye (6/11 fixation losses, 12% false positives, 1% false negatives).
patients, 55 treated with 900 mg/day (300 mg three times daily) of idebenone and 30 with placebo. All 3 major mutation types (11778, 3460, and 14484) were included. The primary endpoint was best recovery of visual acuity with treatment, and they came just short of showing statistical significance for this. However, post hoc subgroup analysis demonstrated statistically significant differences in secondary endpoints, including change in best visual acuity, change in visual acuity of the best eye, and changes in visual acuity of both eyes in patients with discordant visual acuities. Idebenone was, for 6 months, safe and well tolerated. The prospective, randomized, and placebo controlled design of the study was its strong suit. There were limitations as well. Subgroup analysis needs to be interpreted carefully, as each post hoc analysis offers another opportunity for the vicissitudes of chance. That there was not a greater effect seen in the primary endpoint probably reflected the short duration of the study (6 months) and the fact that many patients were entered in the study as much as 5 years after their loss of vision (and therefore with long-standing optic atrophy and less likelihood of recovery).

In the same issue of Brain is an accompanying retrospective review of LHON treated with idebenone. Carelli et al (2) looked at 103 patients with LHON (same 3 mutations), of which 44 were treated. They only included patients who began treatment within 1 year after visual loss and they followed up their patients for much longer (4–5 years). Their study showed that patients who were treated earliest had the best chance of recovery and that this recovery often continued for a year or 2 after treatment. However, this was a retrospective study with all the concomitant limitations of such, including variable treatment protocols (from 270 to 675 mg per day), different outcome measures, and the obvious issues of possible patient selection bias. Interestingly, they only found statistical significance with 11778 patients, probably because the 14484 patients had a high rate of spontaneous recovery and there were too few patients with 3460 for meaningful statistical analysis.

Taken together, these 2 studies complement each other and show similar results. Therefore, this line of treatment may hold potential for LHON and other mitochondrial disorders (12–15). Idebenone is a second-generation quinine (coenzyme Q10 is the first generation). A third-generation quinine molecule, EPI-743, may prove even more effective (16). Nevertheless, there are severe problems in extrapolating from a case report, a retrospective study, and from a randomized-controlled trial that did not reach its primary outcome measure. And will there be long-term risks associated with higher doses of idebenone taken over a lifetime?

REFERENCES


Clinical Observation

FIG. 2. Sequential optical coherence topography. A. Baseline measurements show diffuse swelling of the RNFL, especially superiorly (157 μm in the right eye and 163 μm in the left eye) and inferiorly (153 μm in the right eye and 173 μm in the left eye). B. Two months after starting the treatment, there is a decreased thickness of the superotemporal and inferotemporal nerve fiber layer. C. Five months after starting the treatment, there is normalization of the RNFL, except for small areas of thinning superotemporally and inferotemporally. OD, right eye; OS, left eye.

Q10, resulting in decreased ATP generation through oxidative phosphorylation and increased reactive oxygen species (ROS) (3,6,7).

Idebenone is a synthetic short chain benzoquinone and a coenzyme Q10 derivative that is able to cross both mitochondrial membranes and the blood–brain barrier (8). It is thought to work by shuttling electrons onto complex II, thereby bypassing the defective complex I of the electron transport chain. This may lead to greater ATP production and a reduction of oxidative stress that is detrimental to retinal ganglion cells and their fibers, particularly the small axons in the papillomacular bundle (3,6,9).

Perhaps most critically, the ROS generated by the LHON mutations accumulate and may lead to mitochondrial membrane depolarization with the consequent opening of the mitochondrial permeability transition pores, leading to retinal ganglion cell apoptosis (10). Quinones, such as idebenone, may inhibit this process (11).

Klopstock et al (1) published their results of a prospective, randomized placebo-controlled trial on 85 LHON


Reappraisal of the Optic Nerve Hypoplasia Syndrome

Mark Borchert, MD

Background: Optic nerve hypoplasia (ONH) has been described as an increasingly prevalent cause of congenital blindness. Its association with hypopituitarism and absent septum pellucidum has been recognized for more than 40 years as “septo-optic dysplasia” or “de Morsier syndrome.” More recent studies have suggested that these associations are independent of one another. This review was designed to assess the historical and recent evidence for associations of neuroradiologic, endocrinologic, and developmental problems in patients with ONH.

Evidence acquisition: Historical and contemporary literature review.

Results: The medical literature does not support the notion that Georges de Morsier ever described a case of ONH or recognized its association with hypopituitarism or missing septum pellucidum. Recognition of the critical association of ONH with hypopituitarism should be attributed to William Hoyt. Hypopituitarism and other more recently identified associations with ONH, such as developmental delay, hypothalamic dysfunction, and autism, are independent of septum pellucidum development. Other common neuroradiologic associations, such as corpus callosum hypoplasia, gyrus dysplasia, and cortical heterotopia, may have prognostic significance.

Conclusions: Children with ONH need to be monitored for many systemic, developmental, and even life-threatening problems independent of the status of the septum pellucidum. “Septo-optic dysplasia” and “de Morsier syndrome” are historically inaccurate and clinically misleading terms that should be abandoned.

The case will be made for abandonment of the terms septo-optic dysplasia (SOD) and de Morsier syndrome.

HISTORICAL PERSPECTIVE

The first description of ONH is ascribed to Briere in 1877 (1), but the first artistic rendering of the optic disc appearance was by Schwarz in 1915 (2) (Fig. 1). The first recognition of an association of ONH with agenesis of the septum pellucidum was by Dr David Reeves at Children’s Hospital Los Angeles in 1941 (3,4).

The purpose of Reeves’ report was to demonstrate the youngest case of agenesis of the septum pellucidum diagnosed by air encephalogram (Fig. 2). The 4-month-old patient was coincidentally blind, and examination under anesthesia by Dr S. Rodman Irvine revealed “bilateral primary optic atrophy of undetermined origin, probably, however, on the basis of a congenital aplasia.”

The association of ONH with absence of the septum pellucidum was later erroneously attributed to Georges de Morsier (Fig. 3), who coined the term, “la dysplasia septo-optique” (SOD) (5). However, the “optic dysplasia” recognized by de Morsier was not ONH. In his treatise on cranioencephalodysraphism, his third chapter highlighted his fascination with absence of the septum pellucidum that had incidentally been noted in postmortem brains. From this, he discovered that 1 brain had a unilaterally vertically rotated optic tract (Fig. 4). This was from a woman who died of pyelonephritis at the age of 84 years without any history of vision problems. He also described the case of a living 44-year-old alcoholic man who had “slight narrowing of the visual field with enlargement of the blind spot,” but was incidentally discovered to be missing the septum pellucidum on air encephalogram. De Morsier supplemented these 2 cases with 34 others (11 autopsy cases and 23 radiographic cases) from the literature that had agenesis of the septum pellucidum, 8 of which had some other eye or optic nerve problem. These included 1 case of bilateral anophthalmia, 3 cases of bilateral optic atrophy (1 with Apert syndrome and 1 with osteogenesis imperfecta), and 3 cases of unilateral optic atrophy (2 systemically normal and 1 with...
hemiparesis and mental retardation). The only case with
definite ONH from the literature cited by de Morsier was
the case that had been previously documented by Reeves
(3). It was from this compilation of disparate cases that an
association of eye problems with agenesis of the septum
pellucidum (i.e., SOD) was postulated.

De Morsier believed that agenesis of the septum pelluci-
dum and various ocular anomalies were “not fortuitous”

associations (6). He hypothesized that the septum pelluci-
dum served to connect the corpus callosum to the fornix
and that lacking this supporting structure resulted in pene-
tration of the chiasm by the third ventricle. This malforma-
tion of the chiasm then somehow led to optic nerve or ocular
anomalies.

Three years following de Morsier’s report, Gross and Hoff
(7) reported their autopsy findings from 465 brains obtained
from patients with severe neurologic problems or systemic
malformations. They identified 13 brains with absence of
the septum pellucidum. One of these had bilateral ONH
and 7 (6 bilateral; 1 unilateral) had optic atrophy. They also

FIG. 1. Appearance of ONH rendered by Schwarz in 1915.
Reproduced with permission from Schwarz (2).

FIG. 2. Air encephalogram from first case documenting
absence of septum pellucidum in a child with ONH in 1941.
Reproduced with permission from Reeves (3).

FIG. 3. Photograph of Georges de Morsier (1894–1982)
(courtesy of Avinoam Safran, MD, Geneva, Switzerland).

FIG. 4. Histologic coronal section through the posterior optic
chiasm demonstrates downward displacement and vertical
rotation of the left optic tract (arrow) and cystic opening in
floor of the third ventricle (V3). This is from the case that de
Morsier called “septo-optic dysplasia.” Reproduced with
permission from de Morsier (5).
Identified 12 cases of partial or complete corpus callosum agenesis. Two of these had microphthalmos with bilateral optic atrophy and 1 had unilateral ONH.

Thus, prior to 1970, only 2 cases of ONH associated with absence of the septum pellucidum had been described in the medical literature, and neither of these had been identified by de Morsier.

In 1970, Ellenberger and Runyan (8) described a 23-year-old woman with unilateral ONH, absent septum pellucidum, and dwarfism. In the same year, Dr. William Hoyt wrote the landmark article recognizing the association of ONH with growth hormone (GH) deficiency and predicted the absent septum pellucidum in the case reported by Ellenberger and Runyan. Hoyt et al. (9) described 9 patients with ONH and pituitary dwarfism, 4 of whom were missing the septum pellucidum. They generously, but erroneously, attributed recognition of the association of ONH with agenesis of the septum pellucidum to de Morsier and resurrected the term “septo-optic dysplasia,” which is now commonly referred to as de Morsier syndrome. “Hoyt syndrome” would be a more appropriate eponym, particularly since the association of ONH with hypopituitarism, not septum pellucidum agenesis, is the clinically important observation.

De Morsier would scarcely have recognized the attribution to himself. Trained as a psychiatrist under de Clérambault, he spent his career at the University of Geneva. Lacking a suitable neuropathologist replacement after the death of Edouard Long, de Morsier was enjoined to lecture in neuropathology for 1 h/wk starting in 1933, during which time he attempted to catalog the various craniosynostoses. Ultimately, he was appointed as head of neurology in 1960, a position that he held until his retirement in 1964. Arguably, de Morsier’s greatest contribution to medicine was his description of the Charles Bonnet syndrome, which he named after the 19th-century naturalist, who in 1760 had documented the visual hallucinations of his grandfather (10). There is no record of de Morsier ever identifying a case of ONH.

**PREVALENCE**

ONH has been recognized as an increasingly frequent cause of congenital blindness affecting one or both eyes. In 1997, bilateral ONH surpassed retinopathy of prematurity as the single leading cause of infant blindness in Sweden (11). Only cortical visual impairment of multiple etiologies was more common than ONH in blind children. The prevalence of ONH in Sweden quadrupled between 1980 and 1999 to 7.1 per 100,000, while all other causes of childhood blindness declined as diagnosed by the same major ophthalmic center (12). In 2006, the prevalence of ONH in England had risen to 10.9 per 100,000 children (13).

Owing to incomplete registries of blindness, the prevalence of ONH in North America is unknown. Prior to 1970, it was considered rare. In fact, prior to 1962, only 1 case had been diagnosed in British Columbia, Canada, but 20 cases were subsequently diagnosed by 1974, for an estimated prevalence of 1.8 per 100,000 (14). Arceus noted a similar increase in the incidence of reported cases in the 1970s (15). ONH was identified in 12% of blind infants in Harris County in Texas in the early 1980s (16). Surveys of schools for the blind in the United States in 1999 revealed that ONH accounted for 5.7% to 12.9% of blind students (17,18). Such surveys underestimate the actual prevalence because cognitive or behavioral impairments exclude most children with ONH from schools for the blind. In 2007, the Babies Count registry reported ONH as the third most prevalent cause (behind cortical vision impairment and retinopathy of prematurity) of any vision impairment in children aged 3 years or younger in the United States (19). Of all conditions, ONH was the most likely to cause legal blindness.

**NEUROIMAGING**

**Septum Pellucidum**

Following the resurrection of “SOD” by Hoyt et al., absence of the septum pellucidum garnered inappropriate dogmatic significance. Its association with pituitary dysfunction was documented in retrospective studies hampered by ascertainment bias (20,21). Other studies refuted the association, even to the point of showing no association of any adverse outcome with agenesis of the septum pellucidum (22–24). Indeed, as with de Morsier’s experience, most cases of agenesis of the septum pellucidum are detected accidentally and not associated with optic nerve or hormone problems. The prevalence of absent septum pellucidum in the general population is unknown. In the only prospective study of ONH, absence of the septum pellucidum was not associated with laterality of ONH, vision, pituitary dysfunction, or developmental outcome (25,26).

Nonetheless, the term “septo-optic dysplasia” has persisted and its definition has evolved to include midline brain abnormalities, such as hypoplasia of the corpus callosum or pituitary anomalies on MRI, in addition to absent septum pellucidum. This definition has served to focus investigators on morphogenetic mechanisms. It disregards the fact that a small corpus callosum frequently denotes hemispheric disease and that most neuroradiographic abnormalities associated with ONH are not midline (26). These include hydrocephalus, white matter hypoplasia, cortical heterotopia, pachygryria, polymicrogyria, schizencephaly, and arachnoid cysts. Rather than reassessing the appropriateness of the nomenclature, investigators recognizing these nonmidline findings simply expanded the terminology to include “SOD plus” as a more severe expression on the spectrum of ONH (27).

**Corpus Callosum**

Corpus callosum hypoplasia is the most prevalent neuroimaging abnormality associated with ONH (Fig. 5). It is...
commonly associated with absence of the septum pellucidum; however, absence of the septum pellucidum cannot serve as a surrogate for corpus callosum hypoplasia, as partial agenesis of the corpus callosum may not be associated with absence of the septum pellucidum. Corpus callosum hypoplasia has been associated with developmental delay but not with hypopituitarism in children with ONH (26).

