EDITORIAL
1 The Evaluation of Horner Syndrome
Jonathan D. Trobe

MESSAGE FROM THE DEPARTING EDITOR
Jonathan D. Trobe

MESSAGE FROM THE NEW EDITOR
5 The Way We'll Be: The Future of the Journal of Neuro-Ophthalmology
Lanning B. Kline

ORIGINAL CONTRIBUTIONS
7 Diagnostic Value of Imaging in Horner Syndrome in Adults
Yehoshua Almog, Raz Gepstein, Anat Kesler

12 Positive Apraclonidine Test 36 Hours After Acute Onset of Horner Syndrome in Dorsolateral Pontomedullary Stroke
Maud Lebas, Julien Seror, Thomas Debroucker

18 Clival Epidural Hematoma in Traumatic Sixth Cranial Nerve Palsies Combined with Cervical Injuries
Hugh J. Garton, Stephen S. Gebaraki, Omar Ahmad, Jonathan D. Trobe

26 Nonorganic (Psychogenic) Visual Loss in Children: A Retrospective Series
Irene Toldeo, Luisa Pinello, Agnese Suppiej, Mario Ermani, Ivet Cermakova, Elisa Zanin, Stefano Sartori, Pier Antonio Battistella

31 MRI Demonstrates Restricted Diffusion in Distal Optic Nerve in Atypical Optic Neuritis
Oriol Spliner, Liat Ben Sira, Igal Lebovitch, Anat Kesler

34 Diffusion-weighted MRI Identifies Petrous Apex Abscess in Gradenigo Syndrome
Mohammad Ibrahim, Gaurang Shah, Hemant Parmar

37 Clinical and Imaging Features of Fludarabine Neurotoxicity
Michael S. Lee, Alexander M. McKinney, Jeffrey R. Bruce, Karen SantaCruz

42 Prandial Presbyopia
Allon Barsam, Devinder S. Chauhan, Stacey A. Strong, Gordon T. Plant

45 Congenital Achromatopsia and See-Saw Nystagmus in VACTERL Syndrome
Saurabh Prakash, Serge O. Dumoulin, Nancy Fischbein, Brian A. Wandal, Yaping Joyce Liao

49 Irreversible Optic Neuropathy in Wernicke Encephalopathy and Leber Hereditary Optic Neuropathy
John-Michael Li, Janet C. Rucker

PHOTO ESSAYS
54 Peripapillary Nerve Fiber Layer Thickenings, Telangiectasias, and Retinal Hemorrhages in Wernicke Encephalopathy
Brenda L. Bohnsack, Shriya S. Patel

59 CT Demonstration of Dorsal Midbrain Hemorrhage in Traumatic Fourth Cranial Nerve Palsy
Padmaja Sudhakar, J. Rajiv Bapural

Continued on next page
64 Acquired Enophthalmos in Lupus Erythematosus Profundus
Tina Y. Kao, Michael K. Yoon, Timothy J. McCulley, Beth S. Ruben, Thomas N. Hwang

67 Bilateral Pseudohypopyon as a Presenting Feature of Recurrent Diffuse Large B-Cell Lymphoma
Stephen J. Dorrepaal, Edward A. Margolin, Chen Wang

70 Horner Syndrome Associated With Contusion of the Longus Collis Muscle Simulating a Tumor
Mohammad Ibrahim, Hemant Parmar, Lynda Yang

STATE-OF-THE-ART

73 Rehabilitation for Visual Disorders
Susanne Trauzettel-Klosinski

POINT COUNTER-POINT

85 An Overweight Young Woman With New Headache and Normal-Appearin Optic Discs
Kathleen B. Digre, Deborah I. Friedman

OPINION

91 A “First Cut” at Interpreting Brain MRI Signal Intensities: What’s White, What’s Black, and What’s Gray
Hemant Parmar, Jonathan D. Trobe

LETTERS TO THE EDITOR

94 Another Case of Bisphosphonate-Induced Orbital Inflammation
E. Bo Yang, Emily S. Birkholz, Andrew G. Lee

96 Visual Loss Without Papilledema in Idiopathic Intracranial Hypertension
Matthew J. Thurtell, Nancy J. Newman, Valérie Bloussé

98 Monocular Embolic Retinal Arteriolar Occlusions After Ipsilateral Intracranial Triamcinolone Injection
Gavin McEwan, Elizabeth Hofmeister, Kenneth Kublis, Kent Blade

99 Protracted Cortical Visual Loss in a Child With Ornithine Transcarbamylase Deficiency
Jennifer M. Anderson, Michael C. Brodsky

102 Third Cranial Nerve Palsy as the Presenting Neuro-Ophthalmic Feature of Nasopharyngeal Carcinoma
Yesim Yetimlar Beckmann, Benian Deniz, Fazıl Gelal, Yaprak Seçil

103 Randot Stereoacuity Test and Multiple Sclerosis
Viraj Wiwanitkit

103 Author’s Reply
Güngör Sobaci

BOOK REVIEWS

104 Neuro-Ophthalmology Illustrated
Jonathan D. Trobe

104 Manual of Neuro-Ophthalmology
Padmaja Sudhaikar

Steven A. Newman

105 Using Eye Movements as an Experimental Probe of Brain Function. A Symposium in Honor of Jean Büttner-Ennever (Volume 171, Progress in Brain Research)
Mark Morrow

Eric D. Weber

106 Ocular Pathology, 6th Edition
Nicola Ghazi

Jonathan D. Trobe

107 Atlas of Brain Function, 2nd ed.
Gregory P. Van Stavern

108 Atlas of Interventional Neurology
Valérie Bloussé

108 Dizziness: A Practical Approach to Diagnosis and Management
Ronald J. Tusa

109 Stroke in Children and Young Adults, 2nd Edition
Joel Weinstein

Continued on next page
109 Neurology of the Newborn, 5th Edition
Mark Borchert

110 Multimodal Imaging in Neurology: Special Focus on MRI Applications and MEG
Mark Quigg

110 Exploring the Thalamus and Its Role in Cortical Function, 2nd Edition
Edward H. Bertram

CALENDAR

112 Upcoming Meetings

ERRATA

114 Reflections and Advice From an Aging Academic: Erratum
S1 Foreword: Pioneers of North American Neuro-Ophthalmology
Jonathan D. Trobe

Jonathan D. Trobe
(Originally published on September 2001)

S8 An Interview with William F. Hoyt, MD
Laming B. Kline
(Originally published on March 2002)

S20 The Golden Age of Neuro-Ophthalmology at the Bascom Palmer Eye Institute
Joel S. Glaser
(Originally published on September 2002)

S26 The Legend of Lawton
Jonathan D. Trobe
(Originally published on September 2002)

S38 Noble J. David, MD, Reminiscences
Jonathan D. Trobe
(Originally published on September 2002)

S46 Adelbert Ames and the Dartmouth Eye Institute
Susan M. Pepin
(Originally published on December 2003)

S54 C. Miller Fisher: The Master of Clinicopathologic Correlation
Jonathan D. Trobe
(Originally published on March 2004)

S67 Thomas R. Hedges, Jr.; Witness to the Birth of Modern Neuro-Ophthalmology
Nicholas J. Volpe and Laura J. Balcer
(Originally published on September 2004)

S77 Neuro-Ophthalmology at the Mayo Clinic
Jacqueline A. Leavitt and Brian R. Young
(Originally published on December 2004)

S84 Otto Lowenstein, Pioneer Pupillographer
H. Stanley Thompson
(Originally published on March 2005)

S90 Schatz
Jonathan D. Trobe
(Originally published on September 2005)

S100 Irene E. Loewenfeld, PhD: Physiologist of the Pupil
H. Stanley Thompson and Randy H. Kardon
(Originally published on June 2006)

S110 Simmons Lessell: The Gaon of Neuro-Ophthalmology
Jonathan D. Trobe
(Originally published on March 2007)

S123 Joel Glaser: A Scholar's Scholar
Jonathan D. Trobe
(Originally published on September 2007)

S131 Robert B. Daroff, MD: Pioneer of Ocular Motor Research
Jonathan D. Trobe
(Originally published September 2009)
The Evaluation of Horner Syndrome

Jonathan D. Trobe, MD

In this issue of the *Journal of Neuro-Ophthalmology*, Almog et al (1) present the results of their review of 52 adults referred for outpatient or inpatient consultation to a neuro-ophthalmologist for evaluation of Horner syndrome.

They found that in two-thirds of patients, the cause of the Horner syndrome will already be known at the time of the first neuro-ophthalmic consultation (usually surgery or trauma to the head, neck, or chest, dorsolateral medullary stroke, or carotid dissection). Among one-sixth of the patients in whom the cause of Horner syndrome is not yet known, there will be clinical clues to allow localization of the lesion, such as acute neck or face pain (cervical region), arm pain or weakness (brachial plexus or paraspinal region), or sixth cranial nerve palsy (cavernous sinus); in those patients, targeted imaging will usually find the lesion. In the remaining one-sixth of patients, there will be no localizing clues for the Horner syndrome; in those patients, nontargeted imaging of the head, neck, and chest will rarely find a responsible lesion (only 1 case of thyroid carcinoma).

This “real world” study, together with previous studies, provides valuable guidance in the evaluation of Horner syndrome in adults and suggests the following approach:

**Step 1.** Confirm that there really is a Horner syndrome. The clinical features—ptosis and miosis—are calling cards, but they may be exceedingly subtle or transient (2). (The report of anhydrosis or absent facial flushing is helpful but rarely elicited.) Because there are other causes of miosis and ptosis (3), topical pharmacologic testing should be used—and results may be positive even if signs are equivocal or completely absent (2)! Cocaine has been the traditional agent, but it is a weak pupil dilator and, as a controlled substance, often is not readily available. It has been supplanted by topical 0.5% apraclonidine (4) (except in children younger than 1 year of age, in whom it may cause serious acute dysautonomia [5,6]), although wider experience will be needed to establish how reliable it is, especially in an acute Horner syndrome (7,8).

The traditional use of pharmacologic agents such as topical hydroxyamphetamine to assist in localization is a waste of time. These agents are difficult to obtain and do not provide information reliable enough to allow targeted imaging (9).

**Step 2.** Determine whether there has been previous accidental or surgical trauma to the neck, upper spine, or chest that will explain the Horner syndrome. (Include carotid endarterectomy/stenting and epidural anesthesia among legitimate causes [10,11].) If so, no further diagnostic work-up is necessary.

**Step 3.** Determine whether there are localizing clinical features for the Horner syndrome. For example, ataxia and nystagmus would suggest a medullary lesion. Arm pain/weakness/numbness or myelopathic features would direct attention to the lung apex, brachial plexus, and cervical spine. Acute neck or face pain would direct attention to the cervical carotid artery. (The oculosympathetic fibers crawling up the outside of the cervical carotid artery are exquisitely vulnerable to compression, trauma, dissection, and inflammation, including arteritis.) Beware of attributing persistent Horner syndrome to trigeminal autonomic syndromes such as cluster headache; carotid artery dissection can perfectly mimic these syndromes (12). Ear pain or hearing loss would direct attention to the temporal bone and carotid canal (13). Ipsilateral sixth cranial nerve palsy would direct attention to the cavernous sinus. Perform targeted (selective) imaging on the basis of this kind of information. If there are no localizing features, then the Horner syndrome is considered “isolated,” and you move to . . .

**Step 4.** Perform nontargeted (nonselective) imaging of the upper chest and neck as far up as the skull base to encompass the second (preganglionic) segment and the extracranial part of the third (postganglionic) segment of the oculosympathetic pathway. If the Horner syndrome is truly “isolated,”
imaging need not extend above the skull base, as a cavernous sinus or orbit lesion would be extremely unlikely to be the cause. Anticipate that the yield of a causative lesion will be low (many such cases remain unsolved) but, as Almog et al (1) point out, even if 1 tumor is found, the gesture may be life-saving.

What kind of imaging should be performed? Because carotid artery dissection is such a common cause (even in the absence of pain), a vascular study must be included. To rule out nonvascular masses of the neck or chest, soft-tissue imaging must also be there. Although MRI/MRA has often been recommended in this setting (11,14), my neuroradiologic colleagues advise CT/CT angiography (CTA). CT provides adequate resolution of soft tissue masses, and CTA provides good pictures of the carotid artery lumen (15). Narrowing of the lumen is likely to be the most important predictor of stroke. MRI/MRA does have the advantage of showing not only the vascular lumen but also its wall. When the patient lies perfectly still, the wall hematoma can be beautifully visualized on fat-saturated T1 axial MRI. But MRI is often difficult to obtain promptly, relatively expensive, and readily degraded by patient motion.

How urgent is imaging? It is not urgent unless the patient reports recent ipsilateral neck trauma, neck/face pain, ipsilateral transient monocular visual loss, or contralateral transient weakness or numbness, which suggest acute cervical carotid dissection. Within the first 2 weeks after onset of Horner syndrome, there is a substantial risk of hemispheric (middle cerebral artery distribution) stroke (16), which may be attenuated by aspirin or anticoagulation treatment (although there are no rigorous studies to prove that point). If the Horner syndrome has been present for more than 4 weeks, the threat of stroke is much less, but imaging should not be unduly delayed.

In children with clinical features of Horner syndrome, topical cocaine should be used in preference to apraclonidine to confirm the diagnosis if the child is younger than 1 year old (5). Neither heterochromia nor a history of birth trauma entirely excludes the possibility of a causative mass in the chest or neck, usually a neuroblastoma, although the chance of negative results is high (17,18). Urine catecholamine metabolite studies, which have traditionally been performed in the investigation of neuroblastoma, are not sufficiently sensitive to that diagnosis (19). MRI (rather than CT) of the neck and chest must be performed. There may be an additional yield from I-123 metaiodobenzylguanidine (MIBG) scintigraphy, which can “light up” small tumor foci beyond the detection of MRI (20).

REFERENCES
The Way We’ve Been: 

This issue marks a transition between the third and fourth epochs of the Journal of Neuro-Ophthalmology. The editorial material and the Editorial Board belong to the third epoch; the new Journal design represents the fourth epoch. With the next (June) issue, Dr. Lanning Kline (University of Alabama) will take over as the new editor with a new Editorial Board (see Message from the New Editor in this issue of the Journal).

The Journal began in 1981 with Dr. J. Lawton Smith as founding editor. For the next 13 years, it remained very much “Dr. Smith’s journal,” with many articles originating in his home institution, the Bascom Palmer Eye Institute, University of Miami, and Dr. Smith writing a commentary on each one.

In 1994, the Journal moved to Albert Einstein College of Medicine, New York, as Dr. Ronald M. Burde became the second editor. Submissions began to come from across North America and even overseas. Articles expounding on experimental basic science were more prominent.

In 2001, the editorial office moved to Ann Arbor, Michigan, as I became the third editor. During this epoch, the journal remained quarterly but got a new design and its page count edged up to 100 pages per issue as the number of submissions doubled. With more than 50% of articles coming from outside North America, the journal became truly international. We are especially pleased to have published so many articles from Asia, including the People’s Republic of China. Among the published articles from foreign countries, the largest number came from Japan, Israel, Turkey, India, and South Korea.

The receipt, processing, review, and copyediting of text and illustrations became entirely electronic. No more paper! No more mailing costs! The Journal’s website was born. Subscribers could now choose between a handheld hard copy and a screen copy. Video to illustrate eye movements began to appear in the web version. Our publisher reduced the embargo on published articles in the Journal to 1 year. All electronic content was released after that time into the public domain, so that full-text versions could be read at no charge by anyone with access to the Internet and a search engine! With such a short embargo (matched by very few peer-reviewed journals), we were able to guarantee our authors an enormously expanded readership.

We introduced a “double masked” process for peer review. Authors did not know who had reviewed their papers (standard practice) and reviewers did not know who had written them (not standard practice). Such a balanced review process, we believed, would give authors a fairer shot. But when we canvassed the opinions of some seasoned reviewers, several insisted that not knowing who had written the paper would hamper their judgment because the track record of the authors is an important element in making that judgment! The Journal’s editorial board strongly favored double masking, but several members were convinced that they would still know who had written the articles. Nearly everyone guessed wrong. Reviewers were even wrong in deciding whether articles had come from North America or abroad!

The number of illustrations increased dramatically, most of them relating to brain imaging, which has become an integral part of our specialty. Annual reviews of afferent and efferent neuro-ophthalmology, which were a feature in the second epoch of the Journal, were replaced by commissioned State-of-the-Art pieces on “hot topics” in wide-ranging disciplines including neuroimaging, radiation oncology, neurobiology, medical resource allocation, and even open access publishing. To give our readers a brief view of what was happening in neuro-ophthalmology around the world, we started covering the more important meetings, including those of the American Academy of Neurology and the Association for Research in Vision and Ophthalmology. Our roving reporters (Mark Moster, MD, Howard Pomeranz, MD, PhD, and Swaraj Bose, MD) scurried to the relevant presentations and dispatched learned summaries. We even covered our own annual North American Neuro-ophthalmology Society meetings, partly as an excuse to publish candid photographs of our members.

“You can talk, you can talk, but you gotta know the territory.” So said the salesmen in the famed American musical comedy, The Music Man. Knowing the territory was the job of our reviewers—several hundred of them. If the quality of the publications has gone up, it is largely their doing. The members of the Editorial Board absorbed most of that task, but there were others who rendered extraordinary service.

For special thanks, I single out the Editorial Board members in Ann Arbor. Wayne Cornblath, MD, sized up problematic papers with blazing acumen. Steve Gebarski, MD, our consultant neuroradiologist, took on the huge burden of certifying imaging studies and offering to choose better illustrations from CDs that authors sent in. Dheeraj Gandhi, MD, an interventional neuroradiologist, spent hours analyzing nuances in vascular images and guiding...
authors toward a better selection. Andrew Lieberman, MD, PhD, gave valuable advice in neuropathology. Oren Sagher, MD, provided help on neurosurgical submissions. David Musch, PhD, brought epidemiologic and biostatistical expertise when we needed it. Gale Oren, MILS, the librarian of the Kellogg Eye Center, reviewed every reference of every article accepted for publication. She corrected bibliographic errors in 30% of those references! Richard Hackel, MA, CRA, and Robert Prusak, CRA, applied their skills in Adobe PhotoShop to the illustrations, transforming them into images that would look pretty in print.

Most importantly, there are the Journal’s three magnificent editorial assistants. Jill Hanekamp developed the first electronic platform for the Journal. Mireille Prusak refined it. Donna Donato made it even better. During this decade they processed more than 2,000 manuscripts and never lost one. The editorial office did not use a standardized manuscript processing system, which has become standard for most journals (and will be used in the fourth epoch of the Journal) because we pledged to offer the personalized service of a boutique operation. I hope our authors would agree that we made good on that pledge.

It has been a privilege to be the editor. I have had great satisfaction in working with and learning from our authors and especially in attracting so many submissions from Asia, an exciting source of things to come. Best wishes to my successor, who will inherit a splendid emblem of the fascinating field of neuro-ophthalmology.

Jonathan D. Trobe, MD
Editor-in-Chief, 2001–2010

The Way We’ll Be: The Future of the
Journal of Neuro-Ophthalmology

Thirty years ago Lawton Smith, MD, published the inaugural issue of the Journal of Clinical Neuro-Ophthalmology. He felt passionately that our subspecialty have its own voice and a forum to present and discuss interesting case studies and clinical reports. At the time, some doubted Dr. Smith’s decision to launch the journal because it would divert neuro-ophthalmology literature from mainstream ophthalmology journals. But ultimately his decision proved to be correct and the Journal began to flourish.

In 1994, the North American Neuro-Ophthalmology Society (NANOS) adopted the Journal as its official publication and Ronald Burde, MD, became the editor-in-chief. Dr. Burde decided on “a change in editorial direction” with “an emphasis now placed on publishing papers reflecting both the basic and clinical sciences of our specialty.” The name of the journal was changed to the Journal of Neuro-Ophthalmology.

In 2001, the torch was passed to Jonathan Trobe, MD, as the third editor-in-chief. Dr. Trobe instituted a variety of sections, including Photo Essays, Reviews, Viewpoints, and Neuro-Ophthalmology-at-Large. Setting high standards through meticulous copyediting and excellent illustrative material, Dr. Trobe further raised the standards and impact of the Journal.

As a new leadership team now takes the helm, the Journal continues to evolve. A new cover and interior design appear with this issue. I have appointed two associate editors, Nancy Newman, MD, and Agnes Wong, MD. Section editors have been assigned to oversee specific aspects of the Journal:

- State-of-the-Art Reviews: Grant Liu, MD, and Randy Kardon, MD, PhD
- Basic Science in Neuro-Ophthalmology: Jeffrey Bennett, MD, PhD, and Lynn Gordon, MD, PhD
- Point Counter-Point: Andrew Lee, MD, and Valérie Biousse, MD
- Photo Essay: Tim McCulley, MD

Literature Commentary: Mark Moster, MD, and Michael Lee, MD
Clinical-Pathological Case Study: Neil Miller, MD
Books Received: Michael Vaphiades, DO
Neuro-Ophthalmology News: Kathleen Digre, MD

Eleven additional colleagues will also serve on the editorial board, many giving the Journal strong international representation.

We have transitioned to an electronic submission system (http://www.editorialmanager.com/jno) providing an efficient and rapid method to move manuscripts through the peer review process. The Journal will also now provide online publication ahead of print. Once published online, these articles will be made available on PubMed and can be cited. It is important to note that PubMed recognizes the date of online publication as the date of official publication. Online publication ahead of print will, therefore, lead to a rapid turnaround time from acceptance to publication. To help navigate these processes, Jason Roberts, PhD, has been appointed managing editor of the Journal. He brings a wealth of experience and knowledge in the mechanics of medical publishing, the application of ethical standards, and the running of an editorial office.

I hope you will find the changes energizing and exciting. However, for the Journal to continue to improve, we all need to participate! Although the focus of the Journal will remain primarily clinical, basic science research studies are also welcome. In addition, I strongly encourage those making presentations at the Walsh and NANOS meetings to submit their material to the Journal.

As we enter the fourth decade of publishing the Journal of Neuro-Ophthalmology, we look back with gratitude at our rich legacy of leadership: Lawton Smith, Ronald Burde, and Jonathan Trobe.

Lanning B. Kline, MD
Editor-in-Chief, 2010
“Gentler the path with familiar footsteps to follow.”
Diagnostic Value of Imaging in Horner Syndrome in Adults

Yehoshua Almog, MD, Raz Gepstein, MD, Anat Kesler, MD

Background: The yield of imaging in Horner syndrome has been explored only in children. This study evaluates the yield of imaging in adults.

Methods: This was a retrospective cohort study of 52 patients with Horner syndrome examined in 2 neuro-ophthalmology hospital clinics. Patients were divided into 3 groups according to the ability to determine the etiology at the time of the first neuro-ophthalmology consultation: group I, etiology of Horner syndrome known at the initial neuro-ophthalmologic examination; group II, etiology of Horner syndrome not known at the initial neuro-ophthalmologic examination, but sufficient information obtained to allow targeted imaging; and group III, etiology of Horner syndrome not known at the initial neuro-ophthalmologic examination, and sufficient information not obtained to allow targeted imaging. The yield of investigation and the frequency of the different etiologies were evaluated.

Results: In 32 (62%) patients, the etiology was already known at the initial neuro-ophthalmologic examination (group I). The most prevalent etiology was surgical trauma. In 11 (21%) patients, a targeted imaging workup was possible, revealing an etiology in 7 patients (group II). Carotid dissection and cavernous sinus mass were the most common etiologies. In 9 (17%) patients, a nontargeted imaging evaluation was necessary, revealing an etiology in only 1 patient, who had a previously undetected thyroid malignancy (group III).

Conclusions: The etiology of Horner syndrome is usually known at the time of initial presentation to a neuro-ophthalmologist. When the etiology is not known and clinical information permits a targeted imaging evaluation, an etiology can usually be determined, most commonly a cervical carotid artery dissection or a cavernous sinus mass. When the etiology is not known and clinical information is insufficient to allow a targeted imaging evaluation, an etiology is rarely discovered. Even so, nontargeted imaging is warranted because life-threatening lesions, such as thyroid malignancies, may rarely be detected.

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Horner syndrome classically presents with ipsilateral blepharoptosis, pupillary miosis, and facial anhidrosis (1) and is caused by a lesion along the oculosympathetic pathway from the hypothalamus to the eye (2). The long and complicated course of the oculosympathetic pathway predisposes it to a wide variety of pathologic processes, ranging from harmless vascular headaches to life-threatening conditions such as carotid artery dissection or malignancy (3). Yet the reported incidence of the various etiologies of Horner syndrome varies widely (4–7) and recommendations for the required investigations differ as well (8–11).

A comprehensive workup often includes expensive imaging tests that are unrevealing. The yield of such imaging in Horner syndrome has been explored only in children (9–11).

We reviewed 53 cases of Horner syndrome in adults who were examined in the neuro-ophthalmology clinics of 2 medical centers to answer 2 questions: 1) To what extent can the etiology be determined at the initial neuro-ophthalmologic examination without further investigations? 2) What is the yield of an imaging workup when the etiology is not clear at the initial clinical encounter?

METHODS

A retrospective chart review was performed for all patients with Horner syndrome examined in the neuro-ophthalmology clinics of the Tel Aviv Medical Center between 1992 and 2001 and Meir Medical Center between 2001 and 2006. The data from both centers were obtained from the personal databases of one of the authors (Y.A.). The study population included outpatients referred by community ophthalmologists and neurologists and those examined in the emergency room or as inpatients. Referral
patterns and patient demographics were similar in both medical centers.

Patients had to fulfill the following criteria to be enrolled in the study: 1) ptosis and miosis in the same eye; 2) “positive” results on a 10% cocaine test indicated by an increase in anisocoria 30 minutes after topical instillation; 3) performance of a “targeted” imaging evaluation when the etiology of Horner syndrome could be reasonably inferred from the clinical examination; 4) performance of a “nontargeted” imaging evaluation (MRI of the head and neck, CT or MRI of the chest, or, when appropriate, CT angiography, MRA, or thyroid and pituitary function tests) when the etiology of Horner syndrome could not be reasonably inferred from the clinical examination.