Corpus callosum hypoplasia is detected in 1.8 to 2.05 per 10,000 live births and in 2.3% of developmentally disabled individuals (28,29). Forty-nine percent of patients with corpus callosum hypoplasia have other central nervous system abnormalities, including nonmidline defects typically associated with ONH (cortical heterotopias, schizencephaly, white matter hypoplasia, polymicrogyria) (28). However, ONH occurs in less than 10% of children with corpus callosum hypoplasia (29). Corpus callosum hypoplasia is associated with a myriad of syndromic conditions and chromosomal abnormalities, but pituitary dysfunction in those without ONH is uncommon (30). Although both ONH and corpus callosum hypoplasia may be the consequence of more generalized problems with CNS development, the presence of ONH appears to be uniquely associated with hypothalamic dysfunction.

Pituitary Gland

Pituitary abnormalities on neuroimaging include empty sella, ectopic posterior pituitary, nonvisualized infundibulum and posterior pituitary. These findings occur in 13%–34% of children with ONH, and nearly all of those have hypopituitarism (26,31). However, hypopituitarism occurs in 75% of patients with ONH, the majority of whom have no pituitary abnormalities on neuroimaging. It is also interesting that absence of the posterior pituitary bright signal on T1 MRI has been associated with anterior pituitary function (31). However, most of these patients do not have diabetes insipidus, as would be expected if vasopressin granules are the cause of the bright signal (32).

Optic Nerve

Attempts to diagnose ONH based on neuroimaging measurements of the optic nerve or chiasm have been promising (33,34). Such studies have been retrospective, lacked controls with normal and atrophic optic nerves, or failed to adjust for age in young patients. With continued improvement, it seems likely that high-resolution MRI could be used to distinguish ONH from optic atrophy. Assessment of the intracranial portion of the optic nerves is more reliable for detecting ONH than assessment of the orbital component (35).

CLINICAL DIAGNOSIS

The diagnosis of ONH is made by ophthalmoscopic confirmation of a small optic disc. This may be difficult with the binocular indirect ophthalmoscope due to limited magnification. With inadequate resolution, small pale optic discs may be difficult to distinguish from the surrounding hypopigmented scleral canal and therefore misdiagnosed as normal-sized discs with optic atrophy. The optimal method for diagnosing ONH in a young child is with direct ophthalmoscopy. This is usually not difficult in visually impaired children who have minimal objection to the light or the proximity of the examiner, as long as the examiner does not touch the child’s face. There are several funduscopic findings that assist the clinician in establishing the diagnosis of ONH. First, and most important, is an assessment of the area of the disc relative to the size of the central retinal vessels overlying it.

Second, tortuous retinal arterioles, venules, or both may accompany ONH (Fig. 6). Alternatively, the vessels may be uncommonly straight with decreased branching (Fig. 7). Such a nonbranching vascular pattern has also been recognized in children with primary GH deficiency (36). It is not known if these vascular patterns in ONH correlate with endocrine dysfunction.

FIG. 5. ONH is commonly associated with ectopic posterior pituitary (A) or other pituitary abnormalities. The corpus callosum may be normal (B) or hypoplastic (C). Hypoplastic corpus callosum is frequently associated with cortical dysgenesis, such as polymicrogyria (D).
Finally, in patients with ONH, a ring of hypopigmentation or hyperpigmentation often, but not always, surrounds the disc defining the area of the putative scleral canal (Figs. 6, 7). This is presumably caused by migration of sensory retina and/or pigment epithelium from their original margin at the edge of the optic canal to a new position at the border of the hypoplastic optic disc (37). This “double ring” sign does not define ONH as a similar appearance may be present in other conditions, such as myopia.

Although generally impractical, many authors have suggested that ONH can be confirmed with measurements of the optic disc from fundus photographs, particularly disc diameter (DD) or area relative to various retinal landmarks. In normal children, the ratio of the horizontal DD to the distance between the macula and the temporal edge of the disc (DM) is greater than 0.35 (25,38,39) (Fig. 7). DD/DM ratios less than 0.35 somewhat correlate with vision outcomes (40). Although most patients with DD/DM ratios less than 0.35 have generally been described as having ONH, some with DD/DM ratios of 0.30–0.35 have normal vision. Some overlap in optic disc size between normal and ONH is not surprising. The precise risk for systemic complications in these borderline cases has not been determined.

De Silva et al (41) found that the average DD/DM ratio at birth of preterm, but otherwise normal, infants was 0.26. Compared with measurements from adults made by other investigators, they estimated that the DD increases 44% in a lifetime compared with increases in DM of only 11%. This results in increased DD/DM ratio with age. Therefore, the age of the patient may need to be considered when measuring DD/DM ratios.

Attempts to diagnose ONH or predict vision from other imaging modalities, such as optical coherence tomography (OCT), have not been reported. Eyes with ONH may have a poorly developed foveal umbo on OCT in spite of a normal foveal appearance on ophthalmoscopic examination (42). The foveolar thickness is normal, but absence of the ganglion cell and nerve fiber layers results in a retina of uniform thickness, in which the umbo cannot be distinguished with OCT.

Some authors have broadly defined ONH to include any optic disc with congenitally decreased neuronal area (43). As such, those eyes with a normal-sized optic discs, but with enlarged cups, would qualify as having ONH. This appearance typically occurs in premature infants with periventricular leukomalacia (44). Although such optic nerves have fewer than the normal number of axons and may be technically hypoplastic, these children are not at risk for the same developmental and endocrinologic complications as children with small discs of typical ONH. They should, therefore, not be considered in the same diagnostic category. A similar argument can be made for eyes with major congenital malformations, such as microphthalmos, large colobomas, or persistent hyperplastic primary vitreous, which may consequently have small optic nerves.

VISION

Poor visual behavior is usually the first sign of ONH. Nystagmus usually develops at 1–3 months of age followed
by strabismus, typically esotropia, in the first year of life. Children with markedly asymmetric or unilateral ONH may present primarily with strabismus rather than nystagmus. Patients with relatively symmetric hypoplasia may have asymmetric vision from superimposed amblyopia due to strabismus or anisometropia.

Approximately 80% of children with ONH are bilaterally affected and two thirds of those are asymmetrically affected (26). The unilateral cases are usually detected at a later age than those with bilateral involvement. Children with unilateral ONH are at risk for hypothalamic/pituitary dysfunction (69%) and developmental delay (39%), although that risk is significantly lower than patients with bilateral ONH (81% and 78%, respectively) (25,26).

Visual acuity ranges from no light perception to near normal. More than 80% of bilateral cases are legally blind (45). Most children experience some improvement in their vision in the first few years of life. This may be due to optic nerve myelination that occurs in the first 4 years of life, leading to improved axonal conduction (46).

HYPOTHALAMIC DYSFUNCTION

Hypothalamic dysfunction is the most common nonvisual problem in patients with ONH and results in loss of regulation of homeostatic mechanisms controlling behavior and pituitary gland function.

Hypopituitarism

In most cases of ONH, hypopituitarism is believed to be due to hypothalamic dysfunction rather than pituitary dysgenesis. Children with ONH and hypopituitarism usually have moderately elevated serum prolactin levels, as this hormone is normally suppressed by the hypothalamus. In a prospective study, hypopituitarism was not correlated with laterality of ONH (25). GH deficiency was the most common endocrinopathy (70%), followed by hypothyroidism (43%), adrenocorticotropic hormone deficiency (27%), and diabetes insipidus (5%). This high prevalence of endocrinopathy is consistent with previous retrospective studies (47,48). Delayed or precocious puberty is common, but the incidence is unknown.

Evolving pituitary dysfunction in children with ONH is poorly understood, but cases of acquired hypopituitarism have been reported (48,49). Normal pituitary function at the time of initial evaluation does not preclude development of endocrinopathy in the future.

Thirst/Hunger

Ventromedial nuclei within the hypothalamus suppress hunger and eating in response to leptin, whereas lateral hypothalamic nuclei stimulate feeding behavior and regulate metabolism (50). Children with ONH frequently exhibit hyperphagia with obesity or hypophagia, with or without wasting. Some children also have an aversion to certain textures of food. Water-seeking behavior (and consequent enuresis) is also common and may be mistakenly attributed to diabetes insipidus.

Sleep

The biological clock is generated within the suprachiasmatic nuclei of the anterior hypothalamus above the optic chiasm. These nuclei receive photic information via the optic nerves to synchronize the clock to the 24-hour light–dark cycle. The circadian pacemaker is reset each day with visual stimulation (51–53). Disturbance of the circadian system can have significant pernicious effects on physiology and behavior (54,55). Many children with ONH have sleep or wakefulness disturbances over the 24-hour day (56,57). Alternatively, they may have inadequate retinohypothalamic input to daily entrain the circadian clock, resulting in free-running sleep–wake cycles asynchronous with other family members. In either case, such sleep irregularities commonly result in behavioral difficulties and disruption of family life.

Temperature Regulation

The medial preoptic region of the hypothalamus is involved in body temperature regulation and, through communication with the paraventricular nucleus, regulates fever response (58). It is not surprising that many infants and children with ONH have problems with body temperature regulation and may be frequently hospitalized to rule out sepsis (59).

DEVELOPMENTAL OUTCOMES

In 1984 Margalith et al (60) were the first to report developmental delays in ONH, estimating neuropsychological handicaps in nearly three fourths of cases of ONH. Burke et al (61) estimated delayed development, based on neuropsychological examination, at a similar frequency. Observations of developmental delay in association with ONH range from isolated focal defects to global delay (62,63). Garcia-Filion et al (26) found developmental delays in 71% of ONH patients using standardized neuropsychological instruments in a prospective study. Motor delays were the most common (75%) and communication delays were the least common (44%). Independent risk factors for significantly delayed cognitive and overall development included hypoplasia of the corpus callosum and hypothyroidism but not absence of the septum pellucidum. Developmental delay occurred in unilateral (39%) and bilateral (78%) cases of ONH.

Autism spectrum disorders are overrepresented in the visually impaired population, with prevalence estimates up to 25% in children (64). The prevalence of autism appears even higher in children with ONH. In a group of 13 Swedish children with ONH and blindness, 6 had autism and 3 had an “autistic-like” condition (65). Parr et al (66) reported that, in a sample of 83 children with ONH and moderate to severe vision impairment (worse than 6/30), 37% (31 of 83) had social, communicative, and repetitive or restricted
behavioral difficulties and the majority of those (26 of 31) had a clinical diagnosis of autism spectrum disorder. Precise prevalence estimates of autism require modifications of the autism diagnostic instruments for visually impaired subjects. Such modifications have not yet been validated.

PATHOGENESIS AND GENETICS

The presumed association of midline cerebral defects with ONH has led to a focus on the genetic mechanisms involved in division of the prosencephalon into cerebral hemispheres and formation of the pituitary gland. Several candidate genes have been identified as responsible for cases of septo-optic dysplasia. These include mutations of HESX1 associated with holoprosencephaly and SOX2 associated with anterior pituitary hypoplasia and hypogonadism. Only 5 cases of ONH in humans have been associated with the HESX1 mutation (67,68). Some of these were in cases of severe forebrain malformation, such as alobar holoprosencephaly (69). Such major malformations would be expected to impact the development of subsequent structures, such as the optic nerves, corpus callosum, and septum pellucidum. The vast majority of cases of ONH cannot be attributed to specific mutations. In fact, less than 1% of cases of ONH in large series were found to have an HESX1 mutation, and none were found to have SOX2 mutations (70,71).

The dearth of families with more than 1 affected child and the lack of substantiated reports of transgenerational transmission argue against a hereditable cause for most cases of ONH. Fundus photographs from the only multigenerational report are not convincingly representative of ONH (72). There have been no reports of affected identical twins.

PRENATAL RISK FACTORS

Lack of definitive genetic associations has led to a search for prenatal environmental or biological risk factors for the development of ONH. Nearly all prenatal associations with ONH originate from retrospective review of records or anecdotal reports. The most commonly reported associations include young maternal age and/or primiparity (60,68,70,73,74), maternal use of recreational drugs (8 total cases) (13,45,60,75,76), anticonvulsants (9 total cases) (59,75,77), antidepressants (3 total cases) (20,73,78), and viral infections during pregnancy (4 total cases) (60,61,79). In small case series, ONH has been reported in 25%–48% of children with fetal alcohol syndrome (80,81), but in large series of near-consecutive cases of ONH, any prenatal alcohol exposure was reported in 6%–33%, and there were no reports of excessive prenatal alcohol consumption (82,83).

Two studies have systematically and sequentially investigated prenatal correlates in large cohorts of patients with ONH. The first was a case–control study of 100 severe bilateral cases in Sweden, and data were obtained from interviews conducted in the first trimester of pregnancy by a variety of midwives (73). Those data have the advantage of being relatively unbiased by recall or pregnancy outcomes but have the disadvantage of not capturing associations that may have occurred after the interview. That study found increased risk with young maternal age, primiparity, and early prenatal smoking exposure but not with drug or alcohol exposure.

The second study used a postnatal questionnaire and compared exposures with national registry data from pregnant women during the same period (83). This study confirmed that young maternal age and primiparity were independent risk factors but refuted an association with tobacco, alcohol, or drug exposure. In addition, it suggested prenatal maternal weight loss or poor weight gain and premature labor (without premature birth) as additional risk factors.

MANAGEMENT

Since ONH is particularly associated with abnormal hypothalamic function, physicians should be vigilant for signs of hypothalamic dysfunction along with any vision problems in children and vice versa. All neonates with jaundice and recurrent hypoglycemia should have ophthalmoscopic evaluation, especially if associated with temperature instability. Similarly, all infants with poor visual behavior, strabismus, or nystagmus by 3 months of age should have an ophthalmoscopic examination to rule out ONH.

Once ONH is confirmed ophthalmoscopically, MRI of the brain should be obtained. The MRI can rule out treatable conditions such as hydrocephalus but can also be used to anticipate developmental delay associated with corpus callosum hypoplasia or other major malformations. Findings of schizencephaly or polymicrogyria should prompt neurologic examination in anticipation of focal deficits or seizures. In the past, MRI of the brain was used to identify absence of the septum pellucidum in order to determine the need for endocrinologic evaluation. This feature can now be disregarded, as all children with ONH regardless of the septum pellucidum status need pituitary function evaluated.

Endocrinologic workup should include fasting morning cortisol and glucose, thyroid-stimulating hormone, free T4, and the GH surrogates—inulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3). If the child is less than 6 months of age, luteinizing hormone, follicle-stimulating hormone, and/or testosterone levels should be checked in order to anticipate delayed sexual development. Beyond 6 months of age, sex hormones are not normally produced until puberty, and thus cannot be tested. Microgenitalia, also a harbinger of delayed puberty, can be treated with testosterone during infancy.
Children should be monitored at least semi-annually for growth. With growth deceleration, thyroid function tests should be repeated and provocative GH testing should be performed. These should also be done if IGF-1 or IGFBP-3 is low, even if the child is growing normally. Free T4 should be rechecked at least semi-annually until 2 years of age and annually thereafter until at least 4 years of age.

If fasting morning cortisol is low, it should be repeated or provocative testing for cortisol should be done. This can often be done simultaneously with GH testing, using glucagon as the provocative agent. Children with inadequate cortisol response to provocative tests should be given both oral and injectable forms of glucocorticoids for administration during illness or physical stress.

Occupational, physical, and/or speech therapy are frequently needed by children with ONH. Attention should especially be given to early development of oral motor skills and acclimation to textured foods for those children resistant to eating. Incorporating dialogue into song can sometimes ameliorate delayed verbal communication.

Children with autistic behaviors should be evaluated by a neuropsychologist skilled in autism assessment as well as experienced in dealing with visually impaired children. Lacking such experience, the autism expert should enlist assistance from a teacher for the visually impaired to appropriately modify the testing instruments. Sleep regulation can sometimes be alleviated by entraining the circadian clock with low doses (0.1–0.5 mg) of melatonin in the evening or, alternatively, with soporific doses (3–5 mg) at bedtime (56).

The vision of young children with ONH should be monitored at least annually, and any refractive errors should be treated when the visual acuity reaches a functional level. Patching of the better eye can result in improvement of vision in the worse eye. However, if the ONH is asymmetric, maintenance of improved vision requires prolonged patching that can be disruptive to development in a child with many other handicaps. Thus, amblyopia therapy should be reserved for those cases in which the potential vision in each eye is felt to be fairly good. Children with unilateral or markedly asymmetric ONH should not be treated with patching.

Early surgical correction of strabismus should be reserved for children who have symmetrical functional vision in the eyes, and thus some potential for binocularity. Otherwise, correction of strabismus should be deferred until it is an impending psychosocial issue.

CONCLUSIONS

ONH is an increasingly prevalent, probably nonhereditary, cause of congenital blindness that is the unifying feature of a syndrome that usually includes developmental, hypothalamic, and/or neuroanatomical abnormalities. The first recognized association was with absence of the septum pellucidum, yet it has now been shown that this is the least significant, and least prognostic, of the associated abnormalities. The presence of ONH imparts risk for serious systemic and neurologic problems that need to be carefully monitored. Focus on the septum pellucidum has distracted physicians from the serious and complicated nature of the syndrome. “Septo-optic dysplasia” and “de Morsier syndrome” are inappropriate and historically inaccurate terms that should be abandoned.

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State-of-the-Art Review


Shedding Light on Photophobia
Kathleen B. Digre, MD, K.C. Brennan, MD

Abstract: Photophobia is a common yet debilitating symptom seen in many ophthalmic and neurologic disorders. Despite its prevalence, it is poorly understood and difficult to treat. However, the past few years have seen significant advances in our understanding of this symptom. We review the clinical characteristics and disorders associated with photophobia, discuss the anatomy and physiology of this phenomenon, and conclude with a practical approach to diagnosis and treatment.

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Photophobia is reported in most all forms of migraine and many neuro-ophthalmic disorders. The symptom is a hallmark of primary eye conditions, such as uveitis, and certain retinal dystrophies. It is included as one of the major criteria for migraine in the International Classification of Headache Disorders (1,2). It is listed as a major symptom in blepharospasm. Yet in other clinical settings, some have suggested that photophobia is merely a functional symptom without an organic basis (3).

NOMENCLATURE OF PHOTOPHOBIA

The term photophobia is a misnomer and not quite accurate. It comes from 2 Greek words: photo - “light” and phobia - “fear or dread of”—hence, “fear of light.” It is defined as an “abnormal sensitivity to light, especially of the eyes” (4). In defining photophobia, nearly 8 decades ago, Lebensohn (5) wrote, “exposure of the eye to light definitely induces or exacerbates pain.”

There are other terms and concepts of light aversion that must be distinguished from photophobia. Cummings and Gittinger (6) described “central dazzle” as an uncomfortable, but not painful, sense of excessive brightness. They thought this represented a thalamic dysesthetic or hyperpathia syndrome. Loewenfeld (7) described “the dazzling syndrome” as abnormal light scatter without ocular adaptation. “Hemeralopia” or “day blindness” refers to blurring of vision due to light and is a frequent complaint in patients with retinal (e.g., cone dystrophy) and rarely optic nerve disorders. In these cases, patients report they see better in dim illumination (8). We have used the term “photo-oculodynia” to describe pain or discomfort in the eye from a light source that is not usually painful (9). This term is in keeping with the literature that describes pain from a normally nonpainful stimulus (e.g., cutaneous allodynia) (10,11). In this review, we define photophobia broadly as a sensory state in which light causes discomfort in the eye or head; it may also cause an avoidance reaction without overt pain. We use photo-oculodynia to describe light-induced eye pain from a normally nonpainful source (e.g., ambient lighting).

CONDITIONS ASSOCIATED WITH PHOTOPHOBIA

We performed a chart review of 111 adults (53 men and 58 women) and 36 children who were diagnosed in an eye clinic with “photophobia” (12) (Table 1). A cause was found in the majority of adults, while a diagnosis could not be found in most of the children. One half of the adults were unemployed, and about 25% felt that the symptom greatly affected their quality of life. Their most common ocular condition was dry eyes, while their most common neurologic disorder was migraine. Other neurologic conditions included depression, blepharospasm, and progressive supranuclear palsy (PSP).
<table>
<thead>
<tr>
<th>TABLE 1. Conditions associated with photophobia</th>
</tr>
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<tbody>
<tr>
<td><strong>Ocular</strong></td>
</tr>
<tr>
<td>Anterior segment</td>
</tr>
<tr>
<td>Ocular inflammation (iritis, uveitis)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Corneal diseases (corneal neuropathy, interstitial keratitis)</td>
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<tr>
<td>Blepharitis</td>
</tr>
<tr>
<td>Corneal neuropathy (15)</td>
</tr>
<tr>
<td>Bilateral acute iris transillumination defects of the iris (137)</td>
</tr>
<tr>
<td>Dry eyes: the most common cause of photophobia (including Grave orbitopathy (138))</td>
</tr>
<tr>
<td>Pterygium (139): most common ocular cause</td>
</tr>
<tr>
<td>Corneal neuropathy</td>
</tr>
<tr>
<td>Interstitial keratitis (Cogan syndrome)</td>
</tr>
<tr>
<td>Posterior segment</td>
</tr>
<tr>
<td>Vitritis</td>
</tr>
<tr>
<td>Uveitis</td>
</tr>
<tr>
<td>Photoreceptor dysfunction-retinal dystrophy (16)</td>
</tr>
<tr>
<td>Albinism, achromatopsia, cone dystrophy, retinitis pigmentosa</td>
</tr>
<tr>
<td>Alström syndrome (19)</td>
</tr>
<tr>
<td>Sjogren-Larsson syndrome (140)</td>
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<tr>
<td>Retinal dystrophy (16)</td>
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<td><strong>Optic nerve</strong></td>
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<td>Optic neuritis</td>
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<td>Papilledema</td>
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<td><strong>Chiasm</strong></td>
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<td>Pituitary tumor (including apoplexy)</td>
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<tr>
<td>Hypophysitis (22)</td>
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<tr>
<td>Thalamic pathology (tumor, stroke, hemorrhage)</td>
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<td>Occipital lobe</td>
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<tr>
<td>Alteration in excitability (migraine) (113–115)</td>
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<tr>
<td><strong>Neurologic</strong></td>
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<td>Migraine (the most common neurologic cause)</td>
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<tr>
<td>Blepharospasm</td>
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<tr>
<td>Progressive supranuclear palsy</td>
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<tr>
<td>Traumatic brain injury</td>
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<tr>
<td>Meningeal irritation (meningitis, subarachnoid hemorrhage)</td>
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<tr>
<td><strong>Psychiatric</strong></td>
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<tr>
<td>Agoraphobia</td>
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<tr>
<td>Anxiety disorder (panic disorder)</td>
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<td>Depression</td>
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<tr>
<td><strong>Medications</strong></td>
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<td>Barbiturates</td>
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<td>Benzodiazepines</td>
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<td>Chloroquine</td>
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<td>Methylphenidate</td>
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<td>Haloperidol</td>
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<td>Zoledronate (141)</td>
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<td><strong>Other:</strong></td>
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<tr>
<td>Hangover headache</td>
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<tr>
<td>Neurasthenia (chronic fatigue)</td>
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<tr>
<td>Fibromyalgia</td>
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<td>Measles</td>
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<tr>
<td>Rabies</td>
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<tr>
<td>Inflammatory bowel disease</td>
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<tr>
<td>IFAP syndrome (ichthyosis follicularis with alopecia and photophobia)</td>
</tr>
<tr>
<td>PPK (psoriasiform lesions and palmoplantar keratoderma) (142,143)</td>
</tr>
<tr>
<td>Trisomy 18 (144)</td>
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<td>Zinc deficiency with exocrine insufficiency (145)</td>
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Anterior Segment Disease

Anterior segment disease such as iritis, cyclitis, and blepharitis has long been known to cause photophobia. Leibensohn (5) found that the more superficial the corneal lesion, the more severe the photophobia. These disorders are presumably due to direct irritation of the trigeminal afferents that innervate the cornea and eye. Dry eyes and dry eye syndrome are a common ocular cause of photophobia (13). Data suggest that dry eyes can eventually lead to a corneal neuropathy that may persist after the dry eyes have cleared (14). Rosenthal (15) proposed that if a patient has symptoms of dry eyes and photophobia, but the examination does not support the diagnosis of dry eyes, one should consider “corneal neuropathy until proven otherwise.” Rosenthal used corneal biomicroscopy to show changes in the structure of the corneal nerves of patients with dry eyes (15). Corneal neuropathy can be triggered by a variety of conditions including dry eyes, zoster keratitis, diabetic neuropathy, and chemotherapy (14,15).

Posterior Segment Disease

Posterior segment disease, such as retinal dystrophies, retinitis pigmentosa, and cone dystrophies, has been associated with photophobia. At times, hemeralopia or frequent photopsias are the presenting symptoms. Prokofyeva et al (16) reported that in addition to changes in visual acuity and night vision,photophobia was a frequent early symptom of retinal dystrophies and cone disorders. Photophobia may be one of the earliest signs of cone dystrophy before visual loss, and the diagnosis of malingering frequently can be made (17,18). Patients with conditions such as Alström syndrome have photophobia from initial onset (19). It is appropriate to evaluate patients with photophobia for a retinal disorder if the cause of the photophobia is not apparent. If there are other visual symptoms such as visual loss, retinal disorders must be considered.

Intracranial Conditions

Intracranial conditions, such as meningeal irritation from meningitis (20), subarachnoid hemorrhage (21), or pituitary tumors or apoplexy (22) cause photophobia, are thought to be due to irritation of the basal meninges especially around the diaphragma sellae (3). This pain is mediated by branches of the first division trigeminal nerve, which innervates the meninges (23).

Migraine

Migraine is the most common neurologic disorder causing photophobia, and photophobia is one of the major diagnostic criteria for migraine according to the International Classification of Headache Disorders (1,2). Up to 80% of migraine patients experience photophobia during an attack (24). The recent ID Migraine validation study suggested that the presence of photophobia, disability, and nausea predicted migraine approximately 98% of the time (25).

Drummond and Woodhouse (26) showed that migraineurs were more light sensitive both during and between migraine attacks compared with nonmigraine controls. Vanagaite et al (27) reported that patients with migraine experience increased light sensitivity to progressively increased amounts of light during and between headache episodes compared with controls. They concluded that photophobia “seems to be an intrinsic property of migraineurs.” Furthermore, 30%–60% of migraine attacks are triggered by light or glare (28). Different visual stimuli known to provoke migraine include sunlight, flickering from motion pictures, television, and fluorescent lights (28,29). It has been postulated that migraine is associated with “visual pathway dysfunction” from retina to occipital lobes (30).

Migraine is not the only headache type associated with photophobia. Subjects with tension headache have more light sensitivity than controls (31). Unilateral photophobia has been reported with cluster headache, hemicrania continua, and other trigeminal autonomic cephalalgias (32,33). In fact, the presence of unilateral photophobia is considered important in establishing the diagnosis of the trigeminal autonomic cephalalgias (32).

Traumatic Brain Injury

Traumatic brain injury (TBI) is commonly associated with photophobia. Acute TBI causes displacement, irritation, or injury of pain-sensitive intracranial structures, which likely accounts for both the headache and photophobia associated with brain injury (see below for possible pathophysiology). However, photophobia often remains after initial injury. There is an increased sensitivity to light in the subacute period (7–19 days) after head injury (34). Although most patients with mild head injury are improved after 6 months (35), those with postconcussive syndrome retain an increased sensitivity to light (36).