All patients received a complete neuro-ophthalmologic examination. Because our aim was to assess the yield of imaging in cases of Horner syndrome for which the etiology was not apparent at the initial neuro-ophthalmologic examination, all information obtained at the time of that examination was considered part of the history and not part of the workup. Data collected included age, gender, relevant information from the history and physical examination, laboratory tests, and imaging results.

The patients were divided into 3 groups: group I, patients in whom the etiology of Horner syndrome could be determined at the initial neuro-ophthalmologic examination; group II, patients in whom the etiology of Horner syndrome could not be definitely determined but in whom there was enough localizing information obtained at the initial neuro-ophthalmologic examination to permit targeted imaging; and group III, patients in whom the etiology of Horner syndrome could not be definitely determined at the initial neuro-ophthalmologic examination but in whom there was not enough localizing information obtained at that encounter to permit targeted imaging.

Group I patients underwent no further imaging (Table 1). Group II patients underwent a targeted imaging workup based on the suspected etiology or the suspected anatomic site as specified in Table 2. Group III patients underwent a nontargeted imaging work-up; topical hydroyamphetamine testing was not performed. Differentiation between preganglionic and postganglionic Horner syndrome was determined by the presenting signs and symptoms or by imaging studies.

Institutional review board/ethics committee approval was obtained for this study.

**RESULTS**

A total of 52 patients with the diagnosis of Horner syndrome fulfilled study entry criteria based on review of charts from the 2 participating institutions (35 patients from Meir Medical Center and 17 patients from Tel Aviv Medical Center). Among these, 24 were inpatients and
28 were outpatients. There were 28 men and 24 women. Their mean SD age was 50 ± 15 years (range 18–78 years).

In group I, which included 32 patients, the etiology was reached with high probability at the initial neuro-ophthalmologic examination without a need for additional workup (Table 1). In 12 patients, the Horner syndrome was due to surgery on the chest (6 patients), neck (5 patients), or head (1 patient). In 8 patients, the cause was brainstem stroke (Wallenberg syndrome, 6 patients; other brainstem, 2 patients). In 4 patients, it was congenital or very longstanding, based on history, heterochromia, or photographs. In 3 patients, it was caused by chest, neck, or skull trauma without carotid dissection.

In 5 group I patients, the etiology of Horner syndrome depended on prior imaging, which had revealed neck metastasis of ovarian carcinoma (1 patient), old carotid dissection (1 patient), upper lung carcinoma (1 patient), syringomyelia (1 patient), and cavernous sinus metastasis of prostate carcinoma (1 patient).

In group II, which included 11 patients, the etiology of the Horner syndrome was not definite but could be reasonably inferred at the initial neuro-ophthalmologic examination (Table 2). Enough information was obtained at that visit to permit a targeted imaging workup. In 9 patients, the suspected diagnosis was confirmed by imaging (carotid dissection, 3 patients; cavernous sinus mass, 3 patients; and cervical spine lesion, 1 patient). The cavernous sinus masses were suspected because patients also had an ipsilateral sixth cranial nerve palsy. In 4 patients, imaging results were negative. All 4 patients were suspected to have had carotid dissection. In these 4 patients, the etiology of the Horner syndrome remained undetermined.

In group III, which included 9 patients, the initial neuro-ophthalmologic examination did not furnish any localizing information in regard to the Horner syndrome, so that the imaging evaluation could not be targeted (Table 3). In 8 patients, no etiology could be determined even after thorough imaging. The Horner syndrome had been present for at least 1 year in 6 of these patients, as suggested by history or old photographs. None had any systemic disease or neurologic sign relevant to the Horner syndrome. One of the 8 patients had to have a parathyroid adenoma on imaging, but it was located in the neck contralateral to the Horner syndrome, so that its relationship to the Horner syndrome is uncertain. The remaining patient was found to have a thyroid carcinoma.

We were able to localize the Horner syndrome to the central, preganglionic, or postganglionic segments of the oculosympathetic pathway in 36 patients (Table 4). A preganglionic lesion was present in 44%; central or postganglionic lesions were each present in 28%.

Neoplasms were identified as the cause of Horner syndrome in 9 (17%) patients (cavernous sinus, 4 patients; metastatic ovarian carcinoma to cervical lymph node, 1 patient; cervical schwannoma, 1 patient; cervical spine

**Table 2.** Group II: etiology of Horner syndrome could not be determined at the initial neuro-ophthalmologic examination, but the examination provided enough information to permit targeted imaging (11 patients).

<table>
<thead>
<tr>
<th>Suspected Diagnosis</th>
<th>Confirmation of Suspected Diagnosis after Imaging</th>
<th>Helpful Clinical Signs</th>
<th>Imaging and Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid artery dissection (7 patients)</td>
<td>Inpatients Outpatients</td>
<td>Acute painful Horner syndrome (3 patients), after neck trauma (1 patient)</td>
<td>Cervical CT angiography (2 patients), MRA (1 patient) show carotid dissection</td>
</tr>
<tr>
<td>Cavernous sinus mass (3 patients)</td>
<td>Inpatients Outpatients</td>
<td>Ipsilateral sixth cranial nerve palsy and facial hypesthesia (3 patients), ipsilateral sixth cranial nerve palsy (2 patients)</td>
<td>CT of brain shows pituitary adenoma (1 patient), meningioma (1 patient), brain MRI shows meningioma (1 patient)</td>
</tr>
<tr>
<td>Cervical spine lesion (1 patient)</td>
<td>Inpatients Outpatients</td>
<td>Scapular pain, upper extremity hypesthesia</td>
<td>MRI of neck, perispinal mass</td>
</tr>
</tbody>
</table>

Original Contribution

tumor, 1 patient; benign lung tumor, 1 patient; and thyroid carcinoma, 1 patient). The thyroid carcinoma was diagnosed during a nontargeted workup for Horner syndrome, as no signs of thyroid disease were present on the clinical evaluation. In the other 8 patients, the neoplasm had been diagnosed before the initial neuro-ophthalmic examination.

**DISCUSSION**

In this series of 52 adult patients with Horner syndrome, the etiology had already been determined at the initial neuro-ophthalmologic evaluation in 32 (62%) patients based on history, examination features, and prior imaging studies (group I). In 11 (21%) patients, clinical features determined at the time of the initial neuro-ophthalmologic examination allowed a targeted imaging workup, which led to confirmation of the suspected etiology in 7 patients. In the 4 patients in this group who remained without a cause for Horner syndrome, the suspected etiology was acute cervical carotid dissection, but results of neck vascular imaging were negative. It is therefore possible that imaging is not sensitive enough to detect carotid dissections. Only 9 (17%) of our patients had clinical features that did not permit a targeted imaging evaluation, and imaging disclosed an explanation (a malignant thyroid tumor) in only 1 of these.

Digre et al (8) evaluated 33 patients with Horner syndrome using different MRI protocols specifically designed for preganglionic or postganglionic lesions based on topical pharmacologic testing. In that study, there was a high yield (50%) from MRI scanning in preganglionic lesions. Maloney et al (5) reported their results from 450 inpatients and outpatients with Horner syndrome examined in an ophthalmology clinic. Patient characteristics were therefore similar to those of our cohort. In that study, the main purpose was to establish the success of pharmacologic testing to identify the site of the lesion. The yield of imaging was not assessed. The investigators were able to ascertain the etiology of Horner syndrome in 60% of patients. We obtained a higher level of etiologic diagnosis (77%), perhaps because our study was performed after the widespread use of modern imaging.

We did not perform hydroxyamphetamine testing in our cohort because we believe that although this test can differentiate a preganglionic from a postganglionic Horner (12), it cannot establish the etiology of Horner syndrome, and it cannot precisely locate the site of injury. Therefore, it does not exclude the need for investigation. In our study, the most prevalent anatomical location was preganglionic, followed by central and postganglionic origins of equal frequency. Several other studies have addressed the localization of Horner syndrome with varied results (4–7) (Table 4). Maloney et al (5) found only 13% of 270 patients with a known diagnosis to have central Horner syndrome, with an equal incidence of preganglionic (43%) and postganglionic (44%) lesions. In examining 120 outpatients with Horner syndrome, Grimson and Thompson (7) found that most cases were preganglionic, some were postganglionic, and very few (6%) were central in origin. In contrast, Keane (4) examined 100 patients on a neurology ward and found that a majority of cases were of central origin, mostly related to stroke. In these studies, the variance in the incidence of lesions in the 3 segments of the oculosympathetic pathway undoubtedly resulted from the diversity of the populations studied—inpatients versus outpatients and neurology clinics versus ophthalmology clinics. For example, in our group of 21 inpatients, 45% had a Horner syndrome of central origin, comparable to the finding of Keane (4). Because our study represents a combined population of inpatients and outpatients referred from neurology and ophthalmology clinics, we believe it better represents the distribution of the Horner syndrome in the general population.

The incidence of tumors in our study (17%) was very similar to that found by Maloney et al (5) (13%) (Table 5). However, in most cases, the tumor was known at the time of the initial neuro-ophthalmologic examination. Giles and Henderson (6) and Keane (4) found a higher incidence of tumors in an inpatient cohort, but did not indicate in what percentage the tumor diagnosis was already known.

### TABLE 3. Group III: etiology of Horner syndrome could not be determined at the initial neuro-ophthalmologic examination, and the examination did not provide enough information to permit targeted imaging (9 patients)

<table>
<thead>
<tr>
<th>No. Patients</th>
<th>Etiology Found by Imaging</th>
<th>Inpatients</th>
<th>Outpatients</th>
<th>Imaging and Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Yes (1 patient)</td>
<td>0</td>
<td>1</td>
<td>MRI of brain neck and upper thorax shows thyroid carcinoma not previously known</td>
</tr>
<tr>
<td>No (8 patients)</td>
<td>1 7 MRI of brain neck, CT or MRI of upper thorax (8 patients) and MRA carotid dissection protocol (2 patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 4. Location of lesion within sympathetic pathway in our cohort of 36 anatomically localizable lesions

<table>
<thead>
<tr>
<th>Central</th>
<th>Preganglionic</th>
<th>Postganglionic</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>%</td>
<td>28</td>
<td>44</td>
</tr>
</tbody>
</table>
The yield of the workup for Horner syndrome has previously been directly addressed only in the pediatric population (9–11). In 23 consecutive cases of Horner syndrome presenting in children, George et al (9) found that investigation revealed only 2 cases with previously undiagnosed pathology. He concluded that in isolated cases of Horner syndrome, routine neuro-imaging is not needed. On the other hand, Mahoney et al (11) found that a workup yielded a previously unknown tumor in 6 (33%) of 18 children with Horner syndrome. Mahoney et al concluded that MRI of the head, neck, and chest should be included in the routine workup of children with Horner syndrome.

Our study shows that the etiology of Horner syndrome examined in a neuro-ophthalmology clinic is known in nearly two-thirds of patients at the initial visit. In the remaining third, there is generally enough information to allow a targeted imaging evaluation to define the etiology, although imaging results may be negative in some patients suspected of having carotid dissection. In a small minority of patients, the neuro-ophthalmology examination does not provide enough information to target imaging studies. In this group, broad-spectrum imaging results are likely to be negative, but it is worthwhile, as life-threatening lesions may be discovered.

The main limitation of our study was the relatively small number of patients in whom the etiology of Horner syndrome was not known at the initial neuro-ophthalmo logic encounter. A larger study of such patients would provide more definitive information regarding the value of imaging in this group.

REFERENCES

<table>
<thead>
<tr>
<th>Published Studies</th>
<th>Patients</th>
<th>Central (%)</th>
<th>Preganglionic (%)</th>
<th>Postganglionic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maloney (5)</td>
<td>450</td>
<td>13</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>Grimson and Thompson (7)</td>
<td>120</td>
<td>6</td>
<td>57</td>
<td>37</td>
</tr>
<tr>
<td>Giles and Henderson (6)</td>
<td>216</td>
<td>11</td>
<td>88</td>
<td>1</td>
</tr>
<tr>
<td>Keane (4)</td>
<td>100</td>
<td>65</td>
<td>25</td>
<td>12</td>
</tr>
</tbody>
</table>
Positive Apraclonidine Test 36 Hours After Acute Onset of Horner Syndrome in Dorsolateral Pontomedullary Stroke

Maud Lebas, MD, Julien Seror, MD, Thomas Debroucker, MD

Abstract: A 40-year-old man developed a Horner syndrome as part of a dorsolateral medullary brainstem infarction. Thirty-six hours after the onset of the stroke, topical instillation of 0.5% apraclonidine produced reversal of anisocoria. This is the first case in which apraclonidine testing has been applied to a patient with a Horner syndrome caused by a lesion in the first segment of the oculosympathetic pathway and the shortest reported interval between clinical manifestations of the lesion and apraclonidine-induced reversal of anisocoria. A review of all reported cases of apraclonidine testing in Horner syndrome suggests that this is a promising diagnostic adjunct that must be validated in larger studies.

CASE REPORT
A 40-year-old man with no past medical history complained of acute onset of dizziness, nausea, difficulty swallowing, pain around the right eye, and binocular diplopia. On examination, he was found to have full ductions and a comitant left hypertropia, constituting a skew deviation. He also manifested a counterclockwise right-beating horizontal-rotary nystagmus on right gaze and a counterclockwise left-beating horizontal-rotary nystagmus on left gaze. The palpebral fissure measured 7 mm in the right eye and 10 mm in the left eye. In darkness, pupils measured 6 mm in the right eye and 7 mm in the left eye. In bright light, both pupils were equal in size, measuring 3 mm. There was also a right lower motor neuron facial palsy and decreased sensation in the left face and arm. Results of the examination were otherwise normal.

Diffusion MRI disclosed a very small area of high signal in the right dorsolateral pontomedullary junction with corresponding low signal on the apparent diffusion coefficient (ADC) map (Fig. 1AB). MRA showed right vertebral stenosis without dissection (Fig. 1C).

The patient received a diagnosis of acute right dorsolateral pontomedullary infarction (Wallenberg syndrome variant). Thirty-six hours after the onset of symptoms, we instilled 1 drop of 0.5% apraclonidine into each ocular cul-de-sac. Forty-five minutes later, the right pupil became 8 mm with the left remaining 7 mm, thus demonstrating reversal of the anisocoria.

DISCUSSION
Because symptoms of a brainstem stroke are typically reported promptly, the delay between the onset of the
Horner syndrome in our patient and the performance of the apraclonidine test can be estimated reliably at 36 hours. Before our report, the shortest interval was 1 week (2). Although drawn from only one patient, our report of a delay of merely 36 hours suggests that supersensitivity of α-1 receptors occurs very quickly after sympathetic pathway damage. We add one more case to the list of positive results of 0.5% apraclonidine tests for pharmacologic diagnosis of Horner syndrome. (2–8).

Apraclonidine testing has been used in 47 patients with Horner syndrome or suspected of having Horner syndrome in the reported literature (1–11). Among those, 43 (including ours) showed reversal of anisocoria, 3 did not (5,10,11), and 1 case was equivocal (1). Among 16 patients (3,4,9) with physiologic anisocoria [14 of which were cocaine proven (3,4)], none disclosed reversal of their anisocoria. Among 19 controls without anisocoria (4), one had 0.5 mm dilation on one side.

The largest reported series in which apraclonidine was compared with cocaine included 10 patients with Horner syndrome and 10 patients with physiologic anisocoria (3). Among the patients with Horner syndrome, 7 showed reversal of anisocoria in both light and dark and 3 showed it only in light. None of the control subjects showed reversal of anisocoria.

Of the 3 patients with negative apraclonidine results, 2 were thought to represent Horner syndrome of unknown origin (5,11), but neither had been tested with topical cocaine so that one may doubt the diagnosis. One patient who was considered by the authors to have positive results had not been tested with cocaine and had reversal of ptosis after 10 minutes but no pupil change (10). Although the test results were considered positive, ptosis reversal has been shown to occur in patients without Horner syndrome (4). Conversely, the pupil size was assessed a mere 10 minutes after apraclonidine instillation, perhaps too short a time to evaluate reversal of anisocoria. Finally, 1 patient (1) showed anisocoria greater in light than in dark, which was considered diagnostic of Horner syndrome, a conclusion that may be questioned.

This is the first reported case in which the apraclonidine test has been positive in a patient with Horner syndrome caused by disruption of the first (central nervous system) segment of the sympathetic pathway. Among the other 42 patients with Horner syndrome considered to have positive results for apraclonidine testing, 9 were believed to have the lesion in the third segment (postganglionic), 3 were believed to have the lesion in the first or the second segment (preganglionic), 27 contained no lesion-localizing information, and 3 had a lesion of uncertain location.

The supersensitivity that gives rise to the pupil dilation after apraclonidine instillation is based on up-regulation of iris sympathetic receptors, yet the lesion in our patient was located in the first segment, which was two synapses away. This makes the short delay in development of apraclonidine test positivity in our patient more interesting.

Apraclonidine testing in a patient with Horner syndrome caused by brainstem stroke has not been described previously. The other reported etiologies of Horner syndrome in which results of the apraclonidine test have been positive include congenital (2 cases), birth trauma (3 cases), surgery (4 cases) (1 T2 ganglionectomy, 2 cervical spine surgery, and 1 unknown), neuroblasticoma (2 cases), carotid artery dissection (2 cases), cluster headache (2 cases), and goiter (1 case) (Table 1). In 8 patients, a proper workup disclosed no etiology. In 14 patients, the etiology was not reported. In another 4 patients, the reported etiology was presumptively but questionably (owing to limited workup) head trauma (1 case), cervical disc disease (2 cases), and carotid stenosis (1 case).

In 26 of 42 patients with Horner syndrome who had positive results of apraclonidine testing that were reported before our patient, the delay between the onset of Horner syndrome and apraclonidine positivity ranged from 1 week to 10 years (mean 30 months; SD 39 months). In only 3 patients was the delay less than 1 month (1 week [2 cases], 10 days [2 cases], and 14 days [6 cases]; postganglionic in all patients). In 9 additional patients, the delay between the onset of Horner syndrome and apraclonidine testing was
<table>
<thead>
<tr>
<th>Author</th>
<th>No. Patients Tested and Suspected Diagnosis</th>
<th>Failure of Cocaine-Induced Mydriasis</th>
<th>Apraclonidine-Induced Reversal of Anisocoria</th>
<th>Apraclonidine Concentration</th>
<th>Cause of Horner Syndrome</th>
<th>Damaged Segment of Sympathetic Pathway (1st, 2nd, or 3rd)</th>
<th>Interval Between Diagnosis and Apraclonidine Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al (3)</td>
<td>10 Horner</td>
<td>10</td>
<td>3 in bright light only, 7 in light and dark</td>
<td>0.5%</td>
<td>Birth trauma: 3</td>
<td>NA</td>
<td>2.5, 8, and 1.5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Idiopathic: 4</td>
<td>NA</td>
<td>3, 5, 10, and 10 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Head trauma: 1</td>
<td>NA</td>
<td>9 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neuroblastoma: 1</td>
<td>NA</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgical trauma: 1</td>
<td>NA</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td>10 Physiologic anisocoria</td>
<td>0</td>
<td>0</td>
<td>0.5%</td>
<td>NA</td>
<td>NA</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes and other unspecified conditions</td>
<td>NA</td>
<td>&gt;3 months</td>
</tr>
<tr>
<td>Koc et al (4)</td>
<td>9 Horner</td>
<td>9</td>
<td>9</td>
<td>0.5%</td>
<td>NA</td>
<td>NA</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neck MRI and chest X-ray negative</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cervical neuroblastoma extending to the thyroid gland</td>
<td>NA</td>
<td>1 month</td>
</tr>
<tr>
<td>Bacal and Levy (9)</td>
<td>4 Horner</td>
<td>NA</td>
<td>1 eye in 1 subject</td>
<td>0.5%</td>
<td>Left brachial plexus injury</td>
<td>NA</td>
<td>2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Brown et al (5)</td>
<td>3 Horner</td>
<td>3</td>
<td>3</td>
<td>0.5%</td>
<td>Cervical goiter</td>
<td>NA</td>
<td>4 months</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
<td>NA</td>
<td>9 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
<td>NA</td>
<td>8–12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
<td>3rd*</td>
<td>9 years</td>
</tr>
<tr>
<td></td>
<td>5 Horner</td>
<td>NA</td>
<td>0</td>
<td>0.5%</td>
<td>Cervical disc degeneration</td>
<td>3rd*</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Possible cervical disc degeneration</td>
<td>3rd*</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Posterior T2 ganglionectomy</td>
<td>Uncertain</td>
<td>10 months</td>
</tr>
</tbody>
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TABLE 1. continued

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Patients Tested and Suspected Diagnosis</th>
<th>Failure of Cocaine-Induced Mydriasis</th>
<th>Apraclonidine-Induced Reversal of Anisocoria</th>
<th>Apraclonidine Concentration</th>
<th>Cause of Horner Syndrome</th>
<th>Damaged Segment of Sympathetic Pathway (1st, 2nd, or 3rd)</th>
<th>Interval Between Diagnosis and Apraclonidine Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales et al (1)</td>
<td>1 Horner</td>
<td>1</td>
<td>1 (but anisocoria greater in light)</td>
<td>1%</td>
<td>NA</td>
<td>3rd*</td>
<td>1 month</td>
</tr>
<tr>
<td></td>
<td>5 Horner</td>
<td>NA</td>
<td>1</td>
<td>1%</td>
<td>NA</td>
<td>1st or 2nd*</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>Cluster HA</td>
<td>NA</td>
<td>3rd*</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>1st or 2nd*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bohnsack and Parker (6)</td>
<td>1 Horner</td>
<td>NA</td>
<td>1</td>
<td>0.5%</td>
<td>Traumatic carotid artery dissection from carotid artery bifurcation to the skull base</td>
<td>3rd (carotid artery dissection)</td>
<td>14 days</td>
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<td>Freedman and Brown (7)</td>
<td>2 Horner</td>
<td>NA</td>
<td>2</td>
<td>0.5%</td>
<td>Cervical discectomy for C6–C7 herniation</td>
<td>2nd (C6–C7 discectomy)</td>
<td>5 months</td>
</tr>
<tr>
<td>Garibaldi et al (2)</td>
<td>3 Horner</td>
<td>NA</td>
<td>3</td>
<td>0.5%</td>
<td>Cervical spinal surgery</td>
<td>Uncertain</td>
<td>2 months</td>
</tr>
<tr>
<td>Mirzai and Baser (8)</td>
<td>1 Horner</td>
<td>NA</td>
<td>1</td>
<td>0.5%</td>
<td>Congenital; work-up negative (head, neck and thorax MRI; neck and abdomen ultrasound)</td>
<td>Carotid artery dissection 3rd*</td>
<td>10 days</td>
</tr>
<tr>
<td>Chu and Byrne (10)</td>
<td>1 Horner</td>
<td>NA</td>
<td>0</td>
<td>0.5%</td>
<td>Neck surgery for cervical sympathetic chain schwannoma</td>
<td>1st or 2nd (ipsilateral face anhydrosis)</td>
<td>1 year</td>
</tr>
</tbody>
</table>

(continued on next page)
### TABLE 1. continued

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Patients Tested and Suspected Diagnosis</th>
<th>Failure of Cocaine-Induced Mydriasis</th>
<th>Apraclonidine-Induced Reversal of Anisocoria</th>
<th>Apraclonidine Concentration</th>
<th>Cause of Horner Syndrome</th>
<th>Damaged Segment of Sympathetic Pathway (1st, 2nd, or 3rd)</th>
<th>Interval Between Diagnosis and Apraclonidine Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watts et al (11)</td>
<td>1 Horner</td>
<td>NA</td>
<td>0</td>
<td>1%</td>
<td>NA</td>
<td>NA</td>
<td>4 months</td>
</tr>
<tr>
<td>Lebas et al (present case)</td>
<td>1 Horner</td>
<td>NA</td>
<td>1</td>
<td>0.5%</td>
<td>Dorsolateral pontomedullary stroke</td>
<td>1st (brainstem stroke)</td>
<td>36 hours</td>
</tr>
</tbody>
</table>

NA = not available.
MRI = magnetic resonance imaging.
CT = computerized tomography.
US = ultrasound.
1st or 2nd*: central or pre-ganglionic location presumed on basis of pupil dilation following topical instillation of hydroxyamphetamine.
3rd*: postganglionic location presumed on basis of lack of pupil dilation following topical instillation of hydroxyamphetamine.
HA = headache.
The questionable cases for positivity or negativity of the apraclonidine test are underlined. The questionable location case is in italics.

### TABLE 2. Reported results and side effects of apraclonidine testing for Horner syndrome in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Age (months)</th>
<th>No. of cases</th>
<th>Apraclonidine Concentration</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacal and Levy (9)</td>
<td>2</td>
<td>1</td>
<td>1%</td>
<td>None</td>
</tr>
<tr>
<td>Watts et al (11)</td>
<td>2.5</td>
<td>1</td>
<td>0.5%</td>
<td>Drowsiness for 10 hours</td>
</tr>
<tr>
<td>Bacal and Levy (9)</td>
<td>4</td>
<td>1</td>
<td>1%</td>
<td>None</td>
</tr>
<tr>
<td>Watts et al (11)</td>
<td>5</td>
<td>1</td>
<td>1%</td>
<td>Lethargy, bradycardia, shallow respiration, oxygen desaturation H1–H8 after drop instillation</td>
</tr>
<tr>
<td>Bacal and Levy (9)</td>
<td>5</td>
<td>1</td>
<td>1%</td>
<td>None</td>
</tr>
<tr>
<td>Bacal and Levy (9)</td>
<td>6</td>
<td>1</td>
<td>1%</td>
<td>Sleepy all afternoon</td>
</tr>
<tr>
<td>Watts et al (11)</td>
<td>&lt;6 months</td>
<td>3</td>
<td>Unknown</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Mirzai and Baser (8), Chen et al (3), Freedman and Brown (7), Bacal and Levy (9)</td>
<td>7–204</td>
<td>14</td>
<td>0.5%: 12 cases 1%: 2 cases</td>
<td>None</td>
</tr>
<tr>
<td>Watts et al (11)</td>
<td>Not reported</td>
<td>3</td>
<td>Unknown</td>
<td>None</td>
</tr>
</tbody>
</table>
only mentioned as “greater than 3 months.” In 7 patients the delay was not documented (Table 1). In the 3 patients suspected of having Horner syndrome in whom results of the apraclonidine test were reported as negative, the delay between the discovery of anisocoria and the apraclonidine testing was 4 months (11), 1 year (10), and 9 years (5). The article with the questionable case did not mention the delay between the discovery of anisocoria and the apraclonidine testing (1). There are no reported patients in whom results of the apraclonidine test were initially negative and later became positive.