A large contribution to posttraumatic photophobia, especially chronic symptoms, may be due to the comorbidity of migraine-like headache after TBI. In a meta-analysis of pain conditions after TBI, headache prevalence was 57.8% (95% confidence interval, 55.5, 60.2%) (37). A study examining affective symptoms (posttraumatic stress disorder and depression) after mild TBI also found an independent association of TBI with headache (38). However, these large studies did not use the International Classification of Headache Disorders criteria to define headache type, and thus, the photophobia component is difficult to ascertain. A smaller study of returning Iraq and Afghanistan veterans did use the International Classification of Headache Disorders criteria and found a greater likelihood of migraine (which has photophobia as a diagnostic criterion) in veterans with more frequent injuries and abnormal findings on neurologic and neuropsychologic examinations (39). Clearly, these data are not conclusive, and they speak to the need for more precise
ascertainment of both photophobia and headache symptoms after TBI (40).

**Blepharospasm**

Blepharospasm is a focal dystonia associated with involuntary blinking, squeezing, and closure of the eyelids. The cause is unknown but is thought to be due to an excitation/inhibition imbalance in brainstem blink reflex pathways (41). While it has long been known that blepharospasm is associated with photophobia, our understanding of this association is limited. In one large survey of blepharospasm patients, Anderson et al (42) found that 80% reported aggravation of blepharospasm with bright lights while driving, watching television, or reading. In a survey of 316 blepharospasm patients, 94% reported light sensitivity; ambient lighting could provoke spasms about half of the time, but bright light provoked spasms almost all of the time (43). We studied 30 subjects with blepharospasm, 30 patients with a known photophobic state (migraine), and 30 controls with no history of migraine or blepharospasm (44). We found that patients with blepharospasm were as light sensitive as patients with migraine and that both groups were more light sensitive than controls.

**Progressive Supranuclear Palsy**

PSP is associated with photophobia and may be quite specific for the disorder; one study showed that the symptom of photophobia alone differentiated PSP from corticobasal degeneration (45). In a comparative study of PSP and Parkinson disease, patients with PSP had photophobia more frequently (13 of 16 patients vs 6 of 14) (46).

**Psychiatric Conditions**

Photophobia has been reported in association with agoraphobia. Patients with agoraphobia frequently wear dark glasses and feel more relaxed in darkness. Light will frequently trigger anxiety reactions in these patients. In one study, illumination levels were normalized in agoraphobia patients who underwent successful cognitive behavioral therapy (47).

Seasonal affective disorder is treated by viewing light (48), but little literature exists about photophobia and depression. One case report of a woman with bipolar depression revealed that she used eye patches during her depressive phase, and she used her light sensitivity to predict when she would be depressed (49). Gerbaldo and Thaker (50) reported that photophobia occurs in patients with “neurosthenia” (now known as chronic fatigue), bipolar depression, or seasonal depression. In contrast, patients with schizophrenia are known to have “sun-gazing” tendencies without any discomfort (50). In a study of bright light therapy for depression, photophobia and other ocular symptoms also decreased with phototherapy. This initially counterintuitive response, decrease in light aversion with light therapy, suggests a powerful influence of affective circuits on photophobia (51). Patients with anxiety and panic disorder also tend to have a lowered threshold of tolerance to light. The light threshold in these patients also responded to behavioral modifications and therapy (52). Given the comorbidity of these disorders with neuro-ophthalmic disease (especially migraine), one might expect an association. Clearly, more research is needed.

**IS PHOTOPHOBIA REALLY A NONORGANIC SYMPTOM?**

The “sunglasses sign” suggests factitious visual loss (53). Furthermore, photophobia is thought to accompany secondary gain, and a review of cases for an independent visual examination discounted this symptom as factitious (54). For many years, migraine and blepharospasm were thought to be functional disorders (55). Certainly, photophobia accompanies depression and anxiety (52); this can make patient interaction and management difficult. As already discussed, photophobia can be diagnosed in association with migraine, blepharospasm, PSP, depression, and anxiety—all conditions with an anatomical and physiologic basis—and for which many treatments are now available. As will be seen below, photophobia has a rich and growing neurobiology. While photophobia can undoubtedly be associated with factitious disorders, it is unlikely to be a purely “psychiatric” symptom.

**ANATOMY AND PATHOPHYSIOLOGY OF PHOTOPHOBIA**

**Trigeminal Nociceptive innervation**

Photophobia is intimately, likely inextricably, linked to pain sensation. The trigeminal nerve and its nuclei are the primary mediators of pain sensation to the head.

*The eye.* Afferents from the ophthalmic (V1) portion of the trigeminal ganglion transmit pain information from the eye. The conjunctiva, cornea, sclera, and uvea (iris, ciliary body, and choroid) are densely innervated with trigeminal fibers and exquisitely sensitive to pain. Any painful stimulus to these areas (e.g., corneal abrasion, iritis, uveitis) invariably causes photophobia. In contrast, the retina is insensate, as evidenced by the lack of pain with retinal detachment and nonarteritic anterior ischemic neuropathy. The optic nerve does contain trigeminal afferents (not within the nerve, but within blood vessels and dura), which cause pain associated with optic neuritis and arteritic anterior ischemic neuropathy (56,57).

*The orbit.* Other structures in the orbit are also pain sensitive. As would be expected, trigeminal V1 branches are nociceptive. Extraocular muscles have nociceptive afferents that travel along cranial nerves (CN) III, IV, and VI, leading to pain with orbital myositis. The pain of diabetic third nerve palsy is not clearly understood but is likely due
to nociceptive afferents within CN III or the extracocular muscles that it innervates. Orbital blood vessels are trigeminally innervated and contribute to the pain of orbital inflammation and superior orbital fissure syndrome (56,57).

**Autonomic Innervation**

The eye and orbit are densely innervated by autonomic effectors, most of which course along branches of the trigeminal nerve. Although not formally considered autonomic in their own right, trigeminal ganglion neurons are effectors as well as sensors. When activated by a nociceptive stimulus, they release mediators, including calcitonin gene-related peptide and nitric oxide from the very terminals that were activated. This positive feedback loop underlies the trigeminovascular reflex, whereby trigeminally innervated cranial vessels dilate after a nociceptive stimulus, perpetuating nociceptive activation. The trigeminautonomic reflex is a true multisynaptic reflex, involving activation of superior salivatory and Edinger-Westphal nuclei by collaterals from the trigeminal nucleus caudalis (TNC; the first sensory relay in the central nervous system mediating pain sensation from the head). Superior salivatory outputs activate parasympathetic effectors in the pterygopalatine ganglion (which dilate vessels) and in the ciliary ganglion (which mediate lacrimation). Edinger-Westphal outputs mediate pupillary constriction. The trigeminovascular and trigeminoautonomic reflexes are thought to underlie the conjunctival injection, tearing, and periorbital pain of migraine and cluster headache, which are almost invariably also accompanied by photophobia (58–61).

The orbit is also densely innervated by sympathetic efferents. The short ciliary nerves carry sympathetic supply to the blood vessels in the orbit, and the long ciliary nerves supply sympathetic innervation to the pupil. The cornea also receives sympathetic innervation (62). Stimulation of the superior cervical ganglion in humans causes pain (63), and pharmacological blockade of this ganglion produces relief in patients with intractable facial pain who have failed trigeminal section (63).

These findings are consistent with the understanding of sympathetic influences on somatic pain, best demonstrated in complex regional pain syndromes (CRPS; CRPS I: reflex sympathetic dystrophy, CRPS II: causalgia). Usual treatment of CRPS involves sympathetic block to the involved limb. We reasoned that sympathetic blockade might analogously reduce ocular pain and photophobia. Six patients with severe photophobia underwent placebo-controlled superior cervical ganglion blockade. All had marked reductions in spontaneous and light-triggered pain using local anesthesia but not with saline placebo (9). A second study with 19 patients showed similar findings (64).

**Blink Reflex**

The blink reflex is commonly considered as a response to stimulation of the cornea or face, but it is also induced by light, auditory stimuli, and distant somatosensory stimuli (65,66). Each stimulus-induced reflex has individual wiring features, although all have in common motor outflow through the seventh CN. The blink reflex is likely relevant to photophobia, as photophobia causes an increase in blink rate. Conversely, conditions associated with blinking abnormalities (blepharospasm, PSP) also are associated with photophobia (67). This 2-way interaction (photophobia leads to blinking; blinking leads to photophobia) suggests that there is cross talk between the different blink reflex pathways, at least as regards the percept of photophobia. One likely location for this is the medullary laterobulbar reticular formation, which integrates sensory input prior to CN VII output (65).

The corneal blink reflex begins with unmyelinated afferents from ciliary branches of V1, which synapse in the TNC. The supraorbital blink reflex involves mixed (myelinated and unmyelinated) afferents, which synapse in both TNC and the principal trigeminal nucleus. Blink reflex can also be elicited by stimulation of branches of the facial nerve; however, as it has a similar latency to trigeminally evoked responses, it likely involves a similar circuit. Surprisingly, little is known about the light-evoked blink reflex: it is assumed that visual pathways including retina, optic nerve, and olivary pretectal nucleus are involved (65,66). The light-evoked blink reflex is consensual and has a longer latency than other blink reflexes; evidence that it is multisynaptic. It is thought that tactile- or electrical-stimulation–induced blink reflex signals converge on the trigeminal dorsal horn and laterodorsal reticular formation. There are also direct connections between principal nucleus of CN V and the olivary pretectal nucleus, directly to CN VII. The relatively long latency of the consensual blink response to supraorbital stimulation, and the even longer latency of the light-evoked blink response, suggests that these direct connections may not be involved (65,66,68,69).

The circuitry of the blink reflex is very likely a part of the photophobia response given the increased blink rate in photophobic patients (70). Whether such circuit changes are causal or a consequence of some other pathology is unclear. Certainly, in the case of blepharospasm, abnormalities in the blink reflex pathway could be of primary importance (41).

**Light Perception and Photophobia**

The cardinal stimulus for photophobia is light; thus, pathways of light perception must be involved. Interestingly, photophobia can be experienced without image formation, as documented in some blind patients (71–74).

Rods and cones are the primary light sensors in the eye. They transmit photosignals via bipolar and amacrine cells to retinal ganglion cells, which exit the orbit via the optic nerve. Most of these fibers travel to the lateral geniculate nucleus of thalamus and then to occipital cortex, mediating vision. However, some travel to the olivary pretectal
Integration of Light Sensation With Nociceptive and Autonomic Responses in Photophobia

It is intuitive that photophobia has elements of light perception and pain, but what are the neural circuit correlates of this multisensory experience? **Photophobia circuits.** Recent studies have begun to elucidate the functional pathways that mediate photophobia. Two distinct circuits have been identified, and at least a third is possible. Given the redundant and parallel nature of homeostatic networks, it is likely that these networks are interconnected and interact with each other. It is also quite possible that more circuits remain to be discovered.

Okamoto et al (85) recorded in the TNC as they shone light into the eyes of anesthetized rats. They found that the firing rate of TNC neurons increased on light exposure, a finding whose simplest interpretation is a nociceptive response to light (or photophobia). They could eliminate this light-evoked nociceptive discharge by lidocaine injection into either the globe or the trigeminal ganglion, showing that both intraocular afferents and trigeminal neurons were required for the response. Next, via lidocaine injection into the superior salivatory nucleus (SSN) or injection of vasoconstrictors into the globe, they showed that parasympathetic efferents (likely causing ocular vasodilation) were involved. The circuit that emerges (Fig. 1) is of retinal photodetectors (whether rod, cone, or IPRGC is unclear) activating SSN, which in turn evokes ocular vasodilation and activation of pain-sensing neurons on blood vessels.

Noseda et al (86) identified a completely different circuit. By injecting a viral tracer into the globe, they made the surprising finding that a population of IPRGCs make direct connections in thalamic nuclei not normally associated with vision. These nuclei (posterior, lateral posterior, and intergeniculate) are associated with somatosensory and pain. Next, they recorded from these retina-connected thalamic neurons and found that they responded to painful stimulation of the dura and to light. The convergent input from trigeminal and retinal afferents on the same thalamic neurons makes them uniquely positioned to interpret light as a nociceptive signal. In a sense, they can be considered “photophobia neurons” (Fig. 1). Noseda et al further characterized the projection pattern of these thalamic neurons into cortex. They found processes in multiple regions, including visual, somatosensory, and association cortices. This projection pattern suggests a broadly distributed, multisensory, and nociceptive response for photophobia.

The role of the thalamus in this proposed multisensory integration bears mention. The thalamus is a critical state-setting and gain-setting region in the brain. Its role as a relay for sensory information is well understood, but the concept of a relay implies that little processing occurs, and this is not the case. Both gain and precision of sensory signals are actively altered in thalamus (87). Moreover, as the work of Noseda et al (86) demonstrates, there is integration of different sensory pathways within the region. However, the role of the thalamus cannot be properly appreciated in isolation. There is massive reciprocal innervation between thalamus and cortex, making it more physiologically realistic to consider sensory alterations as taking place in a “thalamocortical unit” (88). This has been best demonstrated in the study of sleep and waking state-associated oscillations (89), but it is surely equally relevant for sensory responses, which are themselves significantly modulated by state (90). Future research about thalamic roles in photophobia will hopefully uncover this sort of dynamic interaction.

**Photophobia without the optic nerve?** It may be that photophobia does not depend on any form of retinal phototransduction. Dolgonos et al (91) measured trigeminal blink reflex by stimulating the supraorbital nerve in rats. They replicated the well-known finding that light potentiates (increases in amplitude) the trigeminal blink reflex. What was surprising was that this effect persisted after they sectioned the optic nerve, which should disconnect any photosignal leaving the eye. The authors suggested that “associational ganglion cells” either directly activate trigeminal nociceptors in the orbit or indirectly activate them through effects on uveal blood flow. Another possible explanation, given the recent discovery of melanopsin photoreceptors in the iris (84), is that these intrinsically photosensitive ganglion cells bypass the retina and optic nerve entirely to activate nociceptors either inside or outside the globe.