The use of apraclonidine in young children is limited by side effects related to blood-brain barrier immaturity. In infants younger than 6 months, drowsiness alone was the most common side effect (in 5 of 9 reported cases) after instillation of 1% apraclonidine, but bradycardia, shallow respiration, and oxygen desaturation have also occurred. These manifestations have been reported in a 5-month-old child after instillation of the 0.5% concentration (Table 2). Among 14 children tested when they were older than 6 months, there were no reported side effects (3,7–9). Therefore, apraclonidine testing can probably be safely applied in children who are 6 months of age or older. But if it is to be used in patients younger than 6 months of age, they should be observed for a period of at least 2 hours after instillation of the drops, with admission to a pediatric ward if lethargy, bradycardia, or a reduced respiratory rate occurs (11).

REFERENCES
Clival Epidural Hematoma in Traumatic Sixth Cranial Nerve Palsies Combined with Cervical Injuries

Hugh J. Garton, MD, Stephen S. Gebarski, MD, Omar Ahmad, MD, Jonathan D. Trobe, MD

Abstract: Eight patients sustained a combination of clival epidural hematoma, traumatic sixth cranial nerve palsy (6 NP), and occipitocervical injury. This combination of features has been sparsely described. Whether the hematoma, which represents tectorial membrane injury, is merely a marker for 6 NP and occipitocervical injury or is causative is unresolved, but this imaging finding should alert examiners who note traumatic 6 NP to the need for detailed cervical imaging, as surgical stabilization of this region may be critical to prevent future spinal cord dysfunction.

CASE REPORTS

Case 1

A 38-year-old woman was a restrained driver whose automobile was struck in the rear by a van traveling at 60 mph. The airbag deployed. There was no loss of consciousness. The Glasgow Coma Scale (GCS) score was 15 on the day of transfer from an outside hospital to our emergency room.

Ophthalmologic examination 6 days after admission disclosed 60% abduction of the right eye, 25% abduction of the left eye, marked esotropia, and an otherwise normal examination. There were no other neurologic abnormalities.

Brain and cervical spine CT performed on the day of admission showed an anterior occipital fracture and clival epidural hematoma (CEH) and clival epidural hematoma (CEH) has been reported in only 11 cases (9,10,13–21). Among them, 4 cases also had traumatic 6 NP (20,21). We describe 8 additional cases of the combination of CEH, 6 NP, and occipitocervical spine injury, drawing attention to the need for careful cervical spine imaging when CEH is identified. We discuss several hypotheses to explain this constellation of findings.

A list of 18 patients with a combination of 6 NP after head trauma and cervical spinal injury was produced through the clinical experience of the Inpatient Ophthalmology Consultation Service and the outpatient Neuroophthalmology Service at the University of Michigan Health Center between 1986 and 2008. From among them, a neuroradiologist (S.S.G.) identified 8 cases with CEH, which form the basis of this report.
Case 2
A 44-year-old woman involved in a high-speed motor vehicle accident as an unrestrained passenger was found unconscious at the scene with a subsequent admission GCS score of 8.

Ophthalmologic examination 1 day after admission disclosed a complete loss of abduction of the right eye with a large primary position esotropia. Results of the rest of the ophthalmologic examination were normal. She had a mild right hemiparesis.

CT showed occipital condyle–C1 distraction and subluxation, rotary subluxation of C1–C2, a C5–C6 fracture subluxation, and a CEH (Fig. 2). Results of CT angiography were negative for a vascular injury.

She underwent occiput-to-C2 instrumented fusion with rod-and-wire instrumentation and lateral mass plating at C5–C6 without complications. Eight months after discharge, she underwent transposition of the right superior and inferior rectus muscles for nonimproving complete 6 NP with a large primary position esotropia. After the initial surgical correction, the patient had a small esotropia with double vision. A second extraocular muscle procedure later aligned her eyes in primary position.

Case 3
A 4-year-old girl was a backseat restrained passenger in a head-on automobile accident. She did not lose consciousness and had a GCS scale of 15 at the scene.

Ophthalmologic examination 2 days after admission disclosed 10% abduction bilaterally with marked esotropia. Results of the rest of the ophthalmologic examination were normal. She also had a mild right hemiparesis.

CT showed an anteriorly displaced distracted dens fracture (Fig. 3A). MRI showed not only the fracture subluxation at C1–C2 but also a subtle avulsion of the tectorial membrane at the posterior aspect of the clivus with a small CEH (Fig. 3B).

After initial management in a halo brace, the patient’s cervical alignment could not be maintained, with progressive distraction of C1 from C2. She underwent an instrumented fusion of C1 and C2. At surgery a transverse tear in the dura was noted just above the lamina of C2. Mechanical testing with intraoperative flexion and extension films demonstrated functional stability of the occipitocervical junction.

Within 7 months of hospital discharge, ophthalmologic examination disclosed spontaneous resolution of the 6 NPs. Cervical spine radiographs 1 year after trauma showed a firm spinal fusion between C1 and C2 with good alignment.

Case 4
A 13-year-old boy was a restrained back seat passenger in an automobile struck from behind by a snowplow. At the

FIG. 1. Case 1. Precontrast cervical spine CT. A. Axial bone algorithm through the basiocciput shows a displaced comminuted right occipital condyle fracture (arrow). B. Axial soft tissue algorithm CT section through the basiocciput shows the displaced comminuted right occipital condyle fracture (white arrow), but a beam-hardening artifact partially obscures the occipital epidural hematoma (black arrow). C. Sagittal reformatted image centered on the basiocciput displayed with soft tissue windowing shows the epidural hemorrhage more conspicuously (black arrow).

FIG. 2. Case 2. Precontrast head CT after spinal stabilization shows a large occipital epidural hematoma (black arrow) despite the scatter artifact from the metallic spinal stabilization hardware.
scene, he was conscious but intubated for agonal breathing. No GCS score was documented.

Ophthalmologic examination 3 weeks after admission disclosed complete loss of abduction bilaterally with a large esotropia and alternating fixation. Results of the rest of the ophthalmologic examination were normal. The patient was quadriplegic and ventilator-dependent with some preservation of sensation.

MRI showed atlanto-occipital disarticulation with frank detachment of the tectorial membrane from the posterior aspect of the clivus with a large CEH. The tectorial membrane was completely peeled away from the clivus (Fig. 4).

He underwent stabilization of the atlanto-occipital disarticulation via occiput-to-C3 instrumented posterior fusion. Esotropia was present at the time of discharge from the hospital 3 months after admission, but no further ophthalmologic follow-up information was available. CT at time of discharge 3 months after trauma revealed a firm occipitocervical spinal fusion.

Case 5

A 4-year-old girl was playing in the driveway in front of her house when the family car was accidentally backed out over her. Tire marks were present on her chest. Upon admission, she had a GCS score of 15.

Ophthalmologic and neurologic examinations 2 days after admission disclosed bilateral, nearly complete, abduction deficits as the only clinical impairment. Imaging showed severe atlanto-occipital dislocation with ligamentous injuries and a CEH.

She underwent occiput-to-C2 fusion and an occipital periosteal flap with autologous iliac harvest (22). The

FIG. 3. Case 3. Precontrast cervical spine CT and MRI. A. Sagittal reformatted CT image centered on the basiocciput displayed with bone windowing shows a displaced and distracted dens fracture (arrow). B. Sagittal short tau inversion recovery MRI centered on the basiocciput shows the displaced and distracted dens fracture (white arrow) and a subtle occipital epidural hemorrhage just underneath the tectorial membrane (black arrow). The tectorial membrane has been partially torn away from the clivus. There are large regions of periligamentous hemorrhagic swelling (H).

FIG. 4. Case 4. Precontrast head and cervical spine MRI. A. Precontrast T1 sagittal image shows a large occipital epidural hematoma under the tectorial membrane (black arrow). The tectorial membrane has been torn completely away from the clivus, allowing the large hematoma to dissect up to the level of the dorsum sellae. B. Sagittal short tau inversion recovery magnetic resonance image centered on the basiocciput shows that the tectorial membrane (black arrow) has been torn away from the clivus with a resultant large occipital epidural hematoma (H), spinal cord contusion (white arrow), and periligamentous hemorrhagic swelling (h).
abduction deficits were improving at time of discharge and had fully resolved 13 years later.

**Case 6**

A 20-year-old man was an unrestrained driver in a rollover accident. He had brief loss of consciousness after the incident. During evacuation from the car, he had a respiratory arrest and hypotension. Upon arrival to our emergency room, he was intubated but conscious. The GCS score was not documented.

Ophthalmologic examination 2 months after trauma disclosed bilateral incomplete abduction deficits, right greater than left. He had a 9-prism-diopter esotropia in primary position, increasing to 16 prism-diopters in right gaze. He had incomplete quadriplegia with a Brown-Sequard type pattern of asymmetric myelopathic weakness and sensory findings together with swallowing impairment.

CT and MRI showed atlanto-occipital dislocation with ligamentous injuries and CEH. The patient underwent an occiput-to-C3 fusion.

Ophthalmologic examination 5 months after the trauma revealed improvement in the 6 NPs with alignment measurements of 2 prism-diopters of esotropia in primary gaze increasing to 6 prism-diopters in right gaze. Five years after injury he had fully recovered.

**Case 7**

A 67-year-old woman was a restrained driver in a head-on motor vehicle accident. The GCS score was not documented.

Ophthalmologic examination 5 days after admission disclosed bilateral 6 NPs and a right third cranial nerve palsy. She had a central cord pattern of injury with relative preservation of lower extremity movement but bilateral arm weakness.

CT and MRI showed subluxation of C1-C2 with ligamentous injuries, including rupture of the transverse ligament, and a CEH. She underwent fusion of C1 to C2 with C1-C2 transarticular screw fixation with a Brooks-type fusion.

**Case 8**

An 8-year-old girl was a front seat restrained passenger in a head-on motor vehicle accident at an impact speed of 28 mph (23).

Bedside ophthalmologic examination disclosed visual acuities of 20/20 at near and 80% abduction of the right eye. MRI showed a CEH elevating the tectorial membrane but without associated evidence of fracture or dislocation on plain X-rays.

She was managed in a cervical collar without operative intervention. At 1 month follow-up, the 6 NP had improved to normal alignment in primary gaze, but esotropia of 4 prism-diopters was present in right gaze.

Her brothers, ages 3 and 6, also sustained CEHs in the accident, and each required occiput-to-C2 fusion. Neither had 6 NPs.

**DISCUSSION**

Our series of 8 patients represents the largest reported collection of the combination of CEH, 6 NP, and occipitocervical injury (Table 1). In all but 1 case (Case 8), there was imaging evidence of direct injury to the tectorial membrane (Cases 3, 4, 6, and 8) or disruption of the occipital condylar-C1 joint (Cases 1, 2, 5, and 7). MRI showed that the CEH separated the clivus from the tectorial membrane, a connective tissue band intertwined with the posterior longitudinal ligament and dura that extends from the petroclival junction to the Cl-C2 cervical segment (24).

This membrane is tightly bound to the underlying clivus and cervical bones by connective tissue insertions with rich vascular and neural structures (24). Avulsion of these high tensile strength connective tissues results in a CEH. Because the stability of the occipitocervical junction depends on preservation of the tectorial membrane and the apical ligaments (25), their injury leads to gross instability between head and neck and loss of protection of the underlying neural structures.

The concurrence of CEH, 6 NP, and occipitocervical injury has been previously described in only 4 case reports (9,10,20,21) (Table 2). In 3 of 4 of these reports, patients had bilateral 6 NP. Similarly, 6 of our 8 patients had bilateral 6 NPs.

The association of CEH with 6 NP and occipitocervical injury emphasizes the importance of identifying a CEH in patients presenting with traumatic 6 NP. If it is present, there is a need to obtain careful imaging evaluation of the cervical spine, particularly the occipitocervical region, even when cervical spine injury may not be clinically suspected, as in 5 of our 8 cases. Although imaging of the cervical spine is a routine part of trauma evaluation, occipitocervical injuries, particularly those involving the tectorial membrane, are often poorly seen on plain cervical spine films and may even be difficult to discern on CT without a reasonable index of suspicion. MRI studies provide the best opportunity to visualize the ligamentous structures of the occipitocervical region.

Given the rarity of traumatic 6 NP and occipitocervical spinal injury, their combination is probably not a chance occurrence. Although the sixth cranial nerve is often said to be vulnerable to head trauma because of its intrinsic mechanical properties or its relatively long exposure in the intracranial space, direct cadaver assessments of force required to break this nerve show that it is relatively resistant and tougher, for example, than the fourth cranial nerve (26). The intracisternal course of the fourth cranial nerve is 3 times that of the sixth cranial nerve (27), yet the fourth cranial nerve is less often
Thus, the sixth cranial nerve’s anatomic orientation and interactions with surrounding structures must predispose it to injury. The nerve exits the brainstem at the pontomedullary sulcus and travels for 15 mm in the basal cisterns before passing through a dural ring on the superior clival surface. It is surrounded within the dural canal by venous lakes in continuity with the cavernous sinus, basilar plexus, and superior and inferior petrosal sinuses. Ascending for several millimeters beneath the clival dura to enter the Dorello canal, it is bounded superiorly by the petrosphenoidal

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)/Sex</th>
<th>Mechanism</th>
<th>Side of Sixth Cranial Nerve Palsy</th>
<th>Occipitocervical Imaging Findings</th>
<th>Brain Injury</th>
<th>Spinal Cord Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38/F</td>
<td>Rear impact</td>
<td>Bilateral</td>
<td>Left occipital condylar fracture O–C1 separation left &gt; right Posterior cervical hemorrhage noted at surgery</td>
<td>GCS score 15</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>44/F</td>
<td>Unknown</td>
<td>Right</td>
<td>O–C1 distraction C1–C2 rotatory subluxation C5–C6 fracture Retrolisthesis of C5 on C6, with rupture of the anterior longitudinal ligament and disk space injury</td>
<td>GCS score 8</td>
<td>None (right hemiparesis explained by left internal capsule injury)</td>
</tr>
<tr>
<td>3</td>
<td>4/F</td>
<td>Head on</td>
<td>Bilateral</td>
<td>Type II dens fracture Anterior and posterior longitudinal ligament rupture Partial tectorial membrane tear on imaging but occipitocervical junction to be stable to manipulation at surgery</td>
<td>GCS score 15</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>13/M</td>
<td>Rear impact</td>
<td>Bilateral</td>
<td>Anterior displacement occiput on C10–C1 separation Frank tectorial membrane avulsion no other cervical spine injury</td>
<td>Agonal at scene, MRI shows injury to medulla</td>
<td>Complete injury at C1</td>
</tr>
<tr>
<td>5</td>
<td>4/F</td>
<td>Crush injury</td>
<td>Bilateral</td>
<td>Anterior displacement of occiput on C1</td>
<td>GCS score 15</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>20/M</td>
<td>Rollover</td>
<td>Bilateral</td>
<td>Atlanto-occipital dissociation, tectorial membrane disruption</td>
<td>GCS score not documented, patient conscious on arrival</td>
<td>Brown-Sequard syndrome</td>
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<tr>
<td>7</td>
<td>67/F</td>
<td>Head on</td>
<td>Bilateral</td>
<td>Transverse ligament rupture</td>
<td>Not documented</td>
<td>High cervical central cord syndrome</td>
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<tr>
<td>8</td>
<td>8/F</td>
<td>Head on</td>
<td>Right</td>
<td>Tectorial membrane injury</td>
<td>GCS score 15</td>
<td>None</td>
</tr>
</tbody>
</table>

GCS, Glasgow Coma Scale; O, occipital condyle.

TABLE 2. Previously reported cases of clival epidural hematoma, sixth cranial nerve palsy, and occipitocervical injury

<table>
<thead>
<tr>
<th>Author, Reference</th>
<th>Age (years)</th>
<th>Mechanism</th>
<th>Side of Sixth Cranial Nerve Palsy</th>
<th>Occipitocervical Imaging Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mizushima et al (9)</td>
<td>8</td>
<td>Hyperflexion</td>
<td>Bilateral</td>
<td>Odontoid fracture, type I managed in a collar</td>
</tr>
<tr>
<td>Ratilal et al (10)</td>
<td>26</td>
<td>Hyperextension</td>
<td>Bilateral</td>
<td>Right C6 transverse process fracture, no atlanto-occipital instability by flexion and extension</td>
</tr>
<tr>
<td>Fuentes et al (20)</td>
<td>47</td>
<td>Not available</td>
<td>Left</td>
<td>Bilateral occipital condyle fractures</td>
</tr>
<tr>
<td>Papadopoulos et al (21)</td>
<td>10</td>
<td>Pedestrian versus truck</td>
<td>Bilateral</td>
<td>Atlanto-occipital dissociation</td>
</tr>
</tbody>
</table>

(Gruber) ligament, inferiorly by the clivus, medially by the dorsum sellae, and laterally by the petrous bone (29). The nerve then passes anteriorly through the cavernous sinus to the superior orbital fissure and into the orbit (Fig. 5).

In a 1971 report of 2 patients who had sustained 6 NP without a basilar skull fracture but with cervical spine injury, Schneider and Johnson (6) attributed the spine injury to hyperextension causing a type II dens fracture with posterior dislocation of C1 on C2 in 1 patient, and a C2 ("hangman’s") fracture in the other. In that report (6), they referred to their animal cervical spine trauma model (30,31), in which they had replaced a portion of the calvaria with transparent Lexan plastic and induced cervical hyperextension. They observed that the cerebrum and brainstem moved upward and backward with respect to the skull as the hyperextension movement came to an abrupt end. They proposed that the sixth cranial nerve moves upward against the Gruber ligament at the superior aspect of the Dorello canal, encountering a sheer force perpendicular to the long axis of the nerve (6) (Fig. 6).

In 1976, Takagi et al (7) reported a single case of traumatic 6 NP and argued that upward movement of the brain after hyperextension produced an injury at the petrous apex rather than at the Gruber ligament. They believed that the dural porus acted like a pulley, translating the upward movement of the cisternal portion of the nerve to a longitudinal stretch and forcing the nerve down into the petrous apex. This action would result in a sheering injury, the damage again occurring with a force perpendicular to the long axis of the nerve (Fig. 7). Arias (8) pointed out that injury would occur at the dural ring and petrous apex when the nerve was placed under tension. Describing a patient with bilateral 6 NP and an associated C5–C6 flexion distraction injury in 1996, Uzan et al (11) proposed a similar mechanism in flexion head injuries.

Reporting on a patient with bilateral 6 NP and atlanto-occipital dislocation, Fruin and Pirotte (32) suggested that distraction (stretching) across the cervicomedullary junction was responsible for the lower cranial nerve palsies seen in this setting (Fig. 8).

In a case very similar to those presented here, Calisanel et al (33) proposed an entirely different mechanism, namely direct distortion of the sixth cranial nerve along its subarachnoid course or at the Dorello canal by the clival hematoma (Fig. 9).

Whatever the mechanism of injury, the pathologic lesion in these cases appears to be restricted to a short segment of the sixth cranial nerve. In an autopsy study of the sixth cranial nerve in 10 patients who had suffered head injury, Sam et al (5) found hemorrhagic contusions at the dural ring, petrous apex, and point of apposition of the sixth cranial nerve to the vertical segment of the internal carotid artery (ICA), where sympathetic fibers join the sixth cranial nerve briefly en route to the first division of the fifth cranial (trigeminal) nerve (29). They noted that these 3 sites of nerve injury were associated with points of angulation or tethering along the course of the nerve.

Evidently, such injury can result from either flexion or extension of the head. Our Cases 1, 2, 4, 5, and 6 had varying degrees of occiput–C1 separation. These injuries

**FIG. 5.** Normal extra-axial path of the sixth cranial nerve in relation to the tectorial membrane, clivus, and petrous apex. C1, atlas; C2, axis; DP, dural porus; GL, Gruber ligament; ICA, internal carotid artery; PA, petrous apex; VI N, sixth cranial nerve.

**FIG. 6.** The hypothesis of Schneider and Johnson (6). The sixth cranial nerve suffers shear stress against the Gruber ligament as the brainstem and cisternal segment of the nerve move upward and posteriorly during hyperextension injury. DP, dural porus; GL, Gruber ligament; ICA, internal carotid artery; PA, petrous apex; VI N, sixth cranial nerve.
have mostly been considered as occurring during severe cervical hyperextension and distraction, often with a frontal facial trauma (34–37). Cases 3 and 7 presented with fracture and ligamentous injuries at C2 also consistent with a degree of distraction in conjunction with extension and/or flexion (38,39). Case 8 is unique in having sustained a pure flexion-distraction injury. She and her 2 younger siblings were all improperly restrained in a head-on motor vehicle accident. All 3 children sustained CEHs and the 2 younger siblings had varying degrees of frank occipitocervical dissociation. By modeling this accident based on data retrieved from the vehicle’s “black box” and substituting industry standard anthropomorphic crash dummies, Sochor et al (23) noted that in Case 8 the maximum neck strain occurred in flexion-distraction, with no secondary contact of her head to the vehicle interior. In her case, an improperly applied shoulder harness restrained only the lower torso. The primary mechanism of force application in this accident was in the sagittal plane, with the body and lower neck mechanically coupled to a rapidly decelerating vehicle, whereas the head initially continued in forward progress at the initial vehicle speed.

The unifying feature of our cases is distraction across the craniocervical junction with the tectorial membrane damaged by a straining force. Whether through upward or downward movement of the brainstem in neck flexion or extension, the sixth cranial nerve is probably placed under tension at points where the nerve is tethered (straining force) or angled (sheer stress). We consider it unlikely that the CEH could, by pure compression, have produced injury

**FIG. 7.** The hypothesis of Takagi et al (7). During hyperextension injury, upward movement of the brainstem and cisternal segment of the sixth cranial nerve is translated by the dural porus, acting as a pulley, into strain along the nerve and downward movement of the nerve into the petrous apex/clivus. DP, dural porus; GL, Gruber ligament; ICA, internal carotid artery; PA, petrous apex; VI N, sixth cranial nerve.

**FIG. 8.** The hypothesis of Fruin and Pirotte (32). The sixth cranial nerve experiences strain during occipitocervical dissociation. DP, dural porus; GL, Gruber ligament; ICA, internal carotid artery; PA, petrous apex; VI N, sixth cranial nerve.

**FIG. 9.** The hypothesis of Calisaneller et al (33). Hematoma within and beneath the tectorial membrane directly distorts the sixth cranial nerve. DP, dural porus; GL, Gruber ligament; ICA, internal carotid artery; PA, petrous apex; VI N, sixth cranial nerve.
to the nerve at the more distant sites of the petrous apex or at its point of apposition to the ICA.

REFERENCES
Nonorganic (Psychogenic) Visual Loss in Children: A Retrospective Series

Irene Toldo, MD, Luisa Pinello, MD, Agnese Suppiej, MD, Mario Ermani, MD, Ivet Cermakova, MD, Elisa Zanin, MD, Stefano Sartori, MD, Pier Antonio Battistella, MD

Background: Few studies provide follow-up information or systematic investigation of prognostic parameters of nonorganic (psychogenic) visual loss in children.

Methods: A retrospective case series analysis was performed on 58 patients younger than 16 years old who had nonorganic visual loss and underwent at least a 3-month follow-up clinic visit and/or telephone interview between 1992 and 2007 at a single institution in Italy. All patients underwent a full neurologic, ophthalmologic, and orthoptic evaluation. Visual electrophysiologic tests were performed in many patients as part of the evaluation. Neuroimaging was performed and psychiatric referral was made only as needed. We collected data on the age at onset, time to diagnosis of nonorganic visual loss, type and duration of visual symptoms, and concomitant psychologic or psychosocial difficulties.

Results: Visual deficits consisted mostly of reduced visual acuity (76%) and visual field defects (48%). The diagnosis of nonorganic visual loss could be reached with confidence by means of observing inconsistent performance on a wide array of visual function tests, and, in doubtful cases, by means of electrophysiologic investigations. The mean time from onset to diagnosis was 3.1 months. The mean duration of visual symptoms from reported onset to disappearance was 7.4 months. Complete resolution of all visual symptoms occurred in 93% of patients and did so within 12 months of diagnosis in 85% of patients. There was no correlation between the duration of visual symptoms and age at onset, sex, time to diagnosis, type of ocular symptoms, or presence of psychosocial or psychologic difficulties.

Conclusions: Our study extends the follow-up information and confirms the findings of previous investigators in showing that nonorganic visual loss in children generally resolves spontaneously within 1 year and that no major psychiatric disorders are present or will appear after diagnosis. However, psychosocial stressors are often present and may predispose to this manifestation. There are no obvious predictors of rate of recovery.

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Nonorganic (psychogenic) visual loss in children, which makes up 1%–5% of a general ophthalmology practice (1,2) is defined as an apparent abnormality of visual function not confirmed by identifiable damage of the visual pathways (3). The diagnosis, often a lengthy process (2,4,5), is based on inconsistent performance on a wide range of visual function tests and, in doubtful cases, on electrophysiologic investigations confirming integrity of the visual pathways (2,4,6).

Few studies provide adequate follow-up information or systematic investigation of parameters that predict rate of recovery (1–4,6–18). The purpose of this study was to investigate the clinical characteristics, outcome, and prognostic indicators in a large series of children who received this diagnosis at a single institution.

METHODS

This was a retrospective study of 58 patients under 16 years old who had nonorganic visual loss and who had a follow-up examination at least 3 months later in the Pediatrics Department of Padua Hospital between 1992 and 2007. Patients with coexisting ocular pathologic conditions were included only if the nonorganic visual loss diagnosis was firm.