Thus, there are at least 2 and possibly 3 ways that light from the eye can activate pain circuits: through conventional rod and cone circuits, through IPRGCs, and through melanopsin-containing ganglion-type cells outside the retina. There are also at least 2 pathways by which light-based nociception can take place when exiting the globe, either through optic nerve projections to the pretectal nucleus or direct connections to the thalamus. It is also possible that intraocular trigeminal afferents are directly activated by extraretinal melanopsin-containing ganglion-like cells.
A caveat about the extraretinal pathway is that it may not be directly applicable in humans, as extraretinal melanopsin-containing cells have not been conclusively demonstrated. Although many conventional concepts of photophobia have been challenged in the past few years, it still appears that ocular contents are necessary, as complete enucleation removes the photophobia response (73,92).

Possible molecular targets in photophobia. The intracranial nociception involved in migraine prominently involves activity of the calcium gene–related peptide (CGRP) receptor. As mentioned above, trigeminovascular afferents both release and respond to CGRP, which is both pro-nociceptive and vasodilatory. Because of its prominent role, CGRP is a target for acute migraine treatment, and CGRP antagonists alleviate acute migraine (93,94). Interestingly, mice with gain-of-function mutations in the CGRP signaling pathway demonstrate symptoms consistent with migraine. The most prominent of these is photophobia (95,96).

CGRP binds a heterodimeric receptor formed of the CRLR and RAMP1 proteins, activating adenylate cyclase and cyclic adenosine monophosphate. Recober et al. (97) generated mice with increased sensitivity to CGRP via insertion of a human RAMP1 protein at high expression levels (nestin/hRAMP1 mice). These mice were no different from wild-type littermates in ocular anatomy, motor activity, or anxiety. However, they had a significant increase in light aversion on intracerebroventricular CGRP injection compared to the same littermates. This difference in light aversion was blocked by treatment with a CGRP antagonist, showing that the behavior was mediated by CGRP receptor activity. It will be very interesting to see what elements of the photophobia circuits are altered in RAMP1 mutant mice. Insights gained could lead to anatomically specific targets for migraine treatment (98).

Photophobia circuit alterations in humans: Psychophysics of photophobia. It is clear that there are individual “thresholds” of light sensitivity even in normal people. Most studies that have looked at thresholds of light in individuals showed some normal variation (27). However, subjects with migraine and even tension-type and cervicogenic headache (27) have lower thresholds (27,99). Light sensitivity may also vary by season. Vanagaite et al. found that migraine patients, and to a lesser extent controls, had lower pain thresholds to light in the winter months (November through January).
than in the summer months (May through July). There also appears to be a "summation" or "integration" involved in photophobia. Wirschafter et al (100) showed that binocular viewing lowered the threshold of light, whereas unihocular viewing raised the threshold. Finally, the perception of light brightness is dependent on the state of retinal adaptation (e.g., dark adaptation), as is readily appreciated when stepping from a darkened movie theater into the sunshine (101,102).

The wavelength of light may also affect the photophobia percept. Main et al (103) found that shorter wavelength (blue) light was more uncomfortable for subjects with migraine than for those with tension-type headache or controls. These investigators also reported that longer wavelength (red) light was also less comfortable for subjects with migraine (103). Good et al (29) found that visually provoked beta brain activity was suppressed by red light and enhanced with blue light in migraine patients, showing that the two wavelengths have different effects on cortical activity. The reasons for this difference, and the noxious nature of both blue and red light to migraineurs, are unclear. The fact that intrinsically photosensitive retinal ganglion cells are preferentially sensitive to blue light is intriguing (83,104).

Light stimulation can increase pain in the trigeminal and cervical regions in migraineurs compared with normal controls. Kowacs et al (105) performed pressure algometer readings over the head, before and after stimulation with light up to a discomfort threshold. All migraine subjects had reduced thresholds of light sensitivity, which was not unexpected, but they also had significant and sustained lowering of pressure and pain sensitivity in both trigeminal and cervical sites. Controls did not exhibit this phenomenon.

Functional imaging of photophobia networks in humans. Functional neuroimaging allows the study of photophobia networks in awake humans. This is proving critical in confirming knowledge gained in laboratory animals, but more importantly has allowed unique insights into the conscious perception of photophobia.

Moulton et al (106) performed BOLD functional MRI (fMRI) recordings in an individual with photophobia associated with overuse of contact lenses. During the photophobic state, activation of the trigeminal ganglia, TNC, ventroposteromedial thalamus, and anterior cingulate gyrus occurred, but without photophobia, these structures were not activated. This pattern of activation suggests that photophobia was perceived as a truly painful stimulus. Trigeminal ganglion, TNC, and ventroposteromedial thalamus are all relays in cranial nociception, and the anterior cingulate cortex is an element in the “pain matrix,” a network of cortical and subcortical structures activated during the conscious perception of pain (107).

In a series of patients with laser-assisted in situ keratomileusis–induced photophobia, Malecza et al (108) found that light-induced BOLD fMRI activation was increased in the visual association cortex, compared with controls. This suggests that photophobia may involve alterations in cortical visual processing and pain networks (see below) (108).

The photophobia of blepharospasm has also been investigated with functional imaging. Emoto et al (109) used 18-fluorodeoxyglucose positron emission tomography (PET) to compare blepharospasm patients with and without photophobia to controls. They found that blepharospasm patients with photophobia had significantly increased metabolic activity in the thalamus and dorsal midbrain compared to nonphotophobic patients and controls. The regions with the largest differences between photophobic and nonphotophobic patients were thalamic ventral anterior (VA) and ventral lateral (VL) nuclei and the superior colliculus. Interestingly, the nonphotophobic patients showed significantly decreased activity in the superior colliculus compared to controls. Both patient groups, by virtue of their blepharospasm, had increased rates of blinking compared to controls. VA, VL, and superior colliculus are all involved in motor control; thus, it is interesting that photophobic and nonphotophobic patients—equally affected by the motor symptoms of blepharospasm—showed differential activity patterns. However, superior colliculus is also involved in ocular-related sensorimotor integration; the difference in its activity might be explained by greater nociceptor input in photophobic patients.

Photophobia networks in migraine. Migraine is the most common clinical disorder associated with photophobia. A particular advantage of migraine for the study of photophobia is that (for most) the symptoms are intermittent. The migraine patient can thus serve as his or her own control.

In addition to examining photophobia pathways in rodents (see above), Noseda and Burstein (73) examined humans with migraine-associated photophobia. These patients were unusual in that they all had specific visual pathway defects. Those who had undergone enucleation did not experience increased headache pain on exposure to light, but those with an intact eye did, confirming earlier clinical reports (70–74) and the laboratory work of Oka-moto et al (85), which showed that ocular afferents were necessary for photophobia. The presence of photophobia in legally blind patients supports (but does not confirm) the findings of Noseda et al (86) that IPRGCs, nonimage-forming ganglion cells, were responsible for the photophobia phenotype.

Migraine is associated with alterations in cortical excitability (110), and visual aura can be directly correlated with occipital dysfunction (111,112). Denuelle et al (113) used 15O PET to examine the response to light during migraine, after treatment with sumatriptan, and interictally. They found that light levels that did not cause pain either interictally or after sumatriptan treatment evoked pain during headache, confirming migraine-induced photophobia.
They found that their photophobia stimulus induced a significant increase in cortical blood flow during the migraine attack (both before and after sumatriptan treatment) but not interictally. This shows that the occipital neurovascular response is more sensitive during attacks and is likely involved in the photophobia response (114,115). In a separate study, the same group examined migraine patients exclusively in the interictal period and demonstrated that even at “baseline,” they had larger areas of occipital activation to visual stimulation, and visual stimulation paired with pain, compared to controls (114). Martin et al (116) showed similar findings using BOLD fMRI, with increased area of occipital activation to light during migraine attacks. Although there were some differences between the studies, their combined results show that the migraine-associated photophobia response persists into the interictal period, suggesting long-lasting alterations in sensory gain. The findings of increased response to pain + light, compared to light alone, are consistent with animal work showing multisensory integration during the photophobia response (86).

**APPROACH TO THE DIAGNOSIS OF PHOTOPHOBIA**

Before treating photophobia, one needs to be certain of the cause (Fig. 2). Careful history, along with neurologic and neuro-ophthalmic examination including visual fields, is essential. Pituitary tumor, meningitis, and other intracranial processes can present with photophobia. If there are focal neurologic findings, MRI of the brain is indicated. Other central causes, such as PSP, should be considered. However, the most common causes are dry eyes, “corneal neuropathy,” and migraine. Diagnosing dry eye can be difficult. Examination techniques should include examination of the tear film, tear film breakup time, corneal staining with rose bengal or fluorescein, and Schirmer testing. Corneal neuropathy is also difficult to diagnose. We instill lidocaine eyedrops, and if the pain and discomfort resolve, this diagnosis is possible. Rosenthal (15) reports that corneal nerve imaging by confocal microscopy also may be helpful.

Diagnosing migraine should not be a problem when one looks for pain associated with photophobia, phonophobia, nausea and/or vomiting, and pain that worsens with activity. Blepharospasm is usually not a challenge to diagnose if one observes frequent blinking. However, reflex blepharospasm in response to bright light can be difficult to identify. Look for squeezing of eyes, apraxia of eyelid opening, and involuntary eye closure to even moderate levels of light.

Screening for depression and anxiety is also important. We conducted a study in which patients with chronic photophobia and migraine had increased scores on measures of depression and anxiety, compared to patients with episodic photophobia with migraine and to controls without migraine or photophobia (117).

**TREATMENT OF PHOTOPHOBIA**

There are few neuro-ophthalmic problems that can be as vexing to treat for clinicians. Are there really any known treatments? Certainly, there have been no major randomized controlled trials of treatment of photophobia. Most of the literature consists of case reports, and a few studies with small numbers of subjects.

**Use and Misuse of Tinted Lenses**

One principal treatment is to decrease the dark-adapted state. Patients with severe photophobia who wear darkly tinted lenses should be encouraged to reduce dark adaptation. Chronic darkness will increase the perception and pain of light sensitivity. Lebensohn (5) cautioned that “tinted glasses as a symptomatic remedy for chronic photophobia are to be condemned because of both their ineffectiveness and their habit forming tendency.” Wearing sunglasses to an eye clinic has led many physicians to consider the patient to have some type of psychiatric disorder or at least to predict nonorganic visual loss (118,119).

Some optical tints have been tried successfully to combat photophobia. Red-tinted contact lenses have been tested in individuals with photophobia due to cone disorders (120–124). However, red tint appears to exacerbate migraine-associated photophobia (103).

Sunglasses do make sense in the bright sunlight for patients with migraine, tension-type headaches, and those with light sensitivity. Some tints have been successful in migraine. Good et al (29) found that FL-41 tint, a rose-colored tint, reduced migraine frequency in children by more than one half. Subjects reported a decrease in photophobia and glare in between attacks but no change in the light sensitivity associated with the migraine attack. FL-41 tint filters 80% of short wavelength 50 or 60 Hz flicker that is seen with fluorescent lights. As flicker stimuli can be particularly noxious to patients with migraine (125), the authors reasoned that flicker reduction contributed to the reduction in headaches.

We studied FL-41–tinted lenses and found that they increased the threshold to discomfort in all subjects (controls, migraineurs, and patients with blepharospasm), but they did not differ from gray-tinted lenses in reducing light sensitivity (44). To test whether patients preferred FL-41–tinted over gray-tinted spectacles, we performed a double crossover study of subjects with blepharospasm using gray and FL-41 tint. Patients preferred FL-41 tint over gray spectacles, and they felt that FL-41 significantly reduced their symptoms (70). We also tested the blink reflexes of patients who wore FL-41 tint or placebo pink lenses while reading under a standardized light source. We found that in blepharospasm patients, FL-41 tint greatly reduced the number of blinks and intensity of blinks (70).

Studies using fMRI suggest that there may be different physiologic responses to spectrally specific tints compared to neutral density filtering (which attenuates all wavelengths
equally). Huang et al (126) found that precision ophthalmic tints normalized cortical activation on fMRI, whereas gray lenses did not, in patients with migraine. Why would red- or pink-tinted lenses show this effect? Red tints tend to block blue wavelengths, which more likely may induce photophobia (103).

**Treatment of Dry Eyes**

Aggressive treatment of dry eyes may be helpful. Blepharospasm-associated dry eyes are commonly treated with drops and ointments and possible punctual plugs (127).

Anti-inflammatory drops have been tested in reducing light sensitivity after cataract surgery and have not been found to be helpful (128). Xylocaine has been used after cataract surgery without decrease in light sensitivity (129).

**Dilating Drops**

Cycloplegics can be used to give some relief in patients with ocular inflammation. This is likely due to reduction in ciliary muscle spasm since papillary dilation actually increases light entering the eye.

**Systemic Medications**

Sedatives (e.g., barbiturates, benzodiazepines) that reduce “trigeminal irritability” have been reported to be helpful and allow for prolonged sleep and closed eyes (130). However caution should be exercised with these kinds of medication. Treatment of migraine-associated photophobia with migraine preventive medications including beta-blockers, calcium channel blockers, and anti-convulsants is reasonable (96). Acute migraine should be treated with migraine-specific medications that have been shown to reduce photophobia associated with an acute attack (96). To the extent that other photophobic disorders are due to dysfunctional excitation/inhibition balance, migraine preventives, especially of the antiepileptic class, might be considered. Systemic medications that have been anecdotally reported to reduce the pain associated with photophobia include gabapentin and melatonin.
Given the alleviation of photophobia with antidepressants in patients with comorbid depression (49,50), such treatment appears helpful. If anxiety and panic disorder are present, anxiolytics may be beneficial. While the mainstay treatment of blepharospasm is botulinum toxin (127), clinicians have tried tricyclic antidepressants, baclofen, benzodiazepine, orphenadrine, carbidopa/levodopa, and fluoxetine (131). If corneal neuropathy is suspected, Rosenthal suggests topical lacosamide or systemic anticonvulsants, such as gabapentin, pregabalin, or carbamazepine (15).