Parents or guardians were contacted by telephone in early 2008 for follow-up information by a board-certified child neurologist. The study protocol and consent forms were approved by the hospital’s institutional review board. Once the history and physical examination indicated the
suspicion of a nonorganic disorder, neurologic, ophthalmologic, and orthoptic evaluations were undertaken. The ophthalmologic evaluation included determination of visual acuity for distance and near viewing by Snellen charts, Lea symbols, Early Treatment Diabetic Retinopathy Study (ETDRS) charts, and Teller acuity cards, refractive error determination by dynamic and cycloplegic refraction, visual field examination by Goldmann perimetry, color vision testing by Ishihara plates and Farnsworth D15, contrast sensitivity testing with the Pelli-Robson chart, fogging, polarizing lens, optical penalization test and mirror tests, pupillary reactions, anterior segment examination by slit lamp, and ophthalmoscopy. The orthoptic evaluation consisted of binocular vision (Worth 4 dot), cover, and stereoacuity (Lang II, Titmus) tests.

The diagnosis of nonorganic visual loss was based on inconsistent results of wide-ranging measurements of visual acuity and other visual abilities. Electrophysiologic investigations, including flash and pattern visual evoked potentials (pVEPs) and electroretinography, were undertaken in doubtful cases. Neuroimaging was performed only in selected patients. Once nonorganic visual loss was diagnosed, a consultation was held with parents to assure them that the child had no underlying organic illness.

Adequate follow-up data were obtained for 56 of the 58 patients. An ophthalmologist reevaluated 43 (74%) patients with a mean time from symptom onset of 7.3 months (range 1–60 months). Forty-two subjects (72%) agreed to participate in the follow-up telephone interviews with a mean time from symptom onset of 4.4 years (range 0.5–16 years). Thirty-one patients (53%) received an ophthalmologic reexamination and a clinical telephone interview. The following data were collected: age at onset, sex, type of visual symptoms, duration of symptoms before clinical diagnosis of nonorganic visual loss (time to diagnosis), duration of visual symptoms from reported onset to reported disappearance, duration of follow-up, presence of preexisting eye disease, associated symptoms, and concomitant psychologic or psychosocial difficulties.

Data analysis was performed using an Italian statistical software package (Statistica). By means of logistic regression, the following potential “risk factors” (see Table 2) were tested with respect to their effect on the duration of visual symptoms: 1) age at onset, 2) sex, 3) time to diagnosis, 4) type of ocular manifestation, 5) associated nonocular symptoms, and 6) concurrent problems. The type of ocular manifestation included visual acuity defects, visual field defects, blurred vision, diplopia, dyschromatopsia, ocular pain or burning, and amaurosis (quantitative variables). Visual acuity defects were grouped into 2 dichotomous variables: unilateral/bilateral and severe (≤20/40)/mild (>20/40). Visual field defects were differentiated into 1 dichotomous variable: unilateral/bilateral. Concurrent problems were considered either individually or clustered in 4 main groups. The log-rank test and Cox regression model were used, respectively, for dichotomous and quantitative variables. In particular, we investigated whether psychosocial or psychologic problems contributed to longer duration of symptoms. The data were examined by 2 board-certified child neurologists and by a statistician.

RESULTS

Fifty-eight patients were identified as having nonorganic visual loss. Inconsistent visual acuity testing was present in 55 (95%) of patients. The most reliable method for detecting nonorganic visual loss was the finding that a very low visual acuity did not match a determination of a normal stereoacuity.

Among the 58 patients, 39 (67%) were girls and 19 (32%) were boys, with a female-to-male ratio of 2:1. Age at onset ranged from 5.3 to 15.5 years (mean 9.6 years, SD 2.4, mode 10). Time to diagnosis from the onset of symptoms was less than 1 month in 35 (60%) patients and more than 12 months in 2 (3%) patients (mean 2.8 months). Nine patients had been evaluated elsewhere by ophthalmologists and referred to us for neurologic evaluation because of a clinical suspicion of optical neuritis.

FIG. 1. Visual symptoms and signs in 58 children with nonorganic visual loss.
Subnormal visual function measurements consisted of reduced visual acuity in 76% and visual field defects in 48% (Fig. 1). In this group, 71% reported bilateral symptoms. Visual acuity reduction was severe (≤20/40) in 34 patients, and mild (≥20/40) in 10 patients. Visual field defects had been found in 28 (48%) of patients, consisting of concentric defects in 9 (33%), and were associated with reduced visual acuity in all but 1 patient. The location and size of the visual field deficits changed in sequential testing sessions in all but 1 patient.

The most commonly associated complaints were headache in 31 patients, abdominal pain in 14 patients, and limb pain in 4 patients. Eight patients (14%) had preexisting ocular pathologic conditions, which consisted of refractive errors (4 patients), retinopathy of prematurity (1 patient), strabismus (1 patient), accommodative esotropia (1 patient), and amblyopia (1 patient).

Visual electrophysiologic tests (Table 1), undertaken in 44 patients (76%), were normal in all but 1 patient, who had unilateral amblyopia and a unilateral abnormal pVEP with a normal electroretinogram. Results of neuroimaging (Table 1), performed in 22 patients (38%), were normal in all patients except 1, who had had a temporal lobe low-grade astrocytoma surgically excised before the onset of nonorganic visual loss.

Forty (69%) patients reported a stressful event considered to be a predisposing factor to the nonorganic visual loss, including family problems (24 patients) or psychologic difficulties (24 patients) (Table 2). In 8 patients a preexisting physical illness, including asthma, hepatic disease, autoimmune disease, and cerebral neoplasm, was reported.

Among the 7 patients referred to a child psychiatrist for evaluation after the diagnosis of nonorganic visual loss, 2 received a new psychiatric diagnosis. Among the 56 patients for whom follow-up data were available, 54 (93%) had complete resolution of all visual symptoms. The duration of visual symptoms ranged from 3 days to 48 months (mean 7.4 months). Symptoms resolved within 6 months in 31 (53%) and within 6–12 months in 12 (20%) and lasted more than 12 months in 9 (15%). To date, 4 patients continue to report visual symptoms, although they are now described as having a lower intensity and are fluctuating rather than persistent.

One patient had a relapse 5 years after symptom onset, but neuro-ophthalmologic evaluation reconfirmed the diagnosis of nonorganic visual loss, based on normal neuroimaging. We found no statistically significant correlation between the duration of symptoms and the putative “risk factors.”

**DISCUSSION**

The clinical features of nonorganic visual loss in children in this series are similar to those in previous publications (1,4,7–10). The 2:1 prevalence of girls and the mean age at onset of 9.6 years are consonant with past series (1,4,7–10). Conversion disorder was rare under 6 years of age (14%), as noted previously (9). The main manifestations were bilateral visual acuity defects (76%), often accompanied by bilateral visual field defects, (71%), as reported previously (2,4,7–10). Isolated visual field defects with normal acuity, reported previously in 15% of patients (2), were not found in our series. Many patients complained of additional nonocular symptoms, as described by others (7,8,10).

Preexisting ocular disease (3,8,10), family problems, and difficulty in school were prominent as in a previous series (7). The existence of nonorganic visual loss did not appear to imply important psychopathology or an increase in the risk of later psychiatric disorders (1,2,8,10).

Follow-up information, not widely available in previous reports (7,8,11,14,18) (Table 3), is a contribution of this study. Nearly all patients (93%) eventually showed total remission of the visual complaint. This proportion is higher than the range of 45% to 78% reported previously (1,2,5,7,15–17).

In our series, 73% of patients had recovered within 1 year. In comparison, the largest pediatric series reported

**TABLE 1.** Electrophysiologic and neuroimaging studies among 58 patients with nonorganic visual loss

<table>
<thead>
<tr>
<th>Study</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrophysiologic</td>
<td>44 (76)</td>
</tr>
<tr>
<td>Flash visual evoked potentials</td>
<td>35 (60)</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>22 (38)</td>
</tr>
<tr>
<td>CT</td>
<td>1 (2)</td>
</tr>
<tr>
<td>CT + MRI</td>
<td>5 (9)</td>
</tr>
<tr>
<td>MRI</td>
<td>16 (27)</td>
</tr>
</tbody>
</table>

**TABLE 2.** Concurrent psychosocial or psychologic difficulties

<table>
<thead>
<tr>
<th>Concurrent Difficulties</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems in the family</td>
<td>24 (41)</td>
</tr>
<tr>
<td>Parental psychiatric or severe physical disease</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Death of a relative</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Parental separation/divorce</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Sibling birth or jealousy</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Strict parents</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Adoption</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Problems at school</td>
<td>17 (29)</td>
</tr>
<tr>
<td>Psychologic problems</td>
<td>24 (41)</td>
</tr>
<tr>
<td>Poor self-esteem</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Difficulty in peer socialization</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Mood disorders</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Binge eating disorders</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Behavioral disorders</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Preexisting physical illness</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Reference</td>
<td>Patients</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Behrman and Levi, 1970 (19)</td>
<td>11</td>
</tr>
<tr>
<td>van Balen and Slijper, 1978 (14)</td>
<td>31</td>
</tr>
<tr>
<td>Mäntyjärvi, 1981 (11)</td>
<td>52</td>
</tr>
<tr>
<td>Catalano et al, 1986 (7)</td>
<td>23</td>
</tr>
<tr>
<td>Bain et al, 2000 (10)</td>
<td>30</td>
</tr>
<tr>
<td>Lim et al 2005 (8)</td>
<td>56</td>
</tr>
<tr>
<td>Present study, 2008</td>
<td>58</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Time of Resolution</th>
<th>Persistence of Symptoms (%)</th>
<th>Recurrence of Symptoms</th>
<th>Identifiable Stressful Events</th>
<th>Follow-up Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behrman and Levi, 1970 (19)</td>
<td>&lt;12 mo: 73%</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>0: mean 16 m</td>
</tr>
<tr>
<td>van Balen and Slijper, 1978 (14)</td>
<td>NI</td>
<td>12 (39%)</td>
<td>NI</td>
<td>NI</td>
<td>0: 1 m–4 y</td>
</tr>
<tr>
<td>Mäntyjärvi, 1981 (11)</td>
<td>&lt;12 mo: 37%</td>
<td>13 (25%)</td>
<td>NI</td>
<td>4/52 psychologic</td>
<td>0: 1–4.5 y</td>
</tr>
<tr>
<td>Catalano et al, 1986 (7)</td>
<td>&lt;24 h: 35%&lt;1 mo: 61%&lt;2 mo: 74%</td>
<td>1 (4%)</td>
<td>1</td>
<td>39% school; 35% family</td>
<td>TI: 1–67 m (mean 34 m)</td>
</tr>
<tr>
<td>Bain et al, 2000 (10)</td>
<td>NI</td>
<td>0</td>
<td>60% S (school or family)</td>
<td>0: NI</td>
<td></td>
</tr>
<tr>
<td>Lim et al 2005 (8)</td>
<td>NI</td>
<td>2 (3%)</td>
<td>43% S</td>
<td>0: 1–60 m (mean 31.5 m)</td>
<td></td>
</tr>
<tr>
<td>Present study, 2008</td>
<td>&lt;6 mo: 53%&lt;12 mo: 20%&lt;12 mo: 15%</td>
<td>4 (7%)</td>
<td>69% S; 41% family</td>
<td>0: 1–60 m (mean 7.3 m); TI: 0.5–16 y (mean 4.4 y)</td>
<td></td>
</tr>
</tbody>
</table>

NI, no information; O, ophthalmologic follow-up; S, stressors; TI, telephone interview follow-up.
before ours (11), containing outcome information on 46 of 52 patients, found that only 37% of patients had recovered within 1 year.

Up to 40% of children with nonorganic visual loss have been reported to have visual deficits from 1 to 4 years after initial presentation (1, 11). In our series, 15% of patients had symptoms lasting for 12 months or longer and 7% of patients still complained of visual symptoms at the last follow-up visit, although they were less intense and fluctuating rather than persistent.

Prognostic indicators for rapid resolution in previous reports (15, 16) have included younger age at onset and absence of any associated psychiatric disease. Our study agreed with 1 former study (7) reporting that there was no correlation between the duration of symptoms before evaluation and subsequent recovery time. However, unlike other studies (15, 16), our series showed that neither the age at onset nor the presence of a preexisting or newly diagnosed psychiatric disorder affected the speed of recovery.

We conclude that the best way to uncover nonorganic visual loss is the finding of inconsistency in results over a wide-ranging series of measurements of visual acuity and other visual abilities. The electrophysiologic investigations may confirm the integrity of the visual pathways mainly in doubtful cases (2, 4–6, 9); therefore, we recommend their use in nonorganic visual loss cases. The mainstay of management is reassurance that a full visual recovery is expected (4–6, 9). Psychiatric referral is usually not necessary (1, 2, 8, 10).

Most patients will have early resolution of nonorganic visual loss, but there are no clinical parameters that can reliably predict how fast that will occur.

REFERENCES


Abstract: A 4-year-old healthy girl with acute visual loss in the right eye had ophthalmoscopic evidence of a swollen optic disc combined with central retinal artery and vein occlusion in the affected eye. MRI showed that the intraorbital optic nerve on the affected side was thickened and enhancing. Diffusion-weighted imaging showed restricted diffusion in the distal intraorbital segment of the optic nerve, consistent with infarction attributed to compression or inflammation of the vessels serving the optic nerve and retina. Although such clinical phenomena have been described previously, this is the first patient to demonstrate restricted diffusion in an inflammatory optic neuropathy. The presence of restricted diffusion is helpful in excluding a neoplastic cause of a thickened optic nerve.

CASE REPORT

A 4-year-old healthy girl was admitted with suspected blindness of the right eye of 24 hours’ duration. There was no light perception in the right eye, and a visual acuity of 20/20 in the left eye. Pupils were equal in size with a relative afferent pupillary defect in the right eye. Eye movements were normal with no pain on ocular movement and no proptosis. Ophthalmoscopy of the right eye disclosed a cherry red spot in the macula, scattered hemorrhages and exudates, narrowed arterioles, engorged veins, macular edema, and swelling of the optic disc (Fig. 1). Ophthalmoscopy of the left eye was normal. Neurologic and physical examination results were normal.

Brain and orbit CT demonstrated a thickened right optic nerve as the only abnormality. MRI showed an enhancing, thickened right optic nerve and high T2 signal in the intraconal fat surrounding the nerve (Fig. 2AB). On DWI there was focal restricted diffusion of the distal intraorbital portion of the right optic nerve, confirmed on an apparent diffusion coefficient (ADC) map, and suggestive of infarction of the distal optic nerve (Fig. 2CD). Lumbar puncture yielded a normal opening pressure and cerebrospinal fluid formula.

Treatment with high-dose methylprednisolone was immediately initiated for 3 days. In the following 2 weeks, the optic disc became pale with narrowed retinal blood vessels. There was no improvement in visual acuity over a 2-year follow-up period. Repeat MRI, performed 4 months later, showed reduced bulk and lack of restricted diffusion in the affected optic nerve (Fig. 3).
DISCUSSION

In our patient, the thickened optic nerve and retinal vascular occlusion prompted consideration of optic nerve glioma or meningioma as alternative diagnoses to optic neuritis, OPN, and IOI. However, the imaging finding of restricted diffusion, which we attributed to compressive or vasculitic occlusion within the optic nerve, allowed us to dismiss consideration of a neoplasm and therefore we elected not to perform a biopsy. Instead we treated the patient with corticosteroids but with little hope of improving vision. The disappearance of restricted diffusion and partial reversal of optic thickness on a follow-up MRI confirmed that the process was inflammatory.

Vascular occlusion of the retina and/or optic nerve in the setting of orbital inflammation has been previously described but without use of DWI. Winterkorn et al (4) reported an enlarged optic nerve and ipsilateral central retinal artery and vein occlusion in 2 patients. Both patients had clinical and imaging manifestations consistent with IOI involving mainly the optic nerve and its sheath. The authors postulated that distension of the optic nerve caused mechanical compression of the central retinal artery and vein, leading to occlusion. A more recent single case report

FIG. 1. Ophthalmoscopy of the right eye at presentation shows a pale and swollen optic disc with splinter hemorrhages and exudates, macular edema, scattered retinal hemorrhages and exudates, narrowed arterioles, and engorged veins.

FIG. 2. MRI performed at presentation. A. Postcontrast T1 axial MRI with fat saturation shows enhancement around the thickened optic nerve (arrow). B. T2 axial MRI with fat saturation shows a thick, hyperintense right optic nerve (arrow) and high signal in the surrounding intraconal fat. C. Diffusion-weighted imaging (DWI) shows focal high signal in the right optic nerve (arrow). D. Apparent diffusion coefficient map shows corresponding low signal (arrow), confirming that the high signal in C represents restricted diffusion.
(5) described similar phenomena. Because our patient did not have the typical clinical presentation and the classic imaging findings of IOI, the diagnosis was more likely OPN, although OPN may be a form of IOI (2).

Six case reports have documented restricted diffusion in acute ischemic optic neuropathy (6–11) in perioperative hypotension (6), infection (8–10), ischemic optic neuropathy (7), and ischemic optic neuropathy due to thrombocythemia (11).

The first case report (6) involved a 61-year-old man who experienced severe bilateral posterior ischemic optic neuropathy after cardiac bypass surgery due to hypotension. Routine MRI sequences were normal, but DWI showed restricted diffusion within both intraorbital optic nerves. A later report (7) described restricted diffusion of the optic nerve in a patient with nonarteritic anterior and posterior ischemic optic neuropathy. Three additional reports (8–10) of restricted diffusion of the optic nerve have involved cavernous sinus thrombophlebitis (8), rhinocerebral mucormycosis (9), and fungal sinusitis (10). A recent report (11) involved a patient with bilateral ischemic optic neuropathy due to thrombocythemia.

Restricted diffusion was initially noted in acute ischemia. However, 2 recent studies (12,13) demonstrated this phenomenon in inflammatory and lymphoid lesions of the optic nerve. Restricted diffusion has not been reported in meningiomas and gliomas of the optic nerve and its sheath.

REFERENCES


FIG. 3. MRI scans performed 4 months after presentation. A. T2 axial MRI with fat saturation shows reduced bulk in the affected right optic nerve. B. Diffusion-weighted imaging (DWI) shows a normal signal in the affected right optic nerve. C. Apparent diffusion coefficient map also shows a normal signal, confirming that there is no longer any restricted diffusion.
Diffusion-weighted MRI Identifies Petrous Apex Abscess in Gradenigo Syndrome

Mohannad Ibrahim, MD, Gaurang Shah, MD, Hemant Parmar, MD

Abstract: A 12-year-old boy developed fever, trigeminal pain, altered mental status, and a sixth cranial nerve palsy, features of Gradenigo syndrome. Diffusion-weighted MRI demonstrated restricted diffusion in the ipsilateral petrous apex, identifying an abscess as the cause of his manifestations. The patient was successfully treated with broad-spectrum antibiotics. This is the first report demonstrating the use of diffusion-weighted imaging in Gradenigo syndrome.

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First described in 1907 (1), Gradenigo syndrome classically consists of paresis of the sixth cranial nerve, severe pain in the distribution of the trigeminal nerve, and otorrhea. However, most patients do not have the full triad of manifestations. The syndrome is attributed to inflammation of the petrous apex (“petrous apicitis”), which may occur with petrous apex pachymeningitis, lateral dural sinus phlebitis, or extradural abscess (2). The inflammatory process probably originates in the middle ear, extends to the petrous apex of the temporal bone, and causes localized osteomyelitis and reactive meningitis (2,3). Because the trigeminal ganglion and sixth cranial nerve are separated from the petrous apex only by dura, they are easily engulfed by the inflammatory process (3).

Cross-sectional imaging, including CT and MRI, is essential in confirming the pathologic changes. However, there are only a few CT and MRI criteria for differentiating one cause from another. With this case example, we demonstrate that diffusion-weighted imaging (DWI) is a useful tool for identifying a petrous apex abscess.

CASE REPORT

A 12-year-old boy presented with fever, headache, and impaired mental status. One day into his hospital stay, he developed right periocular pain and a right abduction deficit.

CT showed opacification of the right petrous apex with hypodense fluid (Fig. 1). MRI revealed abnormal T2 hyperintensity (Fig. 2A) and T1 hypointensity of the right petrous apex (not shown), with irregular patchy enhancement after administration of contrast material (Fig. 2B). There was hyperintensity on the isotropic DWI (Fig. 2C) and corresponding hypointensity on the apparent diffusion coefficient map (Fig. 2D). On the basis of the imaging findings, a petrous apex abscess was diagnosed, and the patient was successfully treated with broad-spectrum antibiotics.

FIG. 1. Postcontrast axial CT at the skull base shows abnormal opacification of the right petrous apex (white arrow) in comparison with the aerated left petrous apex (black arrow). There is abnormal thickening of the adjacent dura (arrowhead) suggestive of a reactive inflammatory process.
DISCUSSION

In this case report, DWI was useful in differentiating an abscess from other causes of Gradenigo syndrome by demonstrating restricted diffusion, which probably results from the increased viscosity created by necrotic debris, hypercellularity, and macromolecules in an abscess (4,6).

Use of DWI in the skull base has been limited (4,5) because of the presence of inhomogeneous tissues such as bone, air, and fat, which generate susceptibility, ghosting, and chemical shift artifacts. Susceptibility artifacts caused by field inhomogeneities at the air-bone interface of the temporal bone can be reduced with the use of parallel imaging techniques (7). Additional MRI techniques, such as sensitivity encoding echo-planer and single-shot turbo spin echo imaging, have been shown to greatly enhance the quality of DWI images by reducing the blurring artifacts at the temporal bone.

DWI forms part of the overall imaging assessment of petrous apex disease (8). In petrous apicitis, opacification of the petrous apex is seen on CT as hypodense fluid, whereas MRI will demonstrate this fluid as hypointense on T1-weighted images and hyperintense on T2-weighted images. CT is valuable in demonstrating associated cortical bone erosion. Because of its superior soft tissue discrimination,
MRI is useful for assessing inflammatory soft tissue changes. MRI may also disclose bone marrow changes related to osteomyelitis before bony destruction. Osteomyelitis usually appears hypointense on T1-weighted and hyperintense on T2-weighted images in contrast to the expected T1 and T2 hyperintensity related to the fatty components of the normal bone marrow. Osteomyelitis will show pronounced enhancement (8). In the various causes of petrous apicitis without abscess, restricted diffusion would not be nearly as prominent as with an abscess. Inflammatory granulomatous diseases would not be expected to show restricted diffusion at all.

Neoplastic processes of the petrous apex, such as lymphoma or metastasis, can produce imaging changes similar to those of petrous apicitis, but the clinical presentation is typically indolent and there are usually additional abnormalities elsewhere. DWI may show restricted diffusion in tumors of high cellularity, a phenomenon believed to be related to decreased motion of water protons. However, the hyperintensity is never as high as with abscesses or cerebral infarctions. In addition, tumors will demonstrate diffuse enhancement unlike the patchy enhancement of structures surrounding an abscess, with the center of the abscess itself not enhancing. Cholesteatoma of the petrous apex can also have imaging characteristics similar to an abscess, but its indolent course should distinguish it.

REFERENCES

Clinical and Imaging Features of Fludarabine Neurotoxicity

Michael S. Lee, MD, Alexander M. McKinney, MD, Jeffrey R. Brace, MD, Karen SantaCruz, MD

Abstract: Neurotoxicity from intravenous fludarabine is a rare but recognized clinical entity. Its brain imaging features have not been extensively described. Three patients received 38.5 mg or 40 mg/m² per day fludarabine in a 5-day intravenous infusion before bone marrow transplantation in treatment of hematopoietic malignancies. Several weeks later, each patient developed progressive neurologic decline, including retrogeniculate blindness, leading to coma and death. Brain MRI showed progressively enlarging but mild T2/FLAIR hyperintensities in the periventricular white matter. The lesions demonstrated restricted diffusion but did not enhance. Because the neurotoxicity of fludarabine appears long after exposure, neurologic decline in this setting is likely to be attributed to opportunistic disease. However, the imaging features are distinctive in their latency and in being mild relative to the profound clinical features. The safe dose of fludarabine in this context remains controversial.

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Fludarabine, a purine analog that inhibits DNA synthesis, acts against both dividing and resting cells. Other potential mechanisms of action include inhibition of RNA synthesis and activation of apoptosis. Treatment indications for fludarabine include myeloproliferative malignancies and immunosuppression before a bone marrow transplant (BMT) (1,2). Fludarabine is typically infused once daily for 5 days. In phase I and phase II clinical trials, several patients developed severe neurotoxicity at higher doses (2).

We report the clinical and neuroimaging findings of 3 patients who experienced fludarabine-induced neurotoxicity that prominently involved loss of vision.

CASE REPORTS

Case 1

A 48-year-old man had acute myelogenous leukemia. Eighteen days before receiving a BMT, he received a 5-day infusion of 38.5 mg/m² fludarabine per day, 1965 mg/m² cyclophosphamide per day, and total body irradiation of 400 cGy in 2 fractions. Renal function was normal. Two weeks after receiving the BMT, he developed bilateral upper extremity weakness and declining vision in both eyes. Neuro-ophthalmologic examination revealed an alert, oriented, and cooperative man. Visual acuities were light perception in the right eye and hand motions in the left eye. Results of pupillary, extraocular motility, and slit lamp examinations were normal. Ophthalmoscopy showed Roth spots bilaterally. The optic discs appeared normal. He had weakness of all 4 extremities, which was greatest in the proximal lower extremities. He was generally hyperreflexive with extensor plantar reflexes. There was numbness to all modalities below the T4 dermatome.

Brain MRI showed mild diffuse T2 and FLAIR hyperintense lesions in the periventricular white matter with restricted diffusion and corresponding low signal on apparent diffusion coefficient (ADC) maps, confirming cytotoxic effects (Fig. 1A). The lesions did not enhance. Spine MRI demonstrated no abnormalities.

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Lumbar puncture showed normal cellularity (1 white blood cell and 0 red blood cells), 34 mg/dL protein, 66 mg/dL glucose, and negative results for VDRL, cryptococcal antigen, group B streptococcus, fungal stain, Gram stain, oligoclonal bands, cytology, flow cytometry, and
FIG. 1. Case 1. A. Brain MRI performed 1 month after the patient had received 38.5 mg/m² fludarabine per day intravenously for 5 days. Axial FLAIR (left) shows subtle white matter changes (arrows). Diffusion-weighted imaging (center) shows high signal in the lesions. Apparent diffusion coefficient map (right) shows that the corresponding areas are of low signal, confirming that the lesions contain restricted diffusion. B. Brain MRI performed 2 weeks later shows signal abnormalities of greater intensity and size. C. Autopsy histopathology of the brain shows periventricular white matter axonal and myelin damage. Left panel. Hematoxylin and eosin (original magnification: ×20) stain shows abundant axonal spheroids (arrows). Right panel. Luxol fast blue/periodic acid-Schiff (PAS) (original magnification: ×10) stain shows white matter vacuolization and abundant macrophages with lightly PAS-positive macrophages (arrows).
polymerase chain reaction (PCR) for human herpesvirus-6 (HHV6), vesicular stomatitis virus (VZV), Epstein-Barr virus (EBV), JC virus, and cytomegalovirus (CMV). The myelin basic protein level was elevated 80-fold.

The patient became increasingly encephalopathic over the next week. Repeat brain MRI showed increasing size and intensity of the periventricular white matter lesions (Fig. 1B). Results of a repeat spine MRI were unremarkable. Electroencephalography showed theta and delta slowing consistent with diffuse cerebral dysfunction. The patient died 9 weeks after fludarabine exposure.

Autopsy showed axonal and myelin damage in the periventricular white matter. In the periventricular white matter of the temporal and occipital lobes, prominent white matter vacuolization, axonal spheroids, and abundant macrophages were seen (Fig. 1C), consistent with toxic leukoencephalopathy and previous descriptions of fludarabine neurotoxicity (1-7). The medulla and spinal cord also showed white matter vacuolization, and atypical intravascular cells consistent with leukemia were present.

Case 2
A 58-year-old woman received a diagnosis of multiple myeloma. Four years later, she received at a dose of 40 mg/m² fludarabine per day intravenously for 5 days, a single dose of 1950 mg/m² cyclophosphamide on the first day, and a single 200-cGy fraction of whole body radiation. Renal function was normal. One week later she underwent a nonmyeloablative double umbilical cord BMT.

Five weeks after fludarabine infusion, the patient developed progressive confusion and lethargy. Nine days later she became nonverbal but responded appropriately with head nodding. The following day she denied seeing light.

Brain MRI showed periventricular white matter T2 hyperintensities with restricted diffusion. The lesions did not enhance (Fig. 2A). Two days later, she did not respond to oral commands. Pupils were poorly reactive to light. She showed no spontaneous movement of her extremities, but she would withdraw to painful stimuli. Her extremities were spastic, her reflexes were brisk, and plantar reflexes were extensor. A repeat brain MRI showed that the lesions had expanded in size and intensity (Fig. 2B). Spine MRI disclosed no contributory abnormalities.

Lumbar puncture demonstrated no abnormalities. She was intubated electively 2 weeks later, and support was withdrawn after 1 week. No postmortem examination was performed.

Case 3
A 35-year-old woman received a diagnosis of acute myelogenous leukemia for which she underwent a nonmyeloablative allogeneic peripheral blood stem cell BMT 6 months later. One week before the BMT, she had received 38.5 mg/m² fludarabine per day for 5 days and a single dose of 2010 mg/m² cyclophosphamide for 1 day. Renal function was normal.

Her post-BMT course was complicated by Aspergillus pneumonia leading to sepsis and acute renal failure. Twelve days after the BMT, she was intubated for progressive dyspnea. Before intubation she was interactive and capable of transferring herself; however, the patient did not regain consciousness after sedation was discontinued 8 days later.

Four weeks after fludarabine infusion, she could not follow verbal commands or react to painful stimuli, but she opened her eyes spontaneously. Pupils were normal. Oculocephalic testing revealed normal results. Deep tendon reflexes were reduced in the upper extremities and absent in the lower extremities.

Brain MRI showed subtle T2 hyperintensity in the splenium of the corpus callosum. There was no restricted diffusion or enhancement (Fig. 3A). An electroencephalogram demonstrated diffuse theta and delta slowing.

Results of lumbar puncture was negative, including PCR testing for the JC virus. Repeat brain MRI over the next 2 weeks demonstrated increasing size and intensity to the white matter changes with mild restricted diffusion (Fig. 3B). She failed to improve and died 2 months after the BMT. There was no postmortem examination.

DISCUSSION

Previous reports of fludarabine neurotoxicity have relied on brain CT or have described MRI abnormalities without detail (1-7). Our patients showed variable, ill-defined, mildly hyperintense lesions in the periventricular and peritriatal cerebral white matter on T2 and FLAIR sequences with restricted diffusion but no enhancement. The brain MRI abnormalities were mild in relation to the profound clinical deficits and histopathology. The imaging abnormalities increased in size and intensity in repeated studies. Although clinical and postmortem examination demonstrated spinal cord involvement, spinal MRI did not show any abnormalities.

Other toxic leukoencephalopathies show similar white matter changes, but they occur concomitantly with drug administration and later stabilize or improve with dechallenge (8). Fludarabine neurotoxicity appears unique in the delayed and progressive lesion appearance many weeks after drug cessation.

The progressive neurologic decline may be confused with progressive multifocal leukoencephalopathy (PML), but imaging should differentiate these entities. In contrast to fludarabine toxicity, PML lesions involve the subcortical white matter and do not show restricted diffusion, and lesion size correlates with clinic clinical findings. Similarities include the absence of enhancement or mass effect (9). Initial animal studies of fludarabine in dogs failed to show neurotoxicity after a single dose or 5 daily doses (3). In phase I clinical trials, neurotoxicity occurred in up to 18%
FIG. 2. **A.** Brain MRI performed 7 weeks after the patient received 40 mg/m² fludarabine per day intravenously for 5 days. Axial FLAIR imaging (left) shows periventricular high signal areas. Diffusion-weighted imaging (DWI, center) shows that the lesions have high signal and an apparent diffusion coefficient (ADC) map (right) shows corresponding low signal, indicating restricted diffusion. **B.** Brain imaging performed 1 week later shows increasing size and intensity of the lesions on FLAIR (left), DWI (center), and ADC map (right).

FIG. 3. **Case 3.** Sequential axial FLAIR imaging studies at 4 weeks (A), 5 weeks (B), 6 weeks (C), and 8 weeks (D) after the patient had received 38.5 mg/m² fludarabine per day intravenously for 5 days. The lesions show progressive increase in size and intensity.
of patients treated with high-dose fludarabine (60–150 mg/m² per day for 5 days) (1,2,4,5). Further study revealed that the toxicity appeared to be dose dependent. Among 443 patients receiving fludarabine, 36% receiving high doses (>450 mg/m² total dose) developed severe central nervous system toxicity compared with only 0.2% receiving low doses (<125 mg/m² total dose) (6). Several large BMT centers use daily doses of 40 mg/m² (4,10–15) or 50 mg/m² in a 5-day infusion (16,17). Others have advocated lower doses—18-25 mg/m² per day for a 5-day infusion (1,7). At the University of Minnesota, 245 patients received fludarabine from September 2005 to July 2007 at doses of 38.5 or 40 mg/m² per day for 5 days before BMT.

The neurotoxicity of fludarabine may result in mild symptoms including peripheral neuropathy, altered mental status with hallucinations, motor weakness, paralysis, or seizure. Severe neurotoxicity may produce progressive worsening to death over the course of weeks to months. Visual disturbances are the most commonly reported symptom and result from cortical blindness (4–6), visual pathway demyelination (4–6), and/or retinal bipolar cell loss (7) based on neuroimaging (4–7), clinical examination (4–7), and histopathologic evaluation (4–7). Resolution of neurotoxicity rarely occurs, with most patients suffering irreversible and severe dysfunction. The risk factors for toxicity at recommended doses have not been identified.

Fludarabine is distinctive among agents causing central nervous system toxicity in that its clinical effects do not manifest until weeks to months after exposure (1,2,4-7). This phenomenon can be diagnostically confusing as the offending agent no longer appears on the patient’s medication list at the time of symptom onset. Moreover, in the immunosuppressed patient, the inclination will be to attribute the clinical and imaging abnormalities to an opportunistic infection.

REFERENCES

Prandial Presbyopia

Allon Barsam, MB, BS, MA, MRCPht, Devinder S. Chauhan, MB, BS, MD, MRCPht, Stacey A. Strong, MB, BS, Gordon T. Plant, MD, FRCP, FRCPht

Abstract: Loss of accommodation amplitude during eating (prandial presbyopia) is a rare phenomenon that has been reported in only 1 patient who had head trauma. We report 2 patients who had not had head trauma and whose accommodative amplitudes, measured by dynamic retinoscopy, became markedly diminished within 1 minute of starting a meal and did not recover for 55–60 minutes. Apart from this abnormality, there appeared to be no autonomic or other neurologic dysfunction. The cause of this isolated disturbance in these patients is a mystery.

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Prandial presbyopia is characterized by transient blurring of near vision immediately after initiating a meal. It has been described only once before in a single patient who had previously sustained head trauma (1). We describe 2 patients with prandial presbyopia unassociated with head trauma or other neurologic disturbance.

CASE REPORTS

Case 1
A healthy 42-year-old man presented with a 9-month history of blurred vision when eating. It occurred within 1 minute of his beginning a meal and generally persisted throughout it. He was unable to see his food clearly and could not read the bill at the end of a restaurant meal. Such blurred vision was related exclusively to eating and drinking, and there was no pertinent personal or family history.

Best-corrected visual acuity was 20/20 in both eyes with a distance correction of +2.50 sphere in the right eye and +1.50 sphere in the left eye. Results of a complete ophthalmologic and neurologic examination, including dilated ophthalmoscopy and cranial nerve and orthoptic evaluation, were normal. There were no abnormalities in his cardiovascular response to variations in posture, ambient temperature, and exercise level either before or just after a meal. Infrared pupillometry demonstrated no abnormalities in the amplitude or latency of the pupillary response to light or a near target before, during, or after a meal.

An investigation of the patient’s accommodation was performed immediately before, during, and after a test meal. Heart rate and blood pressure were assessed, and amplitude of accommodation was measured by the “push-up” technique and a Royal Air Force (RAF) rule modified to measure up to 2 m. With the patient wearing his distance correction, each eye was tested using the N5 (20/30) test print, which was gradually brought as close to the patient as possible until the image was reported as blurred. Convergence was tested with a near stimulus at 15 cm. All measurements were taken just before and 1, 5, 10, 15, 25, 40, and 55 minutes after the patient began the meal. Blood glucose was measured before the meal and at 5, 15, and 55 minutes after initiation of the meal.

Accommodative amplitude fell rapidly within 1 minute of the beginning of the meal, reaching its nadir after 10 minutes and returning to the preprandial level at 55 minutes after the meal was begun (Fig. 1). During the test period, the symptoms experienced by the patient were typical of those during previous untested episodes. Apart from accommodative amplitude, all tests yielded normal results.

Case 2
A 34-year-old man had a 10-year history of blurred vision during eating. He stated that the symptoms occurred every time he ate, irrespective of food type. He complained that the blurring would begin within 1 minute of eating and continue for about 15 minutes afterwards. The blurred vision episodes had become more pronounced and longer in duration over the last few months. He did not complain of diplopia or any other ocular or systemic symptoms. There was no history of head trauma. There was no pertinent past
medical history, and he was not taking any medications. He did not drink alcohol or smoke cigarettes.

Visual acuity was 20/20 in both eyes at 20 feet and 20/30 (Snellen equivalent) at 35 cm. He had a near point of convergence of 6 cm in both eyes and a near point of accommodation of 20 cm in both eyes. Visual fields were full to confrontation. Pupil size and reactivity were normal without a relative afferent pupillary defect. Color vision was intact in both eyes with Ishihara test plates. Ocular movements, ocular alignment, and results of ophthalmoscopy were normal.

Distance and near visual acuity, convergence, and dynamic retinoscopy were performed immediately before and after eating (2). Dynamic retinoscopy involved positioning a small letter chart close to the retinoscope peephole and holding the retinoscope-small letter chart complex at a distance of 35 cm from the patient. The patient was then asked to alternate fixation between the distance and the near fixation targets while retinoscopy was performed. The patient was then asked to maintain fixation on the near target to assess the sustainability of accommodation.

Immediately before eating, dynamic retinoscopy revealed +1.00 sphere in the right eye and +1.50 sphere in the left eye with the patient fixating at distance and 2.50 sphere in both eyes with the patient fixating at 35 cm. This accommodative effect was rapid, complete, and steady. At 1 minute after a meal was initiated, visual acuity was 20/20 and reading vision had been reduced to 20/400 unaided in each eye at 35 cm. Dynamic retinoscopy with the patient fixating at distance revealed a +1.50 diopter sphere in both eyes and remained constant when the patient fixated at 35 cm. Near vision improved to 20/30 in both eyes with a +1.50 diopter sphere in each eye.

The results of preprandial dynamic retinoscopy for distance and near noted immediately before eating were restored 60 minutes after the meal was initiated.

The patient was given a diagnosis of prandial presbyopia and was prescribed +1.50 diopter sphere reading glasses for use when eating.

DISCUSSION

In both patients there was a reduction in the ability to accommodate initially after eating a meal, demonstrated through the techniques of dynamic retinoscopy and measurement of accommodative amplitude.

The neural control of the accommodative component of the near triad is thought to lie in the rostral part of the Edinger-Westphal nucleus. Its caudal portion coordinates the association with pupillary constriction (3).

The mechanism of accommodative failure during eating is a mystery. A change in lens volume induced by a change in osmolality of the aqueous would be too slow to cause the rapid onset of the deficit in this setting. Without a history of head trauma, a central failure of synkinesis seems unlikely too.

The single previously published report of prandial presbyopia (1) involved a 35-year-old man with a 10-year history of blurring of near vision that began 30–45 seconds after he began to eat and lasted 10–15 minutes after he stopped eating. He reported that many foods exacerbated the phenomenon, particularly muffins, fruits, and sour foods. The patient did give a history of head trauma when he was 15 years old after a fall from a catwalk, but no examination or investigation was performed at that time. Retinoscopic refraction revealed a loss of 1.5 diopters of accommodative power in each eye 1 minute after he began to eat. In that report, brain and orbit MRI and CT did not reveal any abnormality. Stimulation of individual cranial nerves alone did not result in the loss of near vision. The main differences between that patient and the 2 patients reported here are that our patients had no history of trauma,
there was no food specificity, and there was a longer course of accommodative paresis.

As an explanation for the prandial presbyopia, the authors of the single previous case report (1) suggested an abnormal pattern of activity in a pathway between the paraventricular nucleus of the hypothalamus associated with eating and the part of the Edinger-Westphal nucleus that controls accommodation. They hypothesized that their patient was at an age when his accommodative reserve had diminished, allowing a pathway that was probably present since birth to become symptomatic. The lack of any obvious cause for an acquired abnormality in our patients would be consistent with this theory.

REFERENCES
Congenital Achiasma and See-Saw Nystagmus in VACTERL Syndrome

Saurabh Prakash, PhD, Serge O. Dumoulin, PhD, Nancy Fischbein, MD, Brian A. Wandell, PhD, Yaping Joyce Liao, MD, PhD

Abstract: A 29-year-old man with vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal defects, and limb defects (VACTERL) presented with headache, photophobia, and worsening nystagmus. He had near-normal visual acuity and visual fields, absent stereopsis, and see-saw nystagmus. Brain MRI revealed a thin remnant of the optic chiasm but normal-sized optic nerves. Functional MRI during monocular visual stimulation demonstrated non-crossing of the visual evoked responses in the occipital cortex, confirming achiasma. These findings have not previously been reported in VACTERL.

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The formation of the optic chiasm by the optic nerves has fascinated anatomists for centuries and continues to be vigorously studied today (1). In congenital achiasma, there are few or no crossing fibers, leading to decreased vision, strabismus, and nystagmus (2–7). Although achiasma usually occurs in the absence of other developmental anomalies, we report a case of achiasma in the setting of a congenital syndrome involving vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula with atresia, renal defects, and limb defects (VACTERL), a finding not previously described.

CASE REPORT

A 29-year-old normally pigmented Caucasian man with VACTERL was evaluated for a 2-year history of gradually worsening headache, blurred vision, and nystagmus. As a child, he had mild infantile nystagmus with relatively normal visual function. His axial and appendicular abnormalities, including tracheoesophageal fistula, cleft palate, shortened radius, and finger abnormalities, had been surgically repaired. Attention deficit disorder had been diagnosed when he was a child and bipolar affective disorder in adulthood. Even so, he completed high school and worked full-time.

Best-corrected visual acuities were 20/20 in the right eye and 20/25 in the left eye with a small left relative afferent pupillary defect. Anterior and posterior segments were normal. Goldmann visual fields were slightly restricted bilaterally, left greater than right. Color perception was normal by Hardy-Rand-Rittler pseudoisochromatic plates. Stereopsis was absent by the Titmus stereo test. He had a dissociated vertical deviation.

Extraocular movements were full with prominent pendular nystagmus that manifested cyclical depression and extorsion of 1 eye and concomitant elevation and intorsion of the contralateral eye, consistent with a see-saw pattern (Fig. 1). Because the subject’s eye positions could not be accurately calibrated on infrared oculography due to the nystagmus, the recordings reflected eye positions over time with approximation of the amplitude values. A trial of gabapentin did not reduce the amplitude of the nystagmus (data not shown).

Brain MRI demonstrated absence of the optic chiasm and otherwise normal anatomy, including the size of the optic nerves and optic tracts, pituitary gland, corpus callosum, and septum pellucidum (Fig. 2). On the fast imaging employing steady-state acquisition (FIESTA) sequence, which provided 1-mm axial slices with no skip (0.5-mm overlap between consecutive slices), a thin band could be recognized at the normal location of the optic chiasm.
chiasm (Fig. 2C), which had a signal intensity consistent with connective tissue on the T2 sequence (not shown).

We attempted pattern and flash on-off visual evoked potentials, but responses were poor bilaterally because of significant nystagmus-related artifacts. Blood oxygenation level-dependent (BOLD) functional MRI (fMRI) with monocular presentation of pattern-reversal checkerboard visual stimuli did demonstrate functional non-segregation of the visual pathway, with right eye visual stimulation resulting in neuronal activity restricted to the right visual cortex and left eye visual stimulation resulting in neuronal activity restricted to the left visual cortex (Fig. 3). A subject with a normal optic chiasm should exhibit activity in the visual cortex bilaterally in response to monocular visual stimulation due to decussation of the nasal retinogeniculate fibers.

**DISCUSSION**

Our patient with VACTERL exhibited neuro-ophthalmologic characteristics typical of achiasma, including decreased
visual acuity, lack of stereopsis, intact color vision, and infantile nystagmus with a see-saw pattern (3–8). BOLD fMRI demonstrated functional non-segregation of retinal axon fibers in response to monocular visual stimulation, suggesting the functional absence of an optic chiasm. Brain MRI showed only a thin band of presumed connective tissue in the expected position of the optic chiasm with normal bulk of the optic nerves.

Despite drastic rewiring of the connections and abnormal retinotopic maps in congenital achiasma (2,9,10), individuals with chiasmal malformation typically can adequately perform visually guided activities of daily living. Infantile nystagmus, especially of the see-saw pattern, is a consistent finding (2,3,6,7). This pattern of nystagmus has also been described in acquired lesions of the chiasm (11,12), in cone-rod dystrophy (14), and in Belgian sheepdogs with hereditary achiasma and hemi-chiasma (9,10). The mechanism of see-saw nystagmus remains unknown but may be related to impaired adaptive vestibular control of eye movement, given that see-saw nystagmus has a waveform similar to that of the ocular tilt reaction, exhibiting dissociated vertical deviation with intorsion of the elevated eye and extorsion of the depressed eye (10).

Functional MRI is a powerful tool to assess non-crossing of retinal axonal fibers at the optic chiasm. It has high spatial resolution, permitting the investigation of anatomic and functional visual pathway organization in humans with chiasmal anomalies. A study of 2 patients has suggested that achiasmic patients have deranged retinotopic maps in the occipital cortex despite relatively normal visual fields and perception (15). This type of altered anatomy and physiology has also been reported in the lateral geniculate nucleus and visual cortex of achiasmic Belgian sheepdogs, with dramatic discontinuity of receptive field representations and proximity of neurons that respond to visual stimuli on opposite sides of the visual field (9,10,16).

**FIG. 3.** Functional MRI during monocular pattern-reversal checkerboard presentation. Coronal images through the visual cortex during right eye stimulation of a control subject (top), during right eye stimulation of our achiasmic patient (middle), and during left eye stimulation of our achiasmic patient (bottom). Right eye stimulation of the control subject activates both occipital lobes. Right eye stimulation of the achiasmic patient activates only the right occipital lobe. Left eye stimulation of the achiasmic patient activates only the left occipital lobe. These findings are consistent with non-crossing of retinal axonal fibers at the optic chiasm. R, right; L, left.
The Belgian sheepdog model of achiasma is inherited in an autosomal recessive pattern, providing support for a genetic basis for achiasma. Consistent with this idea, the association of relative or complete achiasma with midline malformation syndromes such as VACTERL is not surprising and may be under-reported. Mice with a mutation in sonic hedgehog (Shh) have a phenotype resembling VACTERL (17). The Shh gene is also the major molecule implicated in human holoprosencephaly (18), which is thought to be on the spectrum of midline central nervous system developmental anomalies including septo-optic dysplasia (19).

REFERENCES
Irreversible Optic Neuropathy in Wernicke Encephalopathy and Leber Hereditary Optic Neuropathy

John-Michael Li, MD, Janet C. Rucker, MD

Abstract: A 52-year-old woman with alcohol abuse presented with recent worsening of vision, imbalance, and confusion. Examination revealed counting fingers acuity in both eyes with central scotomas, color vision loss, horizontal nystagmus, and gait ataxia. Thiamine was initiated as treatment for a presumptive diagnosis of Wernicke encephalopathy (WE). Brain MRI revealed high T2 signal in the dorsal midbrain and thalami characteristic of WE. The lack of optic disc edema, usually present in patients with WE who have severe optic neuropathy, and lack of visual loss reversibility with thiamine treatment, led to the suspicion of coexisting Leber hereditary optic neuropathy (LHON), which was later confirmed when testing revealed the 14484 mitochondrial DNA mutation. Over the ensuing months, vision did not recover despite improvement of other neurologic findings. Irreversible optic neuropathy in WE should prompt consideration of a coexisting mitochondrial disorder such as LHON.

CASE REPORT

A 52-year-old woman with a history of long-standing severe alcohol abuse and a 35-year history of cigarette use presented with a 2-week history of painless bilateral visual loss of sudden onset preceded by a vague 2-month history of mildly blurred vision. She also complained of imbalance. Her family had noted mild recent confusion. Family history was significant only for glaucoma in her father.

Visual acuity was counting fingers bilaterally at distance and 20/800 at near. She could not see the Ishihara control plate with either eye. On dilated ophthalmoscopic examination, there was subtle temporal optic nerve pallor bilaterally, considered possibly physiologic. Goldmann visual fields revealed bilateral cecocentral scotomas. Saccades, smooth pursuit, optokinetic nystagmus, and vestibulo-ocular responses were normal. Intermittent low-amplitude “shimmering” horizontal nystagmus was detectable in primary position and became more prominent on upward gaze. A formal mental status examination was not performed, but the patient had slowed cognitive responses, was disinhibited, and recalled only 1 of 3 objects at 5 minutes. She had mild bilateral upper extremity tremulousness and marked difficulty with tandem gait. There were no signs of a peripheral neuropathy.

The optic neuropathy was attributed to a metabolic/toxic process. The combination of confusion, nystagmus, and gait ataxia in a severe alcoholic was suggestive of WE. Thiamine supplementation was immediately initiated and discontinuation of alcohol and tobacco was recommended. MRI of the brain and orbits showed increased T2 signal in the dorsal midbrain and bilateral periventricular thalami,

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supportive of the clinical suspicion of WE (Fig. 1). The vitamin B\textsubscript{12} level was normal, and results for methanol and alcohol, a rapid plasmin reagin (RPR) test, and a fluorescent treponemal antibody absorption (FTA-ABS) test were negative. The thiamine level was 0.3 \textmu g/dL, at the lower limit of normal for our laboratory. Testing for the 3 common mitochondrial mutations for LHON was positive for the 14484 mutation. The patient’s final diagnoses were LHON and WE of simultaneous onset.

At a 4-month follow-up examination, ataxia and nystagmus had diminished. There was no change in visual function. Repeat brain MRI revealed lessening of the previously noted T2 signal abnormalities.

DISCUSSION

Our patient had features that supported a diagnosis of WE—a long history of severe alcohol abuse, recent mild confusion reported by her family, ataxia, and nystagmus. Supportive evidence included a low-normal thiamine level and the MRI T2 and FLAIR hyperintensities in the dorsal midbrain and periventricular thalami. Supplementation of thiamine improved the nystagmus and ataxia but not her vision. The lack of visual improvement is atypical for the visual loss previously reported with WE, but characteristic for LHON.

The severely decreased acuity and central and cecocentral scotomas suggested a metabolic/toxic process, such as that caused by mitochondrial dysfunction in drug toxicities and LHON. Although our patient lacked the classic acute optic disc features of peripapillary telangiectatic microangiopathy and retinal nerve fiber layer elevation and hyperemia typically seen with LHON, the absence of such features does not exclude LHON as the cause of visual loss. Importantly, she differed from previously reported patients with visual loss in WE, who have typically manifested bilateral disc edema (Table 1) (4,9). The few patients with normal optic nerve appearance at presentation have had rapid improvement of visual deficits after thiamine supplementation (9).

The mechanism of disc swelling in WE was initially considered to be papilledema from raised intracranial pressure (4). However, cerebrospinal fluid pressure has been normal. Moreover, visual loss has, in most patients, been more severe than that associated with acute or subacute papilledema. Inflammation was therefore later proposed as the mechanism of optic neuropathy (8). The patients lacking optic disc edema suggest yet another mechanism: mitochondrial dysfunction.