Procedures
Various techniques have been described in treating photophobia in difficult clinical settings. Injections to the supraorbital nerve have been reported to cause a reduction in light sensitivity (130). Alcohol (40%–60%) injected into the orbit (1.5 mL) has been reported to be helpful in cases of ocular inflammation to reduce photophobia and did not influence visual acuity (132). In one series, the majority of individuals with whiplash-induced cervicalgia and photophobia found relief with trigger point injections (133). Botulinum toxin injection was found to reduce photophobia associated with posttraumatic headache (134) and is used to treat chronic migraine (135).

Sympathetic blockade was first reported by Magitot (136). Fine and Digre (9) showed that superior cervical blockade by lidocaine did improve light sensitivity in some patients with photophobia. This treatment may be best in patients who have had known injury to the anterior segment and who experience continued photo-oculodynia despite complete resolution of the injury.

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State-of-Art Review


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Dr Lincoff:

An 83-year-old man with Type 2 diabetes mellitus, systemic hypertension, atrial fibrillation, and successfully treated prostate carcinoma (6 years prior to presentation) complained of progressive painful loss of vision in his left eye for 2 weeks. Examination revealed visual acuity of 20/20 in the right eye and no light perception in the left eye. The left pupil was amaurotic, and there was mild left conjunctival injection and chemosis (Fig. 1), 1 mm of left proptosis, full extraocular movements, and no evidence of anterior or posterior uveitis. The right fundus was normal and left was consistent with combined central retinal artery occlusion (CRAO) and central retinal vein occlusion (CRVO) with optic nerve swelling (Fig. 2).

The patient denied temple, jaw, and ear pain, scalp tenderness, migratory arthralgias, and fever. The superficial temporal arteries were palpable and nontender. MRI of the brain and orbits was performed.

Dr Sharma:

The T1-weighted axial image through the orbits (Fig. 3A) reveals mild left proptosis with thickening of the left optic nerve–sheath complex. T2-weighted coronal image (Fig. 3B) shows thickening of the optic nerve with increased signal intensity. T1-weighted axial image obtained following intravenous contrast administration (Fig. 3C) demonstrates tram-track pattern of enhancement along the left optic nerve sheath. T2-weighted coronal image (Fig. 3D) shows that the optic chiasm is normal. Differential considerations at this time would include both inflammatory and neoplastic processes.

Dr Lincoff:

The differential diagnosis of unilateral optic nerve thickening and enhancement causing painful unilateral blindness associated with a combined CRVO/CRAO included embolic, hypercoagulable, inflammatory, infectious, infiltrative, and compressive causes. Despite the lack of constitutional symptoms and signs, giant cell arteritis also was a major concern. A variety of laboratory studies were performed, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) assay, complete blood cell count, angiotensin-converting enzyme, antinuclear antibody, antineutrophilic cytoplasmic antibody, neutrophil cytoplasmic antibody, rapid plasma...
reagin, and prostate-specific antigen levels. The results of these studies were negative or normal. Specifically, the ESR was 2 mm/h, and the CRP was 0.85 mg/L (normal, <1 mg/L). A chest radiograph was normal. Cerebrospinal fluid analysis revealed no cells but a mildly elevated protein of 65 mg/dL (normal, ≤45 mg/dL). Whole-body positron emission tomographic scan revealed only an inflammatory thyroid nodule confirmed by biopsy. A temporal artery biopsy was normal.

The retinal hemorrhages and disc swelling in the left eye resolved over the next 5 months, but the patient developed rubeotic glaucoma treated with 2 intravitreal injections of bevacizumab. In addition, he was given oral prednisone beginning with a dose of 1 mg/kg/d, resulting in resolution of his left periorbital pain within 4 weeks. An optic nerve biopsy was recommended but was not performed because the patient was taking Coumadin for atrial fibrillation.

A repeat MRI was performed 9 months after the onset of symptoms.

**Dr Sharma:**

The follow-up MRI demonstrates progression of the initial abnormality, which is manifest as thickening and hyperintensity of the intracranial portion of the left optic nerve, the optic chiasm, and the left optic tract, as seen on axial and sagittal FLAIR images (Fig. 4A, C). T1-weighted coronal image after intravenous injection of contrast (Fig. 4B) shows thickening and enhancement of the chiasm. In addition, axial FLAIR image (Fig. 4A) demonstrates abnormal signal in the left medial temporal lobe, suggesting extension along the optic radiations. The pattern of progression suggests an infiltrative process.

**FIG. 3.** Magnetic resonance findings at presentation. A. T1 axial image shows enlargement of the left optic nerve. B. T2 coronal scan confirms enlargement of the left optic nerve with increased signal (arrow). C. Contrast-enhanced T1 axial image reveals enhancement of left optic nerve sheath. D. T2 coronal scan demonstrates normal appearance of the optic chiasm (arrow).
Dr Lincoff:

Following temporary cessation of Coumadin, a craniotomy was performed. The intracranial segment of the left optic nerve and the optic chiasm appeared abnormally large, red, and hypervascular. On cross section, the tumor was white with a hemorrhagic center (Fig. 5A, B). A large segment of the intracranial portion of the left optic nerve was resected.

Dr Corbo:

The specimen shows a markedly cellular, diffuse, astrocytic neoplasm with mitotic activity, incipient necrosis, and vascular proliferation (Fig. 6). The tumor cells were positive for the astrocytic marker glial fibrillary acidic protein, and an immunostain for Ki67 revealed a proliferation index of 17%. Thick hyalinized septae were noted throughout the specimen at low power, suggesting infiltration of the optic nerve by the tumor. Pathologic diagnosis: glioblastoma involving the left optic nerve.

FIG. 4. MRI obtained 9 months after presentation. A. Axial FLAIR image reveals enlargement and increased signal in the optic chiasm, left intracranial optic nerve, and left temporal lobe (arrow). B. Contrasted T1 coronal view shows enhancement and enlargement of the optic chiasm (arrow). C. Sagittal FLAIR image demonstrates increased signal in and enlargement of the chiasm and left optic tract (arrow).

FIG. 5. Intraoperative photographs. Appearance of the left intracranial optic nerve before (A) and after (B) resection.

FIG. 6. Biopsy specimen shows a hypercellular neoplasm with abundant mitotic figures (hematoxylin & eosin, × 100).
Dr Lincoff:

Although glioblastoma multiforme (GBM) is the most common glial brain tumor in adults (1), GBMs arising within the anterior visual pathway are uncommon, and cases arising within 1 optic nerve are rare. Of 45 cases of adult malignant optic glioma reported in the literature (2–5), only 3 (2–5) were unilateral (4,5).

Malignant gliomas of the anterior visual pathway are slightly more common in males (51% vs 49%) and usually occur in the sixth decade of life or later, with a mean age at diagnosis of 54 years. High-grade astrocytic neoplasms are defined by the presence of mitotic activity and are classified pathologically as either anaplastic astrocytomas (World Health Organization [WHO] Grade III) or GBM (WHO Grade IV) (6). Whereas Grade III tumors lack necrosis and vascular proliferation, the presence of one or the other is required for a Grade IV diagnosis. Survival depends on tumor grade, resectability, and the age of the patient, but they prove fatal in the majority of cases; the mean survival from the time of presentation usually is less than 1 year. Standard therapy is resection followed by radiation therapy and chemotherapy, with the alkylating agent temozolomide. Some improvement in survival has been achieved with monoclonal antibodies directed against the tumor and anti–vascular endothelial growth factor agents (2).

Because most malignant gliomas of the anterior visual pathway originate in the optic chiasm or distal optic nerve, patients with these lesions usually present with rapidly progressive unilateral or bilateral painless visual loss associated with normal-appearing fundi. When the tumor arises in the proximal optic nerve, severe visual loss associated with a painful CRVO or mixed CRAO/CRVO is the typical presenting sign (1). This mandates neuroimaging to determine if the fundus abnormalities have been caused by infiltration of the optic nerve with secondary vascular compromise and a canalicular compartment syndrome. The ischemic state of the tissues and ensuing necrosis is the cause of the prolonged pain syndrome; once the necrosis is complete, the pain usually subsides. Recognition of this triad of severe orbital or ocular pain, a fundus picture of a CRVO or mixed CRVO/CRAO, and visual loss that may be greater than one might expect from the appearance of the fundus should prompt early diagnosis and treatment of this neoplasm.

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Literature Commentary


Objective: Higher latitude, lower ultraviolet exposure, and lower serum 25-hydroxyvitamin D (25OHD) correlate with higher multiple sclerosis (MS) prevalence, relapse rate, and mortality. We therefore evaluated the effects of high-dose vitamin D2 (D2) in MS.

Methods: Adults with clinically active relapsing-remitting MS (RRMS) were randomized to 6-month, double-blind, placebo-controlled, high-dose D2, 6,000 IU capsules, dose-adjusted empirically aiming for a serum 25OHD of 130–175 nM. All received daily low-dose (1,000 IU) D2 to prevent deficiency. Brain MRIs were performed at baseline, 4, 5, and 6 months. Primary end points were the cumulative number of new gadolinium-enhancing lesions and change in the total volume of T2 lesions. Secondary end points were Expanded Disability Status Scale (EDSS) score and relapses.

Results: Twenty-three people were randomized, of whom 19 were on established interferon or glatiramer acetate (Copaxone) treatment. Median 25OHD dose ranged from 54 to 69 nM (low-dose D2) vs 59 to 120 nM (high-dose D2) (P = 0.002). No significant treatment differences were detected in the primary MRI end points. Exit EDSS, after adjustment for entry EDSS, was higher following high-dose D2 than following low-dose D2 (P = 0.05). There were 4 relapses with high-dose D2 vs none with low-dose D2 (P = 0.04).

Conclusions: We did not find a therapeutic advantage in RRMS for high-dose D2 over low-dose D2 supplementation.

Classification of Evidence: This study provides class I evidence that high-dose D2 (targeting 25OHD 130-175 nM), compared to low-dose supplementation (1,000 IU/day) was not effective in reducing MRI lesions in patients with RRMS.

The authors randomized patients with RRMS to receive either 6,000 IU or 1,000 IU of vitamin D2 (D2) twice daily. They did not find a significant difference in gadolinium-enhancing lesions or T2 lesion volume on brain MRI. Patients on high-dose D2 had worse EDSS and more relapses than those on low-dose D2.

This is the first study to randomize patients with RRMS to receive vitamin D2. Although vitamin D deficiency may be associated with RRMS, this study calls into question exactly how much vitamin D supplementation is safe and effective.

—Michael S. Lee, MD

Although decreased levels of vitamin D have been found in MS patients and associated with severity, we have yet to see a good clinical trial that shows benefit of treatment with vitamin D. The results of this trial are disappointing in that treatment failed to show benefit on MRI or clinical relapses. However, the trial was only 6-month long, and benefit might take longer to occur.

—Mark L. Moster, MD

One more thing, this study took place in Australia, which may receive more sun than Minnesota. It remains to be seen whether a high-dose vitamin D supplement may be more effective in areas that receive less sun exposure.

—Michael S. Lee, MD


Objective: Neuromyelitis optica (NMO) is an inflammatory demyelinating disease of the central nervous system. Circulating autoantibodies (NMO-IgG) against astrocyte water channel aquaporin-4 (AQP4) cause complement-mediated and cell-mediated astrocyte damage with consequent neuroinflammation and demyelination. Current NMO therapies, which have limited efficacy, include immunosuppression and plasma exchange. The objective of this study was to develop a potential new NMO therapy based on blocking of pathogenic NMO-IgG to its target, AQP4.

Methods: We generated nonpathogenic recombinant monoclonal anti-AQP4 antibodies that selectively block NMO-IgG binding to AQP4. These antibodies comprise a tight-binding Fab and a mutated Fc that lacks functionality for complement-mediated and cell-mediated cytotoxicity. The efficacy of the blocking antibodies was studied using cell culture, spinal cord slice, and in vivo mouse models of NMO.

Results: In AQP4-expressing cell cultures, the nonpathogenic competing antibodies blocked binding of NMO-IgG in human sera, reducing to near zero complement-mediated and cell-mediated cytotoxicity. The antibodies prevented the development of NMO lesions in an ex vivo spinal cord slice model of NMO and in an in vivo mouse model, without causing cytotoxicity.

Interpretation: Our results provide proof-of-concept for therapy of NMO with blocking antibodies. The broad efficacy of antibody inhibition is likely due to steric competition because of its large physical size compared to AQP4. Blocker therapy to prevent binding of pathogenic autoantibodies to their targets may be useful for the treatment of other autoimmune diseases as well.

Prior studies have demonstrated the importance of NMO-IgG in the pathogenesis of NMO. This includes the...
correlation of disease activity with antibody level, the improvement with removal of antibody, and the production of similar pathology in mice or rats administered human NMO-IgG.

The authors have created a modified NMO-IgG, which binds to AQP4, is not pathogenic, and does not induce complement activation or cytotoxicity. It blocks the binding of the pathogenic NMO-IgG. These early findings provide hope for a specific targeted therapy with blocking antibodies for NMO and other diseases without the dangerous risks of immunosuppression, normally required in these patients.

—Mark L. Moster, MD

What a great idea! The targeted therapy concept works well for NMO since the pathophysiology for some patients likely involves a single autoantibody to AQP4. Hopefully, further preclinical (and clinical) studies will continue to show minimal cytotoxic injury with very few, if any, adverse events.

—Michael S. Lee, MD


**Purpose:** Thyroid-stimulating immunoglobulins (TSIs) likely mediate Graves ophthalmopathy (GO). The clinical relevance of these functional autoantibodies was assessed in GO.

**Design:** Cross-sectional trial.

**Participants:** A total of 108 untreated patients with GO.

**Methods:** TSIs, assessed with a novel bioassay, bind to the thyrotropin receptor (TSHR) and transmit signals for cyclic adenosine monophosphate (cAMP)–dependent activation of luciferase gene expression. The cAMP/cAMP response element-binding protein/cAMP-regulatory element complex induces luciferase that is quantified after cell lysis. The TSI levels were correlated with activity and severity of GO and compared with a TSHR-binding inhibitory immunoglobulin (TBII) assay.

**Main Outcome Measures:** TSIs, activity and severity of GO, diplopia, and TBII.

**Results:** TSIs were detected in 106 of 108 patients (98%) with GO. All 53 hyperthyroid patients were TSI positive versus 47 patients (89%) who were TBII positive. All 69 patients with active GO were TSI positive, whereas only 58 of 69 patients (84%) were TBII positive. TSIs correlated with the activity ($r = 0.83$; $P = 0.001$) and severity ($r = 0.81$; $P = 0.001$) of GO. All 59 patients with GO with diplopia were TSI positive, and 50 of 59 patients (85%) were TBII positive. Among patients with moderate-to-severe and mild GO, 75 of 75 (100%) and 31 of 33 (94%) were TSI positive compared with TBII positivity in 63 of 75 (84%) and 24 of 33 (73%), respectively. The TSI levels were higher in moderate-to-severe versus mild GO (489% to $137\%$ vs $251\%$ to $100\%$; $P = 0.001$). Chemosis and GO activity predicted TSI levels alone ($P = 0.001$, multivariable analysis). The TSI levels were higher in patients with chemosis ($527\% \pm 131\%$) than in patients without chemosis ($313\% \pm 127\%$; $P < 0.001$).

**Conclusions:** TSIs show more significant association with clinical features of GO than of TBII and may be regarded as functional biomarkers for GO.

In this study, the authors measured thyroid-stimulating immunoglobulin (TSI) among various patients with thyroid eye disease (TED). They compared the TSI level with the TED clinical activity and severity and found a strong correlation. Comparison of serial TSI levels to serial clinical activity and severity was not performed.

Since much of the reconstructive procedures in TED occur during the inactive burned out phase of TED, it would be nice to have a biomarker for this. Although TSI looks promising, I think we need to see serial TSI levels to know for sure.

—Michael S. Lee, MD

The most impressive finding in this study is how sensitive TSI is in patients with GO, even in those with mild disease. This goes along with how I use TSI in my practice, which is to help diagnose GO in patients with subtle findings.

This study used a new, novel, cell-based bioassay for TSI. What we do not know is how sensitive most commercially available assays are.

—Mark L. Moster, MD


**Purpose:** To determine whether an association exists between sleep apnea and open-angle glaucoma, normal-tension glaucoma, nonarteritic ischemic optic neuropathy (NAION), papillodema, or idiopathic intracranial hypertension (IIH) and whether treatment with continuous positive airway pressure affects the development of these conditions.

**Design:** Retrospective, longitudinal, cohort study.

**Methods:** Billing records for beneficiaries of 40 years and older enrolled in a large United States–managed care network from 2001 through 2007 were reviewed. Incidence of open-angle glaucoma, normal-tension glaucoma, NAION, papillodema, and IIH were determined for the beneficiaries and were stratified by sleep apnea status. Cox regression analyses determined the hazard of each of these conditions developing among individuals with and without sleep apnea, with adjustment for sociodemographic, oculoc, and medical conditions.

**Results:** Among the 2,259,061 individuals in the study, 156,336 (6.9%) had 1 or more sleep apnea diagnoses. The hazard of open-angle glaucoma was no different among

Abstract: The literature on cerebrospinal fluid opening pressures for pediatric patients is scant. A retrospective study of measured opening pressures during lumbar punctures of pediatric patients in a controlled uniform setting was conducted. These procedures were performed in an outpatient surgery setting under anesthesia. Patients’ end-tidal carbon dioxide levels were maintained at 40–45 mm Hg. Opening pressures were measured with the patients lying in left lateral decubitus position with their legs extended. Correlations with patients’ ages and body mass index percentiles were investigated. Forty-four patients (median age, 8.9 years; range, 1.1–16.8 years) were included. Patients with chronic headaches, papilledema, or severe abnormalities of cerebrospinal fluid were excluded. The mean opening pressure recorded was 20.3 cm H$_2$O (median, 21 cm H$_2$O; range, 6–36 cm H$_2$O). Poor correlation with both age and body mass index percentiles was evident. The correlation coefficients were 0.09 and 0.14, respectively. Our experience suggests that pediatric reference ranges for opening pressures are closer to those of adults than previously appreciated, and values above 20 cm H$_2$O should not necessarily be considered abnormal.

In August of 2010, a research letter in the New England Journal of Medicine (NEJM) described opening pressures (OP) among pediatric patients undergoing lumbar puncture at all levels of sedation. They found a higher range than previously believed. The current study by Lee (no relation) and Vedanarayanan (definitely no relation) performed a similar study, but all patients underwent general anesthesia. The advantage is that they could manage carbon dioxide...
levels, which may affect OP. They found the mean OP of 20.3 ± 7 cm H$_2$O. The NEJM study data can be downloaded, and it found a mean OP of 19.8 ± 6.8 cm H$_2$O. This numbers are almost identical. Now, the authors looked at the 90th percentile, but as we all know, the 95th percentile is also used as a cutoff for abnormal. So could an OP of 34 be within that normal range too? Previously, I struggled to know what to do with an OP of 26 cm H$_2$O in a patient who I was convinced had pseudopapilledema. This information may also throw into question the diagnosis of pseudotumor without papilledema. How often does it really occur vs are these simply normal OP in patients with headaches?

—Michael S. Lee, MD

This study provides some new information about opening pressure in children. However, it provides only limited information of use to the clinician. Although the patients did not have conditions know to raise intracranial pressure, they all had neurologic diseases, including myopathy, neuropathy, ataxia, seizures, stroke, demyelinating disease, and encephalopathy. I do not think we can be certain that we can consider this population as a normal standard for intracranial pressure. Additionally, we do not really know how being under general anesthesia affects OP, which makes this information less useful for patients having lumbar puncture while awake.

—Mark L. Moster, MD


Abstract: Impairments of face processing occur frequently in frontotemporal lobar degeneration (FTLD) but the neuroanatomical basis for these deficits has seldom been studied systematically. Here, a prospective voxel-based morphometry study is described addressing the neuroanatomy of 2 key dimensions of face processing—face identification and facial emotion recognition—in a single cohort of 32 patients with FTLD (19 with frontal variant and 13 with temporal variant FTLD). For the FTLD group as a whole, face identification was positively associated with gray matter in the right anterior fusiform gyrus while recognition of angry expressions was positively associated with gray matter in the bilateral insular cortex. FTLD provides a perspective on the neuroanatomy of face processing that is complementary to focal lesion and normal functional imaging work.

Traditionally, the elucidation of the functions of specific brain regions has been accomplished via the study of patients with focal brain lesions. More recently, functional imaging of normal subjects has proved helpful. It makes sense that patients who have focal neurodegenerative disease may also provide insights into the neuroanatomic basis of individual functions.

FTLD (traditionally known as Pick disease) is an excellent group of disorders to study because of the typical focality and asymmetry, which presents with specific deficits related to unilateral or bilateral frontal or temporal degeneration. For instance, those with a predominantly left temporal FTLD have impaired naming, word comprehension, and semantics. Those with right temporal FTLD are socially inept and unempathic, with occasional sociopathic behavior. Some with early left FTLD have unmasked their “right brain” and have become quite artistic. Many patients have difficulty with recognizing faces, and others have difficulty appreciating facial emotion, which underlies this study.

The authors looked at brain volumes in focal regions and correlated that with the ability to recognize famous faces and facial emotion. They found that face identification was associated with amount of gray matter in the right anterior fusiform gyrus, while recognition of angry expressions was associated with gray matter in the bilateral insular cortex. These findings explain some of the social abnormalities in FTLD patients and mostly agree with prior findings from lesion and functional imaging work.

Neurodegeneration is never completely focal, and other brain areas are involved. Nonetheless, the preferential involvement of certain areas over others allows much to be learned about normal brain function from patients with diseases such as FTLD.

—Mark L. Moster, MD

Well said, Mark.

—Michael S. Lee, MD
**Noble J. David, MD (1927–2011)**

Noble J. David, MD, best known as “Nobby” to the readers of these pages, was my closest friend. He was also always a very welcome friend to literally thousands of colleagues, students, and patients who will greatly miss him. He passed away on November 30, 2011, at the age of 83, at the Erasmus Hospital in Rotterdam, Holland, where he had valiantly traveled to receive a transcutaneous aortic valve replacement. The procedure went well but he subsequently succumbed to hospital-acquired pneumonia.

I first met Nobby in 1962, when as a senior medical student at the University of Miami, I would attend Neurology Grand Rounds. He and J. Lawton Smith would put on memorable performances facilitating learning of what at that time appeared to be impossibly complex neuro-ophtalmic issues. Our relationship grew closer on my return to Miami for training in Neurology in the 1960s. He eventually became influential in my joining the faculty of the Department of Neurology and subsequently became my Wednesday evening dinner companion for more than 40 years. That meant that I was able to laugh at new jokes, gain insight into the human condition, and keep learning medicine from this profound intellect for more than 1600 Wednesday nights!

The annual resident’s day dinners at his home were legendary. There would be music, Middle Eastern food, and Nobby playing his cello accompanied by other talented colleagues. He was a real “feeder.” He fed us food, he fed us music, and he fed us knowledge.

Nobby’s contributions to medicine, neurology and neuro-ophthalmology were at times ground-breaking and at other times importantly expansive of known facts. In the 1950s, he was able to prove that retinal arterial embolic debris associated with amaurosis fugax was the same material being embolized from the carotid artery bifurcation. This is currently taken for granted in linking carotid atheromatous disease with transient ischemic attacks. Also ground-breaking was his contributions to the development of techniques to better understand retinal circulation, physiology, and disease. I can remember the hours and hours he would toil over fundus photographs of retinal fluorescein angiography.

Nobby further contributed to the literature of several clinical entities that were just becoming understood at the time. Among these were delineation of the distinctions between PSP and simple Parkinson disease; emphasis on saving blindness by early recognition of pituitary apoplexy; the wide clinical spectrum of basilar arterial disease; the clinical course of giant cerebral aneurysms, pituitary adenomas, bilateral anterior cerebral artery infarctions, and subtle visual field defects in occipital lobe strokes. He even alluded to the potential infectious origin of Creutzfeldt–Jakob disease as it developed in a pathologist who may have been exposed through his occupation.

In spite of all his responsibilities as Chief of Neurology at the Miami VA Hospital, Nobby served on the National Advisory Eye Council at the National Institutes of Health, giving of his time to review and evaluate lengthy grant proposals.

At the University of Miami, he was the bridge between the Department of Ophthalmology and the Department of Neurology. He taught and performed investigational work with both Departments, and he facilitated blending of the programs. In 1989, he led the Department of Neurology during a period of transition.

Nobby always characterized himself as a “Dukester” demonstrating a very idealized gratefulness to his undergraduate years, medical school, and graduate training at Duke University.
This past year has been an exceptionally difficult one for the neuro-ophthalmology family in Miami. First the passing of J. Lawton Smith and Joel Glaser and now the passing of Noble J. David.

He leaves behind a loving family and thousands of grateful patients, students, and colleagues. Most certainly, a Memorial fund will be established jointly within the Department of Ophthalmology and Neurology.

I find myself exceptionally fortunate to have enriched my life by having known him. He was, after all, my closest friend.

“Now cracks a noble heart. Good-night, sweet prince. And flights of angels sing thee to rest.”

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I read with interest the article by Brodsky and Karlsson (1) and the authors’ caution that tethering and buckling of the central lower eyelid in downgaze of patients with monocular elevation deficiency can simulate impaired infraduction in the involved eye. However, I wish to express a different opinion on the description of the figure shown by the authors.

Indeed, contrary to the description submitted, figure 1C does in fact demonstrate a deficit of infraduction of the abnormal right eye. Two clear landmarks can be used to come to that conclusion: first, the relative alignment of the upper limbus of each eye that clearly shows a lack of adequate depression movement of the affected eye. Second, the rounded pupil image of the right eye, as opposed to its oval-shaped counterpart (0.5 mm difference in vertical diameter), is in keeping with the difference in downward gaze position of the 2 eyes. Unfortunately, in this case, the pictures do not show which eye is fixating in down gaze due to the lack of corneal light reflection. Furthermore, there is no photographic documentation of ductions.

A review of some of the key publications on double elevator palsy shows a dramatic similarity with the documentation by Brodsky and Karlsson. For example, 4 of 5 cases with adequate pictorial documentation show a hyperdemotion in down gaze of the abnormal eye in textbooks by both Rosenbaum and Santiago (2) and von Noorden and Campos (3). Surprisingly, this deviation in down gaze is poorly discussed throughout the literature, most of the attention being directed at the classical findings of good alignment in primary position, a deficit of elevation in adduction and abduction, and the presence in some patients of a Bell phenomenon.

Finally, this deficit in depression of the abnormal eye referred to here and illustrated by the authors could be an indicator of a miswiring of either the superior rectus or the inferior rectus, another example of the ever-growing spectrum of congenital primary extraocular cranial neuropathies.

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The author reports no conflicts of interest.