Thiamine deficiency has numerous effects at the mitochondrial level, as phosphorylated thiamine is a cofactor for several mitochondrial enzymes including \(\alpha\)-ketoglutarate dehydrogenase, pyruvate dehydrogenase, and transketolase. In thiamine-deficient animal models, malfunction of \(\alpha\)-ketoglutarate dehydrogenase is responsible for tissue damage via failure of the tricarboxylic acid (TCA) cycle and resultant impaired cellular production of ATP (14,15). Pathologic studies have shown that thiamine deficiency has a selective effect on neuronal populations in the thalamus and brainstem, corresponding to the location of neuroimaging abnormalities in human WE (15,16). The mechanisms of cellular death appear to be related to secondary formation of a focal lactic acidosis, \(N\)-methyl-d-aspartate receptor-mediated excitotoxicity, and failure of energy production.

In humans, thiamine deficiency can have manifestations beyond WE. Patients from a family with the A3243G mitochondrial mutation, mitochondrial myopathy, and familial...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Age/Sex (Setting)</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Visual Acuity</th>
<th>Optic Disc Edema</th>
<th>Tests</th>
<th>Outcome (time after treatment initiated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mumford13</td>
<td>24 W (HG)</td>
<td>nausea, decreased focusing ability</td>
<td>mental status changes, ataxia, nystagmus (H,V), coma after intravenous glucose administration</td>
<td>N/A</td>
<td>Yes</td>
<td>CT NL CSF – OP and protein NL</td>
<td>Acuity 20/20; Fields and optic disc NL</td>
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<tr>
<td>Timmings10</td>
<td>47 W (Alcoholism)</td>
<td>diplopia, sudden vision loss</td>
<td>mental status changes, nonreactive pupils, horizontal gaze paresis, nystagmus (V), ataxia</td>
<td>No light perception</td>
<td>N/A</td>
<td>CT ventricular dilation</td>
<td>Count fingers both eyes (4 hours); 20/125 Right eye, 20/80 Left eye (2 weeks); Fields NL (21 days); 20/20 (27 days)</td>
</tr>
<tr>
<td>Suzuki3</td>
<td>22 M (TPN)</td>
<td>sudden vision loss, oscillopsia</td>
<td>nystagmus (V) bilateral sixth cranial nerve palsies</td>
<td>&lt; 20/200</td>
<td>Yes</td>
<td>MRI consistent with WE</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Tesfaye5</td>
<td>21 W (HG)</td>
<td>vision loss to blindness over 10 days</td>
<td>confusion, “restricted gaze”, nystagmus (H, V)</td>
<td>Unable to count fingers at 1 meter</td>
<td>Yes</td>
<td>MRI NL</td>
<td>20/20 Right eye, 20/32 Left eye (24 hours); NL (3 weeks)</td>
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<td>Halavaara1</td>
<td>20 W (Chronic vomiting)</td>
<td>N/A</td>
<td>gaze palsies, nystagmus (H,V)</td>
<td>“reduced acuity”</td>
<td>Yes</td>
<td>MRI consistent with WE</td>
<td>Marked improvement</td>
</tr>
<tr>
<td>Gokce6</td>
<td>47 W (TPN)</td>
<td>confusion</td>
<td>bilateral sixth cranial nerve palsies, nystagmus (H), sluggish pupils, progressed to coma</td>
<td>“Profound vision loss”</td>
<td>Yes</td>
<td>MRI NL CSF protein elevated, OP N/A</td>
<td>20/40 Right eye, 20/63 Left eye (1 month); 20/32 Right eye, 20/50 Left eye VEP delayed right eye NL Left eye walking a few steps (1 year)</td>
</tr>
<tr>
<td>Ferdinands12</td>
<td>22 W (HG)</td>
<td>vision loss, diplopia, progressed to coma after given glucose</td>
<td>ataxia, right gaze paresis, confusion</td>
<td>20/125 Right eye 20/63 Left eye</td>
<td>Yes</td>
<td>MRI consistent with WE; CSF NL; OP N/A</td>
<td>Normal vision (3 days)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Age/Sex (Setting)</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Visual Acuity</th>
<th>Optic Disc Edema</th>
<th>Tests</th>
<th>Outcome (time after treatment initiated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kulkarni²⁸</td>
<td>24 W (Gastric bypass)</td>
<td>vision loss, imbalance</td>
<td>ataxia, nystagmus (H, GEN)</td>
<td>Light perception, central field loss</td>
<td>Yes</td>
<td>MRI consistent with WE; CSF NL; OP NL</td>
<td>20/30 Right eye, 20/20 Left eye, visual fields NL (24 hours)</td>
</tr>
<tr>
<td>Cooke⁷</td>
<td>11 W (11 weeks of vomiting)</td>
<td>vision loss, “central haze”</td>
<td>horizontal gaze paresis, nystagmus (upbeat)</td>
<td>20/200 Right eye 20/80 Left eye</td>
<td>Yes</td>
<td>MRI consistent with WE; CSF NL; OP N/A</td>
<td>20/40 Right eye, 20/80 Left eye (24 hours); 20/40, Ishihara color NL, optic discs NL (2 weeks)</td>
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<tr>
<td>Wilson¹¹</td>
<td>17 W (HG)</td>
<td>confusion, blurred vision</td>
<td>right gaze paresis, nystagmus (GEN), ataxia</td>
<td>N/A</td>
<td>Yes</td>
<td>MRI consistent with WE; CSF NL; OP NL</td>
<td>Improved over days</td>
</tr>
<tr>
<td>Surges⁹</td>
<td>37 M (Alcoholism)</td>
<td>sudden onset blindness</td>
<td>mental status changes, bilateral sixth cranial nerve palsies, nystagmus (downbeat), dilated pupils, ataxia</td>
<td>No light perception</td>
<td>No</td>
<td>MRI NL</td>
<td>NL (12 hours)</td>
</tr>
<tr>
<td>Longmuir²</td>
<td>34 W (Gastric bypass)</td>
<td>vision loss, diplopia</td>
<td>horizontal gaze paresis, nystagmus (GEN), ataxia</td>
<td>20/200 Right eye, 20/70 Left eye</td>
<td>Yes</td>
<td>MRI NL</td>
<td>20/20, Goldmann visual fields NL (14 hours)</td>
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<tr>
<td>Current</td>
<td>52 W (Alcoholism)</td>
<td>vision loss, confusion, imbalance</td>
<td>nystagmus (H), ataxia</td>
<td>Counting fingers, central scotomas both eyes</td>
<td>No</td>
<td>MRI consistent with WE</td>
<td>No recovery</td>
</tr>
</tbody>
</table>

DBN, downbeat nystagmus; GEN, gaze-evoked nystagmus; H, horizontal; HG, hyperemesis gravidarum; M, man; N/A, not available; NL, normal; OP, opening pressure; TPN, total parenteral nutrition; V, vertical; VEP, visual evoked potential; W, woman; WE, Wernicke encephalopathy.

thiamine deficiency have shown improved muscle strength and decreased lower extremity edema with thiamine supplementation (17). Thiamine-responsive peripheral neuropathies and optic neuropathies have also been documented in patients later found to have pyruvate dehydrogenase deficiencies (18). It is speculated that in patients with mitochondrial abnormalities, tolerance to decreased thiamine may be lower and thus higher levels of thiamine may be required to compensate for impaired cellular energy production. In the setting of malnutrition or thiamine malabsorption, these individuals may be more likely to develop WE. Such a phenomenon may have occurred in our patient, given the simultaneous development of visual loss and WE in the setting of a low-normal thiamine level.

Although our patient displayed the classic clinical triad and the imaging findings of WE, we cannot completely exclude the possibility that these features were a manifestation of her mitochondrial mutation alone. Brain lesions on MRI are present in a small percentage of patients with LHON. However, these are most commonly reported in 1 of 2 clinical settings: 1) in patients with a relapsing, remitting illness indistinguishable from multiple sclerosis (MS); and 2) in patients who are neurologically normal except for the visual loss associated with LHON (19). The brain lesions are also characteristic of MS, with multiple T2 hyperintensities in periventricular and subcortical cerebral white matter, brainstem, and cerebellum. Such imaging findings were not seen in our patient.

There is a report of 3 patients with the common LHON mutations who developed an illness resembling Leigh disease with imaging features similar to those of our patient (20). There is overlap between the imaging abnormalities in those reported patients and in WE, with prominent midbrain and periventricular thalamic lesions in both. In contrast to our patient’s monophasic course of thiamine-responsive ataxia and nystagmus with simultaneous vision loss, none of those patients had visual loss temporally related to an illness with features of Leigh disease. Moreover, all 3 patients had a relapsing or progressive neurologic illness over many years.

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Peripapillary Nerve Fiber Layer Thickening, Telangiectasia, and Retinal Hemorrhages in Wernicke Encephalopathy

Brenda L. Bohnsack, MD, PhD, Shreya S. Patel, MD, MPH

Abstract: A young woman who underwent gastric bypass surgery for morbid obesity had intractable nausea and vomiting for several weeks postoperatively, leading to poor intake and excessive weight loss. In the ninth postoperative week, she became confused and off balance and reported blurred and double vision. Examination disclosed slow saccades, nystagmus, and impaired abduction of both eyes as well as memory loss and ataxia. Visual acuity was slightly subnormal, and ophthalmoscopy disclosed a thickened and telangiectatic peripapillary nerve fiber layer with retinal hemorrhages. MRI showed high T2 and FLAIR signal in the dorsomedial thalamus and mamillary bodies bilaterally, substantiating a clinical diagnosis of Wernicke encephalopathy (WE). After thiamine treatment, visual acuity returned to normal and eye movements and alignment almost completely normalized. Fundus abnormalities eventually regressed. Although the ocular motor findings of WE have been well documented, the ophthalmoscopic findings have not. Resembling the findings in Leber hereditary and toxic optic neuropathies, they may represent manifestations of impaired mitochondrial function in retinal ganglion cells and capillaries. Recognition that these ophthalmoscopic findings may occur in WE is important to avoid procedures such as lumbar puncture that may delay urgent treatment with thiamine.

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FIG. 1. A. At presentation, fundus photographs show thickening and telangiectasia of the nerve fiber layer and mirror-image superficial retinal hemorrhages. B. Four weeks after presentation, fundus photographs show partial resolution of the findings in A.
A 22-year-old woman underwent Roux-en-Y gastric bypass surgery for morbid obesity (BMI 63 kg/m²). After the surgery, she had intractable nausea and vomiting with poor oral intake, leading to an 80-lb weight loss over 2 months. She did not take vitamin supplements as instructed. In the ninth postoperative week, she became confused, developed difficulty with balance, and noted blurred and double vision. Apart from myopia, she had no ophthalmic problems and there were no preexisting neurologic problems.

On our bedside examination, best-corrected visual acuity at near was 20/40 in the right eye and 20/25 in the left eye. Pupils, confrontation visual fields, and intraocular pressures were normal. She displayed saccadic smooth pursuit and slow saccades with bilateral abduction deficits and substituted convergence movements on attempted lateral gaze (Video, Supplemental Digital Content 1, http://links.lww.com/WNO/A5). Pretreatment clinical ocular motility examination, impaired by poor cooperation, shows normal alignment in primary gaze position with impaired abduction bilaterally, substituted convergence movements on attempted side gaze, and upbeat nystagmus. Sidebeat, upbeat, and downbeat nystagmus were present in extremes of gaze. The eyes were aligned in primary gaze position. Ophthalmoscopic examination disclosed thickening and telangiectasia of the peripapillary nerve fiber layer in both eyes. Superficial retinal hemorrhages were present near the optic discs in both eyes (Fig. 1A). She was oriented to time and place, had no language deficits but had difficulty with recall of recent events. Her gait was wide-based.

Optical coherence tomography (OCT) demonstrated a thickened retinal nerve fiber layer superiorly and inferiorly in both eyes (Fig. 2). Brain MRI showed T2 and FLAIR hyperintensity in the dorsomedial thalami and mamillary bodies (Fig. 3). The thiamine level was 6.0 nmol/L (normal 4.5–15.1 nmol/L). Based on the clinical and imaging findings, a diagnosis of Wernicke encephalopathy (WE) was made.

The patient was treated with 100 mg/day thiamine intravenously for 7 days followed by 100 mg/day thiamine orally. Within 24 hours, she had marked improvement in mentation and vision. After 48 hours of treatment, distance visual acuity was 20/20 in both eyes. Saccadic and pursuit eye movements were now normal (Video, Supplemental Digital Content 2, http://links.lww.com/WNO/A6). After 48 hours of treatment with 100 mg/day thiamine intravenously, the patient has more normal gaze but still has sidebeat and upbeat nystagmus. The upbeat nystagmus had resolved, but she still had sidebeat nystagmus on left and right gaze. Formal visual fields (Humphrey 24-2 protocol) were normal in both eyes. Ophthalmoscopic examination showed no change. The patient continued to have difficulty ambulating due to ataxia. Two weeks after initiation of treatment, the patient’s ophthalmologic and neurologic examinations were essentially unchanged.

Four weeks afterwards, eye movements were essentially normal (Video, Supplemental Digital Content 3, http://links.lww.com/WNO/A7). Four weeks after onset of the clinical manifestations of Wernicke encephalopathy and treatment with thiamine, the patient’s eye movements were normal and ophthalmoscopic abnormalities were resolving (Fig. 1B).

WE consists of a triad of altered mental status, ataxia, and eye movement abnormalities (nystagmus and ophthalmoplegia) (1). The pathologic substrate is neuronal loss, hemorrhage, and capillary proliferation principally in mamillary bodies, dorsomedial thalami, and periaqueuctal gray matter of the midbrain and pons (Fig. 4). These phenomena are attributed to thiamine (vitamin B₁) deficiency. In the past, this deficiency most often arose in...
chronic alcoholism (1). More recently it has been described in the nutritional deficiency that may follow bariatric surgery (2–8). A rare complication in this setting, WE was documented in 84 cases in a 2008 review (5). Its manifestations are typically noted 4–12 weeks postoperatively. Risk factors include poor oral intake due to nausea and vomiting, rapid weight loss, and glucose administration without thiamine supplementation (5,7).

Although the ocular motor abnormalities of WE are well documented, the optic fundus findings are not (9–12). In his original description of 3 alcoholic patients, Wernicke described “bilateral optic neuritis with massive swelling and many streaky hemorrhages” in 1 patient and “redness of the optic discs” in the other (1,13). In their 1954 report on the ocular signs in 5 patients with WE (4 from alcohol and 1 from malnutrition), Cogan and Victor (9) found no optic fundus abnormalities. In an authoritative 1971 review of 245 alcoholic patients with WE by Victor et al (1), 6 (2%) patients were described as having retinal hemorrhages but none as having optic disc edema. No fundus photographs were published in these reports.

There have been 3 single case reports of the optic fundus findings in WE associated with bariatric surgery (2–4). Mumford (2) described a 24-year-old woman with hyperemesis gravidarum who presented with findings virtually identical to those of our patient, namely impaired consciousness, ataxia, vertical and horizontal nystagmus, and reduced abduction in both eyes. Ophthalmoscopy revealed “marked bilateral papilledema with capillary

![FIG. 3. At presentation, axial MRI FLAIR images show hyperintensity of the mamillary bodies (arrow, A) and medial thalami (arrow, B).](image)

![FIG. 4. Alcoholic Wernicke encephalopathy in autopsied cases. A. Whole-mount section of walls of the third ventricle shows necrosis of medial thalamic nuclei (pale areas, arrows). B. Histologic section from a patient with acute WE shows ring of hemorrhages (arrows) around a blood vessel. C. In the mamillary body of a patient with subacute WE, there are dilated blood vessels (white arrow), hypertrophied vascular endothelium (arrowhead), and preserved neurons (black arrows). (Modified from Graham DI, Lantos PL, eds. Greenfield’s Neuropathology. Vol 1, 7th ed. London: Arnold; 2002:613.)](image)
dilatation and peripapillary flame hemorrhages.” No photographs of the fundus findings were published. Because the optic fundus findings were initially interpreted as consistent with increased intracranial pressure, she underwent brain CT, which was normal, and a lumbar puncture, which showed a normal opening pressure and constituents. It was only after these studies returned normal results that a diagnosis of WE was made. In the meantime, the patient was receiving an intravenous glucose infusion without thiamine and becoming comatose.

Kramer and Locke (3) reported “peripapillary hemorrhage and blurred disc margins” in a patient who had developed visual difficulty 2 months after bariatric surgery. She was also described as having “coarse horizontal nystagmus on lateral gaze and coarse vertical nystagmus varying with direction of gaze.” The neurologic examination was otherwise affected by psychiatric problems and therefore was not reliable. No visual function measures were reported, and no fundus photographs were published.

Kulkarni et al (4) described a 24-year-old patient who reported blurred vision 2 months after bariatric surgery. Visual acuity deteriorated to hand movements in both eyes, and she had sluggishly reactive pupils, bilateral optic disc edema, and peripapillary hemorrhages. Black and white fundus photographs in that report suggested a considerable amount of optic disc edema. There was also sidebeat nystagmus, dysmetria, and gait ataxia but evidently normal mental status. The authors pointed out that this presentation was bound to suggest papilledema, optic neuritis, or bilateral optic neuritis. Brain MRI showed high T2 and FLAIR signal in medial thalamic regions, and lumbar puncture showed a normal opening pressure and constituents, findings consistent with a diagnosis of WE. Methylprednisolone treatment was stopped, and after 24 hours of treatment with 100 mg thiamine intravenously, the patient’s visual acuity improved to 20/30 in both eyes and eventually to 20/20. The degree of visual deficit and optic disc edema in this patient is much greater than that described in other reports of WE, but details in other reports are sparse.

The thickened and telangiectatic peripapillary nerve fiber layer and retinal hemorrhages displayed by our patient are probably similar to the findings originally described by Wernicke and by most subsequent authors. They are strikingly similar to the pathologic characteristics noted in the mammillary bodies in WE (1,14) (Fig. 4).

Thiamine is an important cofactor for enzymes responsible for energy production via the Krebs cycle in mitochondria. Deficiency of thiamine results in a buildup of free radicals and neuronal cell death (14). The fundus findings seen in our patient bear a resemblance to those seen in methanol-induced optic neuropathy (15) and in Leber hereditary optic neuropathy (16), in which mitochondrial abnormalities have been demonstrated on transmission electronic microscopy in the retinal capillary endothelium (17). We postulate that mitochondrial dysfunction first gives rise to the swelling, telangiectasia, and hemorrhage of the retinal nerve fiber layer, which is shown here, and that actual optic disc swelling appears only if mitochondrial damage is severe and prolonged.

Curiously, the slowly progressive optic neuropathy noted in chronic alcoholism produces severe persistent optic neuropathy with pale optic discs but not the fundus findings we describe here. Thiamine deficiency is implicated in that setting, but evidently its manifestations are different from those in patients with reduced nutrient intake after gastric bypass surgery (18–21).

Although not the focus of this report, the eye movements in this patient merit comment. She had a deficit of abduction to both sides that we attribute to convergence substitution movements on attempted lateral gaze rather than impairment of sixth cranial nerve function. Were sixth cranial nerve palsies the cause of the impaired abduction, we would expect considerable esotropia in primary gaze position, yet our patient’s eyes were aligned in that gaze position. Although sixth cranial nerve palsy is conventionally considered the cause of impaired abduction in WE, none of the reported patients was described as having esotropia in the primary gaze position. Instead, the reports described impaired or slow volitional horizontal gaze or gaze-evoked nystagmus. Convergence substitution movements on attempted side gaze are a common phenomenon in patients with impaired horizontal gaze caused by pontine dysfunction (15). Cogan and Victor (9) also pointed out that in a pathologic study of the brains in patients with WE, “destructive lesions of the oculomotor nuclei were infrequent.” Perhaps the mechanism of eccentric gaze misalignment in patients with WE is substituted convergence rather than sixth cranial nerve palsy.

REFERENCES
CT Demonstration of Dorsal Midbrain Hemorrhage in Traumatic Fourth Cranial Nerve Palsy

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Abstract: A 21-year-old man who suffered a traumatic brain injury from a motor vehicle accident recovered brain function except for an isolated left fourth cranial nerve palsy. Brain CT showed a focal hemorrhage in the right dorsal midbrain, directly in the brainstem path of what would become the left fourth cranial nerve. Although there has been previous imaging documentation of midbrain and cisternal hemorrhage in patients with isolated post-traumatic fourth cranial nerve palsy, this is the first report to show a large midbrain hemorrhage on CT. The mechanism is likely to be concussive impact of the dorsal midbrain on the tentorium cerebelli.

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A 21-year-old man had a traumatic brain injury in a motor vehicle accident in which he was struck from behind as a belted front seat passenger by a semi truck. He was unresponsive at the scene and taken to the hospital where he was intubated. Precontrast head CT revealed a right dorsal midbrain hemorrhage with surrounding edema. (Fig. 1A) There were also multiple small hemorrhages in the frontal lobes, posterior horn of the left lateral ventricle, and corpus callosum.

He required ventriculostomy and intracranial pressure monitoring. Over the next week, he gradually regained consciousness and was discharged after 2 weeks without focal neurologic deficits but with a percutaneous gastrostomy tube.

At discharge, he reported that he had binocular vertical diplopia with 1 tilted image especially in downward gaze to the right. He had been entirely healthy before the accident.

Six weeks after the accident, best-corrected visual acuity was 20/20 in each eye. Pupils measured 5 mm in dim illumination and constricted normally to light without an afferent defect. Results of the ocular adnexal examination was normal. Eye movements were full, smooth, and without nystagmus. In primary gaze position, the patient had a 2 prism-diopter left hyperphoria, which became an 8 prism-diopter left hyperdeviation on right gaze. In down and right
FIG. 2. Reported cases of traumatic fourth cranial nerve palsy with imaging evidence of intracranial hemorrhage in the path of the fourth cranial nerve. 

A. Precontrast T1 axial MRI shows hemorrhage in the left dorsal midbrain with pontine extension (arrow). (Modified from Burgerman et al [1].) 

B. Gradient echo MRI exposes hemosiderin (black) in a small dorsal midbrain hemorrhage at the level of the left inferior colliculus. (Modified from Prosst and Majetschak [2].) 

C. Precontrast brain CT shows a large hemorrhage in the rostral left superior cerebellar cistern (Modified from Lavin and Troost [3]). 

D. Precontrast brain CT shows a hemorrhage in the right superior cerebellar cistern (Modified from Arbarbanel et al [4].) 

E. Precontrast axial brain CT shows hemorrhage in the left quadrigeminal cistern. (Modified from Ishizaki and Kurokawa [5].) 

F. Precontrast axial T1 shows high signal in the right ambient cistern consistent with methemoglobin (Modified from Hara et al [6].) 

G. Axial FLAIR study shows hyperintense signal in the right ambient cistern (Modified from Hara et al [6].) 

H. Precontrast axial brain CT shows a hyperdense focus in the collicular region in a patient with bilateral fourth nerve palsies. (Modified from Keane [7].) 

I. Precontrast brain CT shows bullet fragments in the collicular region in a patient with a left fourth cranial nerve palsy. (Modified from Keane [7].)
FIG. 3. Axial schematic illustrations to demonstrate the postulated mechanisms of damage to the fourth cranial nerve in closed head trauma. **A.** Normal anatomy of the brainstem at a cross-sectional level immediately caudal to the inferior colliculus in the tentorial incisura. **B.** Lateral displacement of the midbrain and collision with the tentorial edge causes dorsal midbrain hemorrhage and damage to the intra-axial segment of the contralateral fourth cranial nerve, as in our patient. **C.** Lateral displacement of the midbrain and collision with the tentorial edge causes damage to the ipsilateral extra-axial (cisternal) segment of the fourth cranial nerve. **D.** Posterior displacement of the midbrain and collision with the tentorial edge causes damage to both fourth cranial nerves in the region of the anterior medullary velum.
gaze, he had a 20 prism-diopter left hypertropia. In left head tilt, he had a 6 prism-diopter left hypertropia. In right head tilt, his eyes were aligned as they were in all upgaze positions. With the double Maddox rod test, he had 10° of excyclotorsion. The results of the rest of the neuro-ophthalmologic examination were normal as were the results of the neurologic examination. Three weeks later, precontrast head CT (Fig. 1B) demonstrated resolution of the midbrain hemorrhage.

The location of injury to the fourth cranial nerve in closed head trauma is uncertain. In most cases, brain imaging, whether by CT or MRI, fails to show a lesion. However, there are 7 reports demonstrating radiologic evidence of a causative hemorrhage (1–7). In 2 patients (1,2), the hemorrhage was in the dorsal midbrain contralateral to the side of the fourth cranial nerve palsy as in our patient, but unlike our patient, the hemorrhage was seen only on MRI and not on CT.

In the first of these reported patients, Burgerman et al (1) documented a small dorsal midbrain hemorrhage on MRI in a patient who had residual truncal and left extremity ataxia (Fig. 2A), unlike our patient, who had no focal neurologic deficits apart from the fourth cranial nerve palsy. The lesion had a bright signal on T1 and T2, indicating the presence of methemoglobin in a late subacute hematoma. In the second patient, Prosst and Majetschak (2) demonstrated low signal in a dorsal midbrain hemorrhage on gradient echo (T2*) MRI (Fig. 2B), indicating hemosiderin at the level of the inferior colliculus in a patient with an isolated unilateral fourth cranial nerve palsy.

Four reports (of 5 patients) have documented damage in the brainstem cerebrospinal fluid cisterns along the course of the extra-axial portion of the fourth cranial nerve. In 2 reports, the hemorrhage was located in the superior cerebellar cistern; in 1 report, it was in the quadrigeminal cistern; and in 1 report (2 patients), it was in the ambient cistern.

In 1 of these 4 reports (3), the lesion was demonstrated on precontrast CT (MRI was not done) in the superior cerebellar cistern (Fig. 2C) in a 59-year-old patient who had fallen in the shower. He was being treated with warfarin after mitral valve replacement. That patient had had previous episodes of spontaneous extracranial bleeding. The fourth cranial nerve palsy in that patient was unilateral, isolated, and ipsilateral to the side of the hemorrhage. Another case was that of a 10-year-old child who struck his head in a fall from a swing. Precontrast CT (MRI was not performed) demonstrated hemorrhage in the superior cerebellar cistern on the side of an isolated fourth cranial nerve palsy (Fig. 2D) (4).

In a further report, hemorrhage was present in the quadrigeminal cistern on CT and MRI (low signal on T2; T1 signal not reported) in an isolated ipsilateral fourth nerve palsy in a 72-year-old man who had fallen down the stairs (Fig. 2E) (5). In 2 other patients, an ambient cistern hemorrhage was demonstrated in association with isolated traumatic ipsilateral fourth cranial nerve palsy (6). One of these patients was 65 years old and had fallen intoxicated from his bicycle; the hemorrhage displayed a signal of high intensity on T1 and FLAIR and of isointensity on T2, indicating methemoglobin due to early subacute hemorrhage (Fig. 2F). The second patient was a 16-year-old-boy who had fallen off his motorcycle; his lesion was visible only as a high intensity signal on FLAIR (Fig. 2G).

In 2 additional reported patients, imaging resolution was too low to allow precise localization. In the first case, CT performed on a first-generation EM1010 scanner appeared to show a collicular hemorrhage in a patient with bilateral traumatic fourth nerve palsies (7), upper extremity numbness, and contralateral truncal ataxia (Fig. 2H). The other patient, who had been shot in the head, had a unilateral fourth cranial nerve palsy, ataxia, and extremity sensory loss. CT showed a bullet fragment in the region of the inferior colliculus (Fig. 2I).

Our patient and the reported literature indicate that intrinsic midbrain or perimesencephalic hemorrhages may occasionally be seen on imaging in traumatic fourth cranial nerve palsy. The hemorrhage may result from tearing of intrinsic nutrient blood vessels, thrombosis and subsequent infarction, or bruising by concussion against the tentorium (8,9). Interestingly, most of these hemorrhages have been present at the supratentorial level of the midbrain near the intra-axial course of the fourth cranial nerve (7,9). Impact of the midbrain against the rigid tentorium would be the most plausible mechanism of injury. After head impact, the brainstem moves backwards, so that the tentorium collides with either the dorsal midbrain or the fourth cranial nerve exit zone in the anterior medullary velum (2,10) (Fig 3).

The striking feature of our patient is that a large midbrain hemorrhage, so easily seen on CT, would cause lingering damage limited to the fourth cranial nerve. The explanation seems to be that in this dorsal location other critical brain stem pathways are spared because they are not near the lesion.

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REFERENCES


Acquired Enophthalmos in Lupus Erythematosus Profundus

Tina Y. Kao, BS, Michael K. Yoon, MD, Timothy J. McCulley, MD, Beth S. Ruben, MD, Thomas N. Hwang, MD, PhD

Abstract: Lupus erythematosus profundus (LEP) is an uncommon subtype of lupus erythematosus. A 76-year old man presented with inflammation of the eyelids and underlying orbital soft tissue. A biopsy disclosed inflammation and atrophy of the orbital fat consistent with LEP. Systemic corticosteroid treatment produced resolution of the inflammation. but as the edema subsided, enophthalmos became apparent. LEP should be considered in patients with a characteristic rash and orbital inflammation and may cause acquired enophthalmos.

A 76-year-old Hispanic man presented with a 3-month history of a progressive right periocular discoloration. A violaceous lesion appeared on the right lower eyelid, together with a dull periocular ache, and gradually extended to involve the ipsilateral cheek and upper eyelid. The pain lasted only an hour. He had had Hashimoto thyroiditis, diverticulitis, and chronic hepatitis C.

We noted diffuse red-violet discoloration of the right upper and lower eyelids with palpable induration (Fig. 1). The inferior portion of the upper eyelid was spared. He had trace conjunctival injection in the ipsilateral eye. The rest of the ophthalmologic examination was normal.
Hematocrit was 37.5%, the erythrocyte sedimentation rate was 85 mm/h, the antinuclear antibody (ANA) titer was 1:320 with a diffuse pattern, double-stranded (ds) DNA antibody was 44 IU/ml, and serum gamma globulin was 2.3 g/dL. Leukocyte count and differential, myeloperoxidase antibody and anti-proteinase antibody, angiotensin-converting enzyme, cryoglobulin, and extractable nuclear antigens SSA, SSB, Sm, and ribonucleoprotein (RNP) were normal.

T1 orbital MRI demonstrated a diffuse loss of fat signal and enhancement of the orbital fat and extraocular muscles (Fig. 1). Biopsy of the lower and upper eyelid skin, orbicularis oculi, and lateral rectus muscles, orbital septum, and extraconal and intraconal orbital fat disclosed a predominantly perivascular lymphoplasmacytic infiltrate. Cutaneous sections showed fat hyalinization of the subcutis and an atrophic vacuolar interface reaction as well as hyperkeratosis with colloid bodies. Melanophages were prominent in the dermis. These histopathologic findings were considered consistent with lupus erythematosus profundus (LEP) (Fig. 2).

Treatment with 60 mg oral prednisone daily was started, and skin lesions resolved within 2 weeks. Diffuse periocular lipoatrophy resulting in acquired enophthalmos of 3 mm with depression of the superior sulcus was observed. The enophthalmos stabilized by the third treatment week (Fig. 1). One month after initiation of treatment, during the corticosteroid taper, the patient developed acute diver- ticulitis and subsequently died of related complications.

There are several variations of lupus erythematosus. A relatively common variety is discoid lupus erythematosus (DLE), characterized by cutaneous plaque-like inflammation. In 1883, Kaposi (1) described a variant of DLE now known as LEP. It is characterized by extension to the subcutaneous fat and panniculitis with or without overlying DLE-associated skin changes. LEP can also precede, follow, or occur independently of discoid or systemic forms of lupus erythematosus. Although the disease is considered benign, it can cause significant morbidity, including disfigurement from lipoatrophy after resolution of the lesions. LEP lesions typically involve the scalp, cheeks, arms, shoulders, breast, buttocks, or thighs but rarely affect periorbital tissues (2).

Diagnosis of LEP is based on clinical and histologic findings. However, subcutaneous involvement, confirmed with biopsy, is necessary to establish the diagnosis. Although results are often normal, serologic analysis may show a positive ANA titer. Anti-dsDNA antibodies may be elevated (2). LEP is often associated with other autoimmune disorders such as Hashimoto’s thyroiditis, as seen in our patient.

Although there have been several reports of DLE lesions affecting the eyelids, periocular involvement in LEP is uncommon, occurring in only 2%–5% of patients (3). Patients may have periocular edema (4–7) or proptosis (5,8). There is one report of severe orbital involvement, which progressed to complete orbital infarction and melting (9).

The unusual orbital imaging findings include loss of the fat signal on T1 MRI, consistent with the histologic finding of loss of orbital fat, together with extensive inflammatory and fibrous infiltrate within the septa between fat lobules (Fig. 2). In our patient, this inflammation was apparent as intense enhancement on fat-suppressed postcontrast T1 MRI. During the period of inflammatory swelling, there was no enophthalmos. As the inflammatory infiltrate

![Image of histopathology](image_url)

**FIG. 2.** A. Histopathology of eyelid skin biopsy demonstrates atrophic epidermis, subtle vacuolar interface changes (arrowhead) with colloid bodies, and an infiltrate of lymphocytes in the dermis, where melanophages (arrow) are also conspicuous. B. Intracanal orbital fat biopsy demonstrates lymphoplasmacytic infiltration (arrow) and “hyalinization” of fibrous septae between adipocytes (arrowhead). C. Biopsy of lateral rectus muscle biopsy demonstrates perivascular lymphoplasmacytic infiltrate (arrow) (hematoxylin and eosin stain).
regressed with corticosteroid treatment, enophthalmos developed, most likely unveiling the preexisting fat atrophy that had been masked by orbital edema. We cannot exclude the possibility that systemic corticosteroid therapy contributed to fat atrophy, but no local corticosteroid therapy had been administered, and no fat atrophy was ever observed in the contralateral orbit or elsewhere. Despite pathologic abnormalities in the extraocular muscles on imaging and biopsy, the patient had normal extraocular motility during all stages of disease and treatment. Moreover, despite intense orbital inflammation, our patient reported no persistent pain.

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Bilateral Pseudohypopyon as a Presenting Feature of Recurrent Diffuse Large B-Cell Lymphoma

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Abstract: A 55-year-old man with Gaucher disease and B-cell lymphoma developed a white meniscus along the inferior portion of the anterior chamber of both eyes. In one eye, the meniscus was also temporal, reflecting the fact that he had just been lying on his left side. Aspiration of aqueous fluid confirmed that the meniscus was made up of lymphoma cells, indicating that it was a pseudohypopyon. (A true hypopyon is made up of reactive white blood cells.) Despite intensive chemotherapy, the patient expired within 14 weeks of the discovery of the pseudohypopyon. This is the first report of binocular pseudohypopyon confirmed as lymphomatous by flow cytometric immunophenotyping analysis in a patient with diffuse large B-cell lymphoma.

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A 55-year-old man with Gaucher disease and stage 4 diffuse large B-cell lymphoma was diagnosed with exertional dyspnea due to a large mediastinal mass. The staging workup revealed atypical lymphocytes in the cerebrospinal fluid (CSF) and bone marrow. Initial treatment consisted of 8 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) and 10 cycles of intrathecal methotrexate and cytarabine chemotherapy. Afterward, his disease was deemed to be in remission. Subsequent restaging investigations 2 and 4 months later revealed interval decrease in residual node size, and radiotherapy was not performed.

Six months after the initial diagnosis the patient was admitted to the hospital with progressive bilateral arm weakness and shooting pains in all 4 limbs. Differential diagnosis at the time included lymphomatous infiltration of peripheral nerves and roots, vincristine toxicity, and an acute demyelinating disorder. Intravenous immunoglobulin (IVlg) was administered for 2 days with minimal improvement in the patient’s symptoms.

During the hospital stay, the patient noticed that vision in both eyes would become cloudy upon forward and backward neck flexion. Full resolution of visual symptoms...
occurred rapidly after resuming an upright posture. He had no eye pain or photophobia.

Visual acuity was 20/20 in both eyes, pupillary responses were normal, and intraocular pressures were within normal ranges. On biomicroscopic examination, both irides appeared thickened and “boggy” and a 3+ fine cellular reaction was visible in both anterior chambers. There was an anterior chamber cream-colored meniscus inferiorly in the right eye and inferiorly and temporally in the left eye (Fig. 1). The explanation for the temporal component of the meniscus was that our examination was performed in the morning shortly after the patient had slept on his left side. When he was reexamined several hours later, the temporal component of the left eye meniscus had disappeared.

Anterior chamber paracentesis of the right eye removed 0.15 mL of aqueous, which revealed medium-large atypical lymphoid cells (Fig. 1, inset). Flow cytometry revealed a clonal population of B cells with the phenotype CD19+ (99.3%), CD5, CD23, CD10, FMC7, and lambda light chain restriction (98.5%). The phenotypic findings were consistent with B-cell lymphoma, indicating that the anterior chamber was a pseudohypopyon rather than a true hypopyon made up of reactive white blood cells. Cerebrospinal fluid, obtained by lumbar puncture that day, also revealed malignant lymphocytes.

The patient was treated with high-dose oral dexamethasone and hourly topical prednisolone drops. The hypopyon decreased in size initially but recurred after dexamethasone taper was attempted.

Two weeks later, the patient noticed binocular oblique diplopia. Examination disclosed a partial left third cranial nerve palsy. MRI of the brain and orbits did not reveal any abnormalities. CSF analysis again revealed cellular atypia and a monoclonal B-cell population consistent with lymphoma. He received fractionated X-irradiation to the eyes, orbits, and total brain, with a total dose of 20 Gy in 5 fractions over 5 days. Over the following month, the third cranial nerve palsy and hypopyon resolved.

Two months later, the patient was neuro-ophtalmologically normal. However, clonal B lymphocytes were found in a peripheral blood sample, and treatment with cisplatin, dexamethasone, and gemcitabine was started. He also received red blood cell and platelet transfusions over the following week for anemia and thrombocytopenia. One month later, he died, only 14 weeks after the discovery of the hypopyon.

“Pseudohypopyon” refers to an accumulation of neoplastic cells in the anterior chamber, whereas a true hypopyon is made up of reactive white blood cells. Pseudohypopyon may be seen with a variety of intraocular tumors, including lymphoma, leukemia, and retinoblastoma, and may persist despite corticosteroid treatment (1,2). Typically a pseudohypopyon will settle inferiorly, but layers may settle at different orientations depending on positioning, as occurred in our patient.

Our patient had Gaucher disease, which has a strong association with hematologic malignancy, including diffuse large B-cell lymphoma (3-5). Lymphoma is one of the classic uveitis masquerade syndromes, accounting for up to 1.6% of all patients with uveitis seen in one study at a tertiary ophthalmologic center (6). In an autopsy study of patients with lymphoma at the time of death, 6.7% of eyes were found to have uveal infiltrates (7). Lymphomatous involvement of the anterior chamber may arise either via hematogenous spread or a recurrence of preexisting anterior chamber cells that were suppressed but not eradicated by previous chemotherapy (8).

There are two distinct types of intraocular lymphoma: primary central nervous system (CNS) lymphoma (including primary intraocular lymphoma), and lymphoma that arises outside the CNS and metastasizes hematogenously, usually to the uveal tract. Ocular involvement is much less prevalent in lymphoma arising outside the CNS; isolated pseudohypopyon in such cases is rare (9). There are a few reports of patients in whom pseudohypopyon was among the presenting signs of a systemic lymphoma (2,10–15). Pseudohypopyon has also been reported as heralding a relapse among patients with systemic lymphoma in remission (10,16–19).

Bilateral lymphomatous pseudohypopyon is exceedingly rare. One case was reported in a patient with known cutaneous natural killer cell lymphoma and another in a patient with AIDS and non-Hodgkin lymphoma (18,20). Both of these presentations occurred late in the course of the disease, within 2 months of death. This is the only report of bilateral pseudohypopyon in a patient with diffuse large B-cell lymphoma confirmed by flow cytometric immunophenotyping analysis.

This case illustrates the importance of suspecting masquerade syndrome in patients with an atypical hypopyon and a history of previous hematologic malignancy. Diagnosis of pseudohypopyon may be confirmed with flow cytometric immunophenotyping of an anterior chamber aspirate. Anterior chamber involvement may be a presenting feature of recurrent lymphoma even in the absence of negative imaging and CSF examination results. Bilateral lymphomatous pseudohypopyon has only been reported in advanced disease and portends a poor prognosis.

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We thank Alan Connor, Ocular Oncology Clinic, Princess Margaret Hospital, Toronto, for taking the photograph featured in Figure 1. The patient featured in Figure 1 is deceased. Permission for the publication of this figure was provided by his wife.

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Horner Syndrome Associated With Contusion of the Longus Colli Muscle Simulating a Tumor

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Abstract: A 22-year-old man who was discovered unarousable after an accidental methadone overdose complained of worsening neck pain and left arm weakness over the next week. Examination disclosed a left Horner syndrome and a left brachial plexopathy. Imaging showed a left paraspinal mass adjacent to the sympathetic pathway at the fourth and fifth cervical vertebral levels with imaging features of a tumor. Biopsy was deferred. One month later, the imaging abnormality had nearly disappeared. In retrospect, it represented a contusion injury of the longus colli muscle, a finding not reported previously. Whether it caused the Horner syndrome or was merely a bystander in cervical neck trauma is uncertain. This abnormality should be recognized as a diagnostic confounder.

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A 22-year-old man was found unarousable with his neck hyperextended after an unintentional methadone overdose. During hospital admission, he reported left arm weakness and pain but was not thoroughly evaluated for these symptoms. One week later, he was admitted for worsening left neck and arm pain. Neurologic examination disclosed mild weakness of left shoulder extension and left elbow flexion and extension. There was hypesthesia over the left C5–C6 dermatomes and reduction of left triceps, biceps, and brachioradialis muscle stretch reflexes. Ophthalmic examination disclosed fluctuating mild left upper lid ptosis (1.5 mm at most), and pupils measuring 7 mm on the right and 5 mm on the left, both constricting normally to direct light. Topical ocular instillation of 0.5% apraclonidine reversed the anisocoria and produced left upper lid retraction. The clinical diagnoses were left brachial plexopathy and Horner syndrome. Although trauma was suspected, he underwent head and neck MRI.

Brain MRI was normal. Dissection protocol (no contrast) neck MRI revealed an unexpected soft tissue lesion in the left prevertebral space at the C4–C5 level that was isointense on T1 and hyperintense on T2 sequences (Fig. 1A–B). Postcontrast CT of the neck, performed 1 day later, showed mild swelling and enhancement at this site (Fig. 1C).

Our first impression was of a primary neural or sympathetic chain neoplasm such as schwannoma, neurofibroma, or paraganglioma. Mesenchymal neoplasms such as hemangioma, fibroma, or rhabdomyoma were also on the list. We acknowledged that the imaging abnormality did not appear large enough to have caused the brachial plexopathy, but we wondered if a poorly visualized component had infiltrated the plexus. However, no surgical intervention occurred pending further imaging.
One month later, neck MRI, this time performed with contrast material, revealed marked lessening of the signal abnormality but with mild patchy enhancement of the longus colli muscle (Fig. 2). In retrospect, the diagnosis was traumatic contusion of this muscle.

The diagnostic confusion in this case arose because imaging features of longus colli muscle contusion have not, to our knowledge, been described previously in neck trauma (1,2). In the paraspinal region at the level of C4 vertebra, the sympathetic pathway is surrounded by loose connective

FIG. 2. Neck MRI performed 4 weeks later. Precontrast T1 axial (A), T2 (B), and postcontrast T1 (C) MRI images show marked reduction in the swelling and T2 hyperintensity of the lesion, now clearly evident as being within the left longus colli muscle. The affected longus colli muscle (C, arrows) shows mild residual enhancement but is now almost equal in size to the corresponding muscle on the right (C, arrowhead).


tissue just posterior to the carotid sheath and anterior to the longus colli muscle (Fig. 3) (3). Whether contusive swelling of this muscle caused the Horner syndrome in our patient or was merely a bystander is unresolved. It could not, by itself, have caused the ipsilateral brachial plexopathy. We attribute the longus colli muscle contusion to stretch injury.

We report this case to highlight the imaging finding as a diagnostic confounder.

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Rehabilitation for Visual Disorders

Susanne Trauzettel-Klosinski, MD

Abstract: Rehabilitation for visual disorders demands thorough assessment of many components of vision and a tailored strategy of maximizing residual function. Magnification with optical or electronic aids and the use of eccentric fixation and specific reading training exercises are helpful techniques in patients with central scotomas. Visual exploration training is beneficial in patients with homonymous hemianopias.

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Many diseases of the eyes and visual pathways are associated with persisting visual deficits that require rehabilitation. There is an increasing demand for rehabilitation for these disorders (1,2), particularly in view of increased survival rates and prolonged life expectancy (3–5).

A precondition for successful rehabilitation is an exact assessment of visual impairments. The World Health Organization general classification of impairments, disabilities, and handicaps (ICIDH) (6), later modified to the International Classification of Functioning, Disability and Health (7) can be well adapted to the visual system (Fig. 1). It considers 3 fields: 1) impairment, which assesses the pathologic condition and the function on the basis of the involved organ(s); 2) disability or activity limitation, which indicates the difficulties caused by the impairment; and 3) handicap or participation restriction, which stands for the resulting problems in the patient’s environment.

DIAGNOSTIC PROCEDURES IN VISUAL REHABILITATION

Determination of visual acuity for distance and near viewing, refractive error, and accommodative amplitude and the optimal prescription of glasses come first. Visual fields must also be determined accurately, because defects involving the central field limit the size of the reading visual field (<5° from fixation). Visual field defects in the periphery can lead to orientation difficulties. To detect small defects, one must use a dense grid or a thorough manual strategy. If perimetry cannot be performed with a standardized instrument, bedside confrontation fields are useful to detect large field defects, especially hemianopias. Tangent screen campimetry may also be used.

Contrast sensitivity testing is also critical. Contrast can be improved by optimal illumination or by marking the environment with special high-contrast landmarks.

READING

In modern society, adults spend approximately 2.5 hours per day reading, especially during work activities. Approximately 90% of all jobs require dealing with written material (8). To read newspaper print at a distance of 25 cm, a visual acuity of at least 20/50 (0.4) is necessary. Whereas visual acuity testing depends on recognizing only 1 optotype at a time, reading demands a simultaneous overview of a group of letters. The minimum reading visual field (9) is an area of approximately 2° to the right and left of fixation and corresponds approximately to the “visual span” or “word recognition span” (10,11). Within this area, letters are seen clearly. Figure 2A shows the functional and morphologic data related to a fundus image. The “minimum reading visual field” (turquoise oval) corresponds more or less to the area of the fovea (green oval).

Parafoveal information processing can extend the total “perceptual span” (“reading visual field”) during 1 fixation in the reading direction up to 15 letters (11,12) (Fig. 2B, red oval). This extended perceptual span provides information about word length, capitalization, and word shape, and offers a preview benefit, which is useful in guiding the next saccade to the appropriate landing position. For fluent reading, a total perceptual span of 5° (15 letters) to the right and 1.3–2° (4–6 letters) to the left of fixation is necessary, as shown in window experiments in...
normal subjects (12) and in patients with homonymous hemianopias (13). The perceptual span is a dynamic parameter that is also influenced by top-down mechanisms, such as visual attention.

During reading, the holding positions of the eyes between saccades have a mean duration of 250 ms (14). In normal subjects, eye movement recordings show a typical staircase pattern, a sequence of saccades and holding positions (Fig. 8A). Information processing occurs during the holding positions. The retinal area used for reading comprises only a few square millimeters but is highly magnified in the visual cortex (15). The central 10° diameter of the visual field, which accounts for approximately 2% of the total visual field, is mapped onto nearly 50% of the primary visual cortex (16,17).

**ASSESSING READING ABILITY IN LOW VISION PATIENTS**

**Refractive Error**
Exact determination of refractive error is necessary in low vision patients. If visual acuity is ≤20/200, the measurement should be performed by ETDRS charts because they allow more steps in the low vision range by reducing the distance. Measuring near visual acuity and range of accommodation are also important here.

**Magnification**
Assessing whether magnification would be helpful is an important step. The smallest print size that can be read fluently corresponds to the magnification need. Even though there is a reciprocal mathematical relationship between visual acuity and magnification need, in reality there is often a discrepancy.

**Reading Speed**
Reading speed should be determined by having the patient read a paragraph of text aloud. A whole paragraph of text is preferable to a single sentence for more accurate speed measurement and judgment of fluency and mistakes. For this test, a newly developed set of equivalent texts in different languages is available (18, http://www.amd-read.net).

**Fixation Behavior**
Knowledge of fixation behavior is helpful if discrepancies between good visual acuity and impaired reading performance arise (as in ring scotomas, see below). Clinical methods of judging fixation are 1) determination of the blind spot in perimetry (Fig. 3C); 2) sighting the position of the corneal reflexes when the patient looks at the examiner; and 3) noting the fixation locus and motion of the eye during direct ophthalmoscopy. Further methods are fixation photography and fixation behavior determined with the scanning laser ophthalmoscope (SLO) (Fig. 4).

**Parafoveal Contrast Sensitivity Testing**
This testing provides valuable information on parafoveal deficits (19,20), which can precede central visual loss (20).

**Eye Movements**
Recording of eye movements during reading is a valuable method of showing ocular motor behavior during reading.
FIG. 2. A. Reading-relevant morphologic and functional data on a fundus image. Visual acuity (yellow) decreases rapidly with increasing eccentricity, as does cone density (dark blue). The proportions of the foveola (1°, green circle) and the fovea (5° diameter, green oval) determine the minimum reading visual field (turquoise oval) of 2° to the right and left of fixation and 1° above and below fixation. B. The data in A are related to a reading text. Because of the visual acuity curve (yellow), only in the minimum reading visual field (turquoise oval) can the text be perceived clearly. The total perceptual span (red oval) can be extended up to 5° (or 15 letters) in the reading direction by parafoveal information processing. (Modified from References 22 and 47).
Central Scotomas

Patients who have central scotomas that cover the reading visual field can learn to use eccentric fixation (21) in an intact area of the visual field at the margin of the scotoma (22–24). The new fixation locus becomes the new center of the visual field (25,26). This eccentric fixation locus is called the “preferred retinal locus” (PRL), even though patients often use more than 1 eccentric locus. The eccentric retinal area used for reading does not have sufficient resolution to read normal newspaper print, so that the ability to read can be regained only by magnifying the text (Fig. 3). Eccentric fixation plus magnification of the text is the basis for the effectiveness of magnifying visual aids in patients with a central scotoma (27).

The shift of the scotoma toward the upper visual field theoretically represents the most favorable situation for reading. The line of text becomes free for reading and the lower visual field remains free for spatial orientation on the page. However, not all patients show this favorable fixation behavior. Some 20%–50% of patients shift the central scotoma to the right or left of the normal fovea (23,27–29). It is hard to explain why such an unfavorable fixation locus would be chosen. However, apart from the resolution at a certain eccentricity, sustained focal attention, which facilitates stimulus discrimination (19,30,31), influences the choice of a PRL location. Patients with good attentional capabilities in the lower visual field install their fixation locus below the scotoma. If attentional capabilities are reduced in the lower visual field, patients prefer a fixation locus to the left or right of the scotoma (19,32,33).

Patients who have established an eccentric fixation locus can regain reading ability by text magnification. The spectrum of magnifying visual aids includes handheld magnifiers, stand magnifiers, simple high-plus spectacles, and telescopic spectacles. Handheld and stand magnifiers have the advantage of a comfortable working distance. When magnifying spectacles are used, the text has to be moved much closer, especially when simple
high-plus spectacles are used. Telescopic magnifying spectacles allow a longer viewing distance, but they are cosmetically unfavorable. In patients with a magnification requirement of more than 8-fold, who have no experience with optical magnification, an electronic reading device, such as a closed circuit television (CCTV) monitor, should usually be chosen. It is important to provide sufficient illumination without glare or ultraviolet or infrared light (cold light source). It is helpful to be able to vary the brightness, which can be achieved by a simple dimmer switch. For far distance viewing, handheld telescopes are useful.