REFERENCES

Reply—Monocular Elevation Deficiency: A Cautionary Note

I thank Dr LaRoche for his correspondence (1) about our article (2). His cited pictures of patients with monocular elevation deficiency do indeed show diminished excursion of the involved eye in downgaze. This finding can be confirmed by extending a clear transparent ruler from one lateral canthus to the other to compare the amount of visible sclera superior to each upper limbus. These photographs depict versions, so it cannot be assumed that any of these patients have the “deficit of infraduction” that he posits. Nevertheless, Dr LaRoche has made an astute observation that has managed to elude the strabismus community.

Our patient differed from these cases, in that most of his apparent vertical misalignment in downgaze was due to an exaggerated lower lid retraction in downgaze, which also produced an apparent infraduction deficit. His true hyperdeviation in extreme downgaze was clinically insignificant, as demonstrated by his normal vertical alignment in physiologic downgaze. As congenital deficiency of motor innervation leads to the paradoxical combination of extraocular muscle hypoplasia and fibrosis, I agree with Dr LaRoche that congenital cranial dysinnervation provides the most plausible explanation for this finding (3).

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The author reports no conflicts of interest.

REFERENCES
Central Retinal Artery Occlusion Secondary to Orbital Inflammation in Lupus Erythematosus Profundus

In a recent issue of this journal, Kao et al (1) reported a patient with lupus erythematosus profundus (LEP) who presented with a violaceous periocular discoloration of the right upper and lower eyelids. Precontrast orbital T1 MRI showed diffuse loss of fat signal, and postcontrast fat-suppressed T1 MRI showed enhancement of the orbital fat and extraocular muscles. After treatment with oral prednisone, the patient developed dramatic orbital soft tissue lipoatrophy and enophthalmos.

We recently examined a patient who displayed another neuro-ophthalmic manifestation of LEP: central retinal artery occlusion (CRAO). MRI showed intraconal fat and intraorbital optic nerve sheath inflammation on the affected side, which may have been contributory.

A 51-year-old African American woman with history of biopsy-proven LEP for the past 20 years presented with acute loss of vision in the left eye. A punch biopsy of a left arm lesion 2 years earlier had shown hyperkeratosis, basement membrane thickening with basilar vasculopathy, perivascular inflammation in the dermis, sclerosing septal and hyalinizing lobular panniculitis with deep nodular lymphoid aggregates, and rare lymphoid follicles consistent with a diagnosis of LEP (Fig. 1). There was disfiguring hyperpigmentation and surface irregularity of her nose and fingertips with depressed lipoatrophic areas in the left midface and left arm.

Visual acuity was 20/20 in the right eye and counting fingers in the left eye, with a left relative afferent pupillary defect. Extraocular motility was full in both eyes, and the eyes appeared to be aligned. There was no proptosis or resistance to globe retropulsion. Anterior segment examination and intraocular pressures were normal bilaterally. Fundus examination was normal in the right eye but showed cloudy retinal swelling and a cherry red spot in the left macula consistent with CRAO. Neurological examination was otherwise normal.

FIG. 1. Skin biopsy demonstrates hyperkeratosis, dermal perivascular inflammation, septal panniculitis (white arrows) and lobular panniculitis with lobular hyaline fat necrosis (black arrow), and lymphoid nodules in the subcutis. These abnormalities are consistent with LEP (hematoxylin & eosin, ×20).

FIG. 2. Postcontrast T1 axial (A) and coronal (B) MRI show nodular enhancement of left orbital fat, perioptic dura, and lacrimal gland. The extraocular muscles also are enlarged in the left orbit.
Postcontrast fat-suppressed axial and coronal MRI showed abnormal enhancement of the preseptal and intraconal soft tissue and intraorbital optic nerve sheath and enlargement of all extraocular muscles in the left orbit (Fig. 2). Despite a course of methylprednisolone, ophthalmologic examination and MRI findings remained unchanged 2 months later. She was slowly weaned off the corticosteroid.

We presume that the orbital inflammation in our patient led to the CRAO. Such a phenomenon has often been reported in other orbital inflammatory conditions, such as optic perineuritis (2) and idiopathic orbital inflammation (3). It has been reported only once in LEP in a patient who developed ischemic optic neuropathy and CRAO which led, months later, to melting of the entire orbital contents, including the eye (4)!

A unique aspect of our case is the inclusion of orbital inflammatory findings on MRI. This inflammatory response presumably led to CRAO and underscores the vision-threatening nature of LEP.

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REFERENCES

Central Retinal Artery Occlusion and Recurrent Papillitis in a Patient With Incomplete Behçet Disease: A Comment

I read with great interest the article by Tian et al (1): “Central retinal artery occlusion and recurrent papillitis in a patient with incomplete Behçet disease.” However, I wish to express a different opinion regarding the diagnosis suggested by the authors.

In Figure 2A, there is minimal filling of the choroid and no filling of the optic disc vessels supplied by the choroid. A diagnosis of central retinal artery occlusion (CRAO) cannot be well established because CRAO should not affect the choroidal circulation. Radial vascular filling on the surface of the optic disc is seen, which represents some blood supply from the central retinal artery. A single photograph of the fluorescein angiogram does not offer enough evidence to support the diagnosis of CRAO.

Using published diagnostic criteria (2), the authors diagnosed their patient with incomplete Behçet disease (BD) based on the finding of CRAO, recurrent papillitis, and recurrent oral ulcers. But one has to have at least 3 attacks or oral ulcers in 1 year in order for the recurrent oral ulcers to be a major criterion. In addition, CRAO and recurrent papillitis are not actually minor features. I suggest that a diagnosis of suspected BD may be more appropriate for this case.

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The author reports no conflicts of interest.

REFERENCES

Central Retinal Artery Occlusion and Recurrent Papillitis in a Patient With Incomplete Behçet Disease: A Response

We thank Dr Liu for the interest in our article and will respond to the questions raised (1). First, Dr Liu pointed out that a single photograph of the fluorescein angiogram does not offer enough evidence for a diagnosis of central retinal artery occlusion (CRAO). We have already extensively discussed this with the reviewers and editor of
the journal before our article was accepted. When we did this, we carefully reviewed the fluorescein angiogram and found in the early phase of the study that there was good choroidal filling (Fig. 1). In the Photo Essay, Figure 2A shows a later stage of the angiogram when filling of the choroid was complete, yet there was no perfusion of the retinal vessels. Furthermore, the appearance of the vascular occlusion in Figure 2A is actually more suggestive of an occlusive vasculitis than a CRAO caused by emboli, adding further support for the diagnosis of Behçet disease (BD).

Second, regarding the issue of diagnostic criteria for BD, our patient admitted to recurrent oral ulcers more than 5 times per year. Finally, we agree that CRAO and recurrent papillitis are not listed as minor features in the diagnostic criteria of BD (2), but “vasculitis” and “central nervous system symptoms” are included. If we accept that the vascular occlusion observed in each eye of our patient was caused by vasculitis and that the optic nerve is part of the central nervous system, then we have 2 minor features of BD. While recurrent oral ulcers are a major feature, it is noteworthy that diagnostic criteria for BD vary and have been revised many times. The International Study Group for BD proposed that the diagnosis be considered when recurrent oral ulcers plus 2 other features are present, in the absence of other clinical explanations (3). In our patient, we performed a wide range of ancillary tests to exclude other disorders, which can cause an obliterative vasculitis.

Most importantly, we wish to remind clinicians that CRAO and recurrent papillitis can be caused by a vasculitis, such as BD. Prompt treatment can be helpful to prevent further loss of visual function.

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REFERENCES

Leber Hereditary Optic Neuropathy Mimicking Thyroid-Related Optic Neuropathy

We read with great interest the article “Leber Hereditary Optic Neuropathy Mimicking Neuromyelitis Optica” by McClelland et al (1). We recently evaluated a similar patient with Leber hereditary optic neuropathy whose symptoms were initially suggestive of dysthyroid optic neuropathy and whose older age and optic nerve enhancement on MRI resulted in extensive testing for neuromyelitis optica (NMO) and other etiologies that delayed diagnosis.

A 67-year-old Caucasian man presented in with a 3-month history of painless progressive vision loss. His medical history was significant for hypertension, diabetes mellitus, kidney failure, and Graves disease. The patient had undergone radioactive iodine thyroid ablation 15 years previously. He had bilateral hand numbness. MRI of the cervical spine in October 2010 showed severe degenerative disease at the levels of C5–C7 with neuroforaminal stenosis, central canal stenosis, and compressive myelopathy. MRI of the brain revealed few nonspecific periventricular white matter changes consistent with small vessel ischemic disease.

When the patient was referred for neuro-ophthalmic examination, visual acuity was 20/400 bilaterally, without a relative afferent pupillary defect. Ocular motility was normal. External examination showed superior and inferior scleral show and bilateral upper lid retraction consistent with thyroid eye disease; on slit-lamp biomicroscopy, there were mild, bilateral nuclear sclerotic cataracts with normal
intraocular pressure in each eye. Funduscopic examination showed normal optic nerves and mild nonproliferative diabetic retinopathy with scattered microaneurysms bilaterally. Automated (24-2) visual fields showed central defects in each eye.

Erythrocyte sedimentation rate and C-reactive protein levels were normal. Orbital computed tomography showed prominent intracanal and extracanal fat with proptosis and optic nerve straightening bilaterally (Fig. 1). A diagnosis of bilateral optic neuropathy secondary to thyroid eye disease was made, and the patient elected to undergo bilateral orbital decompression surgery.

Over the ensuing 6 months, the patient continued to experience vision loss to no light perception, right eye, and bare light perception, left eye. The pupils were nonreactive to light, and both optic discs became pale. The patient was admitted to hospital and started on empiric steroid therapy. Repeat MRI of the brain and orbits was unremarkable, except for minimal right optic nerve enhancement. Cerebrospinal fluid analysis was normal as were paraneoplastic and NMO serologies. Testing for LHON showed a 14484 mtDNA mutation.

McClellan et al (1) presented a case of LHON with multiple sclerosis-like symptoms masquerading as NMO. The patient presented with vision loss, contiguous myelopathy in more than 3 spinal cord segments, and was NMO-IgG seronegative. Interestingly, both the cases presented by McClellan et al and another published report (2) of LHON with an NMO-like presentation bear many similarities to our patient. All 3 cases harbored the 14484 LHON mutation, had evidence of diffuse cervical spine myelopathy, presented at an age later than that typically associated with LHON (range, 39–65 years), and had subacute, slowly progressive bilateral visual loss, which is atypical for LHON. In both our patient and the one reported by McClellan et al, there was a notable absence of circumpapillary telangiectatic microangiopathy classically associated with LHON.

Our case was additionally complicated by the presence of thyroid eye disease that led to the mistaken diagnosis of dysthyroid optic neuropathy due to stretching of the nerves. Kobayashi et al (3) documented a case of LHON in a woman with hyperthyroidism and speculated that thyroid disease may act as a potential trigger for LHON given the role of thyroid hormone in mitochondrial biogenesis. The spectrum of LHON is variable, and the caveat remains that clinicians must consider this diagnosis regardless of older age, female gender, slowly progressive vision loss, and initially normal-appearing optic nerves with minimal enhancement on MRI.

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The authors report no conflicts of interest.

REFERENCES
The 6th Meeting of the Asian Neuro-Ophthalmology Society (ASNOS) was held at the Kobe International Conference Center in Kobe, Japan, on November 25–27, 2011, in conjunction with the 49th Annual Meeting of the Japanese Neuro-Ophthalmology Society (JNOS). The ASNOS was organized by Satoshi Kashii, MD, PhD, Department of Visual Sciences and Ophthalmology, Aichi Shukutoku University, in association with Osamu Mimura, MD, PhD, Department of Ophthalmology, Hyogo College of Medicine, who hosted the domestic JNOS (Fig. 1). There were 642 participants at both meetings, including attendees from Japan, China, Korea, Indonesia, Thailand, Singapore, Philippines, and India.

The Walsh in Asia session kicked off the ASNOS meeting. This was the fourth time this clinicopathologic case presentation conference was held in the style of the Frank B. Walsh Society Meeting. Walsh in Asia was initially introduced into ASNOS by Dr. Johathan Trobe’s University of Michigan team, in collaboration with the Ronald M. Burde Clinical Neuro-Ophthalmology Society of Japan. Neuro-pathologist, Edwin L. Munoz, MD, St. Luke’s Medical Center, Philippines, and neuro-radiologist, Kei Yamada, MD, Kyoto Prefectural University of Medicine, Japan, provided insightful and educational commentary to a number of challenging and interesting cases. These included POEMS syndrome (vs Castleman disease), primary chiasmal involvement with large B-cell malignant lymphoma, and melanoma-associated retinopathy.

Scientific sessions comprised 87 platform and poster sessions (Table 1). Two featured lectures were given at the ASNOS meeting by Christian Lueck, MD, Canberra, Australia, on “Disorders of Cortical Visual Processing” and Lanning Kline, MD, Birmingham, Alabama, on “Publishing in Neuro-Ophthalmology: The Art & Science.” The JNOS special lectures were delivered by Ryuji Kaji, MD, PhD, Tokushima, Japan, on “Botulinum Toxin Therapy in Ophthalmology,” and Yasuto Itoyama, MD, PhD, Tokyo, Japan, on “Multiple Sclerosis and Neuromyelitis Optica.” The JNOS Educational lecture was given by Masato Hashimoto, MD, PhD, on “Diagnostic MR Imaging for Neuro-Ophthalmology.” A symposium on “Neuro-Ophthalmology: From Diagnosis to Treatment” was held at a JNOS general session.

A special recognition award was presented to William F. Hoyt, MD, for his promotion and advancement of clinical neuro-ophthalmology in Asia. Many of his former fellows in Japan and Asia gathered together to celebrate this event. The next ASNOS will be held in Indonesia in 2013.
The Journal of Neuro-Ophthalmology gratefully acknowledges the following 2011 reviewers:

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