The success rate of magnifying visual aids for reading is high. In a cohort of 763 patients in our low vision clinic, only 13% were able to read newspaper print before consultation; 90% were able to do so afterwards. Patients with a central scotoma (n = 293) showed a success rate of 94%. Those with age-related macular degeneration (AMD) (n = 191) showed a success rate of 94% (34), confirmed in a recent study with 835 patients with AMD (35).

Training in reading involves proper handling of the visual aids, reading exercises with the aim of enlarging the perceptual span, optimizing eye movements (36), and learning to use the optimal retinal locus. Concerning this last component, several studies have reported positive results (37,38), but there is considerable controversy about criteria and methods for choosing the optimal area (39).

**Ring Scotomas**

These defects may easily remain undetected because visual acuity can be good. However, a discrepancy between good visual acuity and impaired reading performance often indicates a ring scotoma. The central seeing island may be too small to include a sufficient number of letters for fluent reading (Fig. 5, 5.2, 5.4, 5.8). If patients learn eccentric fixation for reading magnified texts, they can regain reading ability.

**Constricted Fields**

In degenerative retinal diseases and in the late stage of glaucoma, visual fields are often constricted (Fig. 5, 5.3 and 5.9). The central seeing island may be too small for reading, and no peripheral visual field area is available. Reduction of letter size with contrast enhancement may be helpful. When the constriction limits the field to less than 30°, orientation and mobility will be impaired.

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*FIG. 4. Fixation of a target and of a line of text observed with the scanning laser ophthalmoscope in a normal subject (A–B) and in a patient with a central scotoma due to Stargardt’s disease (C–D). (The text is seen as upside down only for the examiner; it appears upright to the patient.) The patient can read the text with the eccentric retinal locus and 2.5-fold magnification.*
### CHIASMAL DISORDERS

In patients with bitemporal hemianopia, the limited temporal fields cause orientation problems. Depth perception may be impaired, which leads to difficulties with near distance tasks such as sewing, threading needles, or using precision instruments. In these cases, convergence causes crossing of the 2 blind temporal hemifields, resulting in a completely blind triangular area posterior to fixation (40).

**Hemifield Slide Phenomenon**

Another problem is the hemifield slide phenomenon (Fig. 6), which results from the lack of a normal overlap of the nasal visual fields and which prevents fusion. Therefore, preexisting phorias easily develop into tropias. In cases of preexisting esophoria or intermittent esotropia, patients will experience a separation of the nasal hemifields, causing a blind area in the center of the field. Patients with preexisting exophoria or intermittent exotropia will have an overlap of the 2 hemifields, and patients with preexisting hyperdeviations will experience a vertical separation of the images crossing the vertical meridian (40). The hemifield slide phenomenon can be especially disabling in reading long numbers in tables and bank statements.

Patients must be made aware of the hemifield slide phenomenon to guard against misinterpretations of reading material. Monocular reading can be helpful in such cases. The use of a ruler can be a valuable aid to improve navigation on the page.

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### Table: Visual Field Defects

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Scotoma type</th>
<th>30° Visual field</th>
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<tbody>
<tr>
<td>Maculopathies</td>
<td>1 central</td>
<td>1</td>
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<tr>
<td></td>
<td>2 ring</td>
<td>2</td>
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<tr>
<td>Peripheral retinal degeneration</td>
<td>3 constricted</td>
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<td>Optic neuropathies</td>
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<td></td>
<td>9 constricted</td>
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<tr>
<td>Bilateral occipital lesions</td>
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<tr>
<td></td>
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<td></td>
<td>11 bilateral homonymous</td>
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<td></td>
<td>with macular sparing</td>
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**FIG. 5.** The principal visual field defects in retinal, optic nerve, and bilateral occipital lobe lesions. The visual rehabilitative approach is based on the functional effects of the field defect independent of its origin.
Retrochiasmal Disorders

In retrochiasmal lesions, the visual field defect is homonymous, sometimes limited to a quadrant. It may spare or split the macular (fixational) region. When the lesion spares the occipital pole, macular sparing of 2–5° in the blind hemifield along the 0° meridian often occurs (16,17,41,42). If the occipital pole is spared, the visual field will be constricted with defects respecting the vertical midline and showing a “step” at the vertical midline (Fig. 5, 5.11). An isolated lesion of the occipital pole causes a small paracentral homonymous hemianopic defect. Bilateral occipital pole lesions may produce binocular central scotomas (Fig. 5.10).

Visual rehabilitation is conducted along the guidelines described earlier for central scotomas and constricted fields, except that the problem may be even more challenging as the defects are always binocular.

Retrochiasmal lesions may be associated with traumatic brain injury (TBI), an important cause of disability (43–45). TBI often includes perceptual disorders, which are frequently overlooked (46). Their rehabilitation requires a multidisciplinary approach.

Reading With Homonymous Hemianopia

When the field center is involved (“macular splitting”), homonymous hemianopia causes severe reading problems because half of the reading visual field is missing (Fig. 7A). In “macular sparing,” the reading visual field may be preserved and reading can be normal (Fig. 7B). Paracentral homonymous scotomas typically cause severe problems with reading because they obscure half of the reading visual field (Fig. 7C). These small paracentral scotomas are often overlooked in automated perimetry if the grid of the test program is not dense enough.

The severity of the reading problem in homonymous hemianopia is also influenced by the side of the defect in relation to the reading direction. In left-to-right readers, a right homonymous hemianopia is extremely impairing because the patient cannot see the oncoming groups of letters or words (Fig. 8C) (13). On the other hand, a patient with left homonymous hemianopia gets through the line quite easily but has difficulties finding the beginning of the next line (Fig. 8B).

Eccentric fixation may help some patients with macular splitting (Fig. 9). The use of eccentric fixation (Fig. 9A) causes a little sacrifice of visual acuity but creates an extended perceptual span that is crucial for fluent reading (Fig. 9B). Eccentric fixation causes a shift of the field defect toward the hemianopic side in conventional perimetry (Fig. 10B), which can be misinterpreted as improvement of the visual field. This process indicates high cortical plasticity, because the new eccentric fixation locus is used not only as the new center of the visual field, but also as the new center of the coordinates of the reading eye movements, which means a shift of the sensory and motor reference (47). Patients spontaneously develop unstable asymmetric fixational eye movements with saccades toward the hemianopic side (Fig. 10A). This phenomenon also leads to a shift of the vertical field border in conventional perimetry (Fig. 10B).

Rehabilitation of the Hemianopic Reading Disorder

Orientation on the page can be improved by visual and tactile tools such as a ruler or a forefinger, especially in guiding patients with left homonymous hemianopias in finding the beginning of the next line of text. Another approach is turning the text to a vertical or diagonal orientation, but this technique has never been tested in a large patient group. Training in predictive saccades can be beneficial in those with left homonymous hemianopias. Such saccades improve their ability to find the beginning of the next line of text. Scrolled text training programs have been shown to be effective in this regard (48–50).

Hemianopic Orientation Disorder

Patients with homonymous hemianopias are severely impaired in regard to spatial orientation. However, many spontaneously develop a beneficial compensation strategy: exploratory saccades toward the hemianopic side for better usage of their field of gaze.
This spontaneous compensation strategy can be supported and improved by saccadic training (see below). Fig. 10C shows the shift of the field defect by saccades in a natural scene. In conventional perimetry, this behavior shifts the field defect to the blind side (51), a pattern that can be misinterpreted as an improvement in the visual field (compare Fig. 10B–C).

In saccadic search paradigms, a development of saccadic strategies can be observed. In early stages, patients often use a staircase pattern of saccades to find the target (Fig. 8B) and later show overshoot as a predictive strategy (52).

**Optical Devices**

Most patients are confused by the double images and disturbances in spatial orientation caused by optical devices used in an attempt to improve vision in homonymous hemianopia. Binocular sector prisms cause a relocation of the field or a shift of the position of the field loss (53). Although binocular prisms are not effective in treating...
hemianopia, they have been shown to be beneficial in patients with hemispatial neglect (54). Monocular prisms and mirrors have been used to shift the image of the blind hemifield toward the normal hemifield (55). Unfortunately, these devices usually cause diplopia and confusion. Creating confusion is intentional, because it induces an eye or head movement toward the blind side. However, the diplopia in the central visual field is described as very unpleasant (55). Even so, Hedges et al (51) reported a benefit in 20% of their patients. Monocular sector prisms placed across the whole width of the lens, but only in the peripheral field, have been reported to be beneficial by expanding the field without causing central diplopia. In 1 study (56), 47% of the patients were still wearing the peripheral prisms after 12 months. However, there was no control group and no control treatment in that study. Optical aids may be helpful in a few patients, but these interventions cannot be generally recommended.

Training to Improve the Hemianopic Orientation Disorder

In evaluating the many programs that allege success, the following issues should be considered: 1) spontaneous recovery must be ruled out, especially in the first weeks after the neurologic insult (spontaneous recovery normally does not occur after 6 months) (57,58); 2) a control group is essential; 3) the methods used to measure improvement must be reliable; and 4) the improvement must be durable.

Spontaneous recovery may occur in 7%–53% of patients, depending on the definition of improvement and the cohort of observed patients (57,59,60). Hier et al (61) reported an improvement of 60%–80%, probably due to compensatory strategies rather than a real change in the visual fields.

The main problem with conventional perimetry in assessing improvement is insufficient fixation control. The vertical visual field border depends essentially on the quality of fixation. If fixation is unstable or eccentric, the visual field border is shifted toward the hemianopic side in conventional perimetry, which can mimic an improvement of the visual field defect (Figs. 9 and 10). This phenomenon has been shown clearly with fundus-controlled perimetry by SLO (41).

Restitution Training Versus Compensation Training

There are 2 different approaches in visual rehabilitation for homonymous hemianopia: restoration of lost visual field ("restitution training") and compensation strategies for visual field loss ("compensation training"). In 2 studies of restitution training, the stimulation has been at the border of the hemianopic field (62,63). Here the risk is stray light and especially eye movements toward the stimulus. The authors of the first study (62) reported an improvement of the visual field of up to 40°, but these results could not be confirmed by Balliet et al. (64). In a later study (63), "visual restitution therapy" (VRT) was performed by presenting perimetric targets above the threshold along the visual field border. The authors described an extension of the seeing hemifield by approximately 5°. Our laboratory performed a SLO study before and after VRT using fundus perimetry with simultaneous fixation control and a grid of 0.5° spatial resolution horizontally and 1° vertically in the 10° visual field (65). Neither that study nor a study with conventional perimetry (66) could show any improvement in the visual field.

Stimulation of the visual field using flickering letters and other targets in a more peripheral area (at 10°) in the visual field was reported to normalize contrast sensitivity in the blind field in 2 patients (67). To examine this effect, our laboratory used a flickering letter stimulation at 22°
eccentricity (peripheral to the blind spot), a location that reduces the risk of eye movements toward the stimulus (68). No changes of the visual fields were observed.

The reported effects of the 3 restitution studies (62,63,67) should be distinguished from the “blindsight” phenomenon, which is an unconscious perception of visual stimuli via the superior colliculus to extrastriate regions without activation of striate visual cortex or V1 (69,70). Whether blindsight training can improve this kind of residual vision to a level that is relevant for everyday life is unresolved (71).

The aim of compensation training is to enlarge the field of gaze by frequent eye movements into the blind hemifield and by shifting attention to the blind side. Such training has been reported to be effective in improving the use of the blind hemifield (50,72–74). A multichannel approach with additional acoustic stimuli was also reported to be beneficial (75). However, these earlier studies were done without a control group. Therefore, our laboratory performed a randomized controlled trial with an explorative saccade training based on a search task, which clearly showed the beneficial effect compared with a control group (68). Reaction times for a digit search task and a natural search task decreased, and exploration of natural scenes was improved. In contrast, the control group, which received visual field stimulation training (flickering letter at 22° eccentricity), a form of restitution training, did not show a change in exploration behavior. Visual fields remained unchanged, a result indicating that stimulation in a more eccentric visual field area does not have an effect either.

Saccadic training is recommended for patients with hemianopias to improve the usage of their field of gaze and thereby their orientation, mobility, independence, and quality of life (68; http://www.uak.medizin.uni-tuebingen.de/sba/).

REFERENCES


An Overweight Young Woman With New Headache and Normal-Appearing Optic Discs

A 25-year-old overweight nulliparous woman complains of headache for the past 6 months that is worsening in the past month. She has no visual complaints. Past medical history and review of systems are unremarkable. She acknowledges a weight gain of 20 pounds in the past year. A neurologist found no abnormalities on examination 2 weeks ago. Results of brain MRI are normal. Your neuro-ophthalmologic examination is normal except for scattered high threshold points and mean deviations of -3 dB on a 24-2 Humphrey visual field protocol. The optic discs appear normal although there are no spontaneous venous pulsations.

Question 1: What is your diagnosis?

Dr. Digre:

There are many questions that I would ask. For example, is there a family history of headache or migraine? A positive family history suggests that this is a headache-prone individual and that this headache may be migraine. What is the life history of the patient with headache? Did she have headaches when she was younger, and have they only recently worsened? Does she have chronic headache with acute attacks? What accompanies the headache? Are photophobia, phonophobia, nausea, vomiting, and worsening with activity present? Does she take herbal medicines or ointments containing vitamin A? Is there depression or menstrual irregularity? Does she have other symptoms of fatigue or daytime sleepiness?

The history must also be searched for reasons to have a new chronic daily headache with “normal imaging,” including high intracranial pressure (ICP), Chiari malformation, and chronic parasanal sinus disease. These are features easily missed on imaging or go unreported. I inquire about hypothyroidism, anemia, metabolic disorders that can be associated with chronic headache, and factors that change episodic headache into chronic headache, such as viral illness, head injury, overuse of medications, use of illicit drugs, depression, and sexual, emotional, or physical abuse (1). Obesity alone has been associated with the conversion from acute to chronic headache (2).

In any overweight patient, I am especially interested in manifestations of increased ICP, such as pulse-synchronous tinnitus, visual symptoms, postural exacerbation of headache, worsening of headache at night, and neck or interscapular pain (3). Wang et al (4) found that the most helpful historical features in identifying increased ICP were obesity, blurred vision, seizure, and pulsatile tinnitus.

I would look for subtle signs of papilledema. Is there a physiologic optic disc cup? The absence of spontaneous venous pulsations does not always mean elevated ICP (5). I also look for subtle esophoria, which can accompany increased ICP. I might attribute the visual field result, which here showed scattered high threshold spots with a 3dB mean deviation, to having a headache during the test (6).

I would carefully review her “normal” MRI scan, looking for features suggesting increased ICP that may not be reported by the radiologist, such as empty sella, dilated
optic nerve sheaths, narrowing of the transverse venous sinus, and tonsillar ectopia (7,8).

The most common cause of headache in this patient would be migraine or another primary headache disorder. My diagnosis would depend on whether I can elicit features contributing to a primary headache disorder or whether I must seek an alternative explanation.

Dr. Friedman:

I cannot make a diagnosis without knowing more about the characteristics of the headache and other aspects of the patient’s history. Is there a prior history of headaches? If so, were the previous headaches like this one? Is this a daily headache? If so, has it been daily since onset? What are the character, location, and level of disability produced by this headache? For example, does it awaken her from sleep? Is it constant or intermittent? If intermittent, what is its duration and frequency? Are there associated symptoms, such as photophobia, phonophobia, nausea, vomiting, osmophobia, worsening with activity, or pulsatile tinnitus? What medications is she taking, including those that are obtained over the counter? How much caffeine does she consume and with what consistency? Is there a family history of headache?

Question 2: The patient’s headache is of moderate grade, not particularly disabling, slightly relieved by acetaminophen, aspirin, or nonsteroidal anti-inflammatory drugs (NSAIDS). She takes no other medications or supplements. There are no other pertinent symptoms. She cannot identify provocative or ameliorative features of the headache. There is no family history of headache. Your review of the brain MRI confirms that it is entirely normal. What would you do?

Dr. Digre:

This patient would seem to have a “new headache” and therefore warrant further workup. However, most new headaches in patients with normal neurologic examinations and normal MRIs are “primary,” that is, without identifiable “structural” cause (9). From its description as moderate in severity and attenuated by simple analgesics, her headache is probably due to tension. A headache diary may be helpful to chart provocative and ameliorating factors (10). If the patient wished, I would treat with a prophylactic medication such as low-dose nortriptyline (11) or topiramate (12), which has weight-losing properties. I would warn about rebound headaches from medication overuse, and I would reexamine her to assess effectiveness.

If the headache were to become more debilitating or the patient developed other symptoms, I would consider further workup, including a complete blood count to rule out anemia, a thyroid hormone test to rule out hyperthyroidism or hypothyroidism, and erythrocyte sedimentation rate to rule out autoimmune disease. If results of these are negative, I would consider performing a lumbar puncture to rule out idiopathic intracranial hypertension or viral meningitis (13,14).

Dr. Friedman:

My review of the “normal” MRI assumes that there are good enough views to see subtle changes associated with increased ICP, such as empty sella, dilated optic nerve sheaths, flattening of the posterior sclera, or Chiari malformation (8). If she is taking over-the-counter analgesics frequently, there may be a component of medication overuse (“analgesic rebound”) headache. I would ask about caffeine use, aspartame intake, and sleep habits/snoring that might suggest obstructive sleep apnea. I would review current medication use to be sure that she did not recently start taking something that could cause headaches.

I would recommend starting a prophylactic medication for chronic tension-type headache. Because she is obese, I would discuss weight loss because obesity is a risk factor for chronic daily headache. As she has recently gained 20 pounds, my first choice would be topiramate, because it may produce weight loss. My second choice would be a tricyclic antidepressant (amitriptyline or nortriptyline), but such medication tends to cause weight gain. Perhaps a low dose would be well tolerated. Because I consider the visual field to be abnormal, I would reexamine her in 4–6 weeks and repeat the test.

Question 3: The patient’s neurologist begins treatment with topiramate, but at 200 mg/day; there is no reduction in headache. The patient returns to you, having read that idiopathic intracranial hypertension (pseudotumor cerebri) can be a cause of headache, especially in overweight young women. Your findings have not changed. There is no optic disc edema. She asks if a spinal tap is indicated. Is it?

Dr. Digre:

Because my suspicion of raised ICP is low in this patient, I would first push hard for a trial of symptomatic treatment. If it were unsuccessful, and she insisted, I would arrange for a spinal tap.

Most patients with chronic headaches have chronic migraine together with exacerbating factors such as obesity, frequent medication overuse, or depression (15). Primary headache disorders, including migraine alone, do not elevate ICP (16,17).
Chronic headache may be caused by increased ICP. However, this patient does not have any symptoms to suggest that cause. I would review the history and suggest continued treatment with topiramate to see if it will be successful later or try a different prophylactic headache medicine. Prophylactic medicines may take a long time to relieve headache.

Women who have increased ICP (measured by lumbar puncture) as the cause of chronic headache usually have at least 1 clinical or imaging clue to the presence of elevated ICP. Marcelis and Silberstein (19) described 10 adults with increased ICP (opening pressure 230–450 mm H$_2$O) and no papilledema as determined by an ophthalmologist. In the 7 patients who underwent fluorescein angiography, results were always normal. All 10 patients were followed for up to 30 months without the development of papilledema. The authors suggested that obese women with chronic daily headaches that are poorly responsive to medical therapy who have tinnitus and an empty sella on imaging should undergo a lumbar puncture to determine whether intracranial hypertension is present. Wang et al (4) reported 25 patients who had headache, no papilledema (in the 17 who underwent ophthalmoscopy), and opening pressures of 240 mm H$_2$O or greater on at least 1 lumbar puncture. The patients with increased pressure were overweight, complained of blurred vision, or had seizures.

Other investigators have found that headache and high ICP can exist in overweight women without an obvious clinical clue. In a large headache clinic population, Mathew et al (20) found that 12 patients (15%) with chronic daily refractory headache had opening pressures of up to 450 mm H$_2$O. Vieira et al (21) reported that 6 (10%) patients with chronic migraine had documented increased ICP. All had a body mass index (BMI) of 25 kg/m$^2$. Among patients with tension headache or chronic migraine, Bono et al (22,23) found that if magnetic resonance venography (MRV) showed dural venous sinus stenosis, increased ICP was likely. Torbey et al (24) reported that ICP monitoring of 10 patients with intractable headaches disclosed B-waves and that 9 of 10 patients had plateau waves indicating increased ICP.

I am concerned that measurements of opening pressure in these reports may have overestimated its level, particularly if the patient was not relaxed, the legs were not outstretched, or the pressure was taken with the patient sitting up. A slight Valsalva maneuver can elevate opening pressure (25).

**Dr. Friedman:**

I agree with the performance of a lumbar puncture in this patient and I will explain why.

I acknowledge that idiopathic intracranial hypertension (IIH) without papilledema is very rare although the diagnostic criteria allow for this “variant” of IIH. Digre et al (26) found that only 20 (5.7%) of patients with IIH in their practice lacked papilledema. But it happens.

IIH should be considered as a secondary cause of headache in anyone with new daily persistent headache, chronic daily headache, or frequent headaches that are treatment resistant or worsening headaches in a patient with a previously stable episodic headache disorder (13). Nonetheless, having performed ophthalmoscopy on every new patient that I have evaluated for headache over the past 20 years, I have never found papilledema in any of them.

The concept of IIH without papilledema in patients with refractory headaches was first reported by headache specialists. Among 85 patients with refractory transformed migraine at the Houston Headache Clinic who had a lumbar puncture to exclude chronic meningitis or increased ICP, elevated opening pressures (270–450 mm H$_2$O) were found in 12 (14%) (20). Acetazolamide or furosemide was added to the antimigraine therapy, leading to “a reduction in the number of days with severe headache, reduced consumption of abortive agents, and overall improvement of quality of life” (20). Opening pressures on lumbar punctures performed 3–20 months later ranged from 210 to 360 mm H$_2$O. Statistical analysis was not performed.

A larger case-control study compared clinical features in patients with IIH with and without elevated opening pressures (4). IIH without papilledema was diagnosed in 25 headache patients based on an opening pressure of at least 200 mm H$_2$O on 2 occasions. Sixty control subjects consisted of those with intractable chronic daily headache and a normal opening pressure. Statistical predictors of high ICP were obesity, history of seizure, blurred vision, and pulsatile tinnitus (highest predictive factor). Those with high opening pressure were considerably more overweight than those without it. The headache profiles were similar in both groups. Analgesic overuse was common (80%) in both groups.

In that study, the patients in both groups were treated with serial lumbar punctures. A 56% improvement in headache occurred in these patients, but the response in the control group was not reported. There was a similar response in both groups to dihydroergotamine and diuretics. Five patients with elevated opening pressures underwent shunt surgery (2 had 1 operation, 2 had 3 operations, and 1 had 4 operations). Three of the 5 shunted patients consistently reported improvement in headache. Diuretics and corticosteroids conferred no additional benefit in shunted patients.

Another study compared clinical features in headache patients with and without papilledema (26). BMI and age at onset were not significantly different between the 2 groups. Obesity (mean BMI 34.5 kg/m$^2$) was present in 18 (90%) of the patients without papilledema. Patients with papilledema presented within 1 year of symptom onset, whereas patients without papilledema presented an average of 5 years after symptom onset. Patients without papilledema had headaches with migrainous features, and these patients were less likely than patients with papilledema to experience transient visual obscurations, pulsatile
tinnitus, diplopia, or visual loss. If visual field loss was present, it was usually nonorganic. Headache response to therapy was no different in the 2 groups, although 3 of 4 patients without papilledema had improvement in their headaches with shunting. Most patients without papilledema had spontaneous optic disc venous pulsations, consistent with the fact that their cerebrospinal fluid (CSF) opening pressures were lower (mean 312 mm H₂O) than those in patients with papilledema (mean 330 mm H₂O, \( P < 0.01 \)).

Headache treatment in both groups consisted of diuretics (usually acetazolamide) with or without other migraine medications.

A Swedish study (27) compared opening pressure and other parameters in 10 patients with IIH with papilledema and 10 consecutive patients with chronic tension-type headache. Nine patients in each group were women. As in the study by Digre et al (26), the mean BMI was the same (31 kg/m²) in both groups. All patients with IIH had opening pressures greater than 350 mm H₂O. The patients with chronic tension-type headache had opening pressures between 180 and 250 mm H₂O and 50% were between 200 and 250 mm H₂O.

I have identified at most 3 patients (all women) whom I believe to have had IIH without papilledema or any imaging abnormalities. Two were slim with no risk factors for IIH, and 1 had only intermittent symptoms at intervals of weeks to months between “bouts” of severe headaches that only responded to lumbar puncture. Although this patient lacks papilledema, the change in her baseline headache pattern is a “red flag” for a secondary cause of headache. Although uncommon, IIH without papilledema is a diagnostic consideration and I would perform a spinal tap.

There are many factors to consider in regard to lumbar puncture technique. I generally perform a tap in an obese patient in the sitting position and move the patient to the lateral decubitus position to measure opening pressure, using an anxiolytic drug if needed. If the patient is morbidly obese, I would have a member of the interventional radiology staff perform the puncture under fluoroscopic guidance.

A possible confounder is the use of sedatives during the procedure. Lumbar punctures are performed in our radiology department, often under conscious sedation. The potential hypercapnia from hypoventilation during sedation may cause artificially high opening pressure measurements. However, a very anxious patient may cry or perform a Valsalva maneuver and raise CSF pressure. Neville and Egan (25) found that patients could easily increase their opening pressure during a lumbar puncture by 150 mm H₂O or more with a Valsalva maneuver. It is hard to convince patients to have another spinal tap if they have a bad experience the first time.

**Question 4:** A lumbar puncture is performed under fluoroscopy without sedation. You are told that the opening pressure, measured in the lateral decubitus position with the patient relaxed, is 240 mm H₂O. The cerebrospinal fluid constituents are normal. After the lumbar puncture, the patient experiences a new, more severe headache than she had had before the spinal tap, but it is postural and disappears after 10 days, leaving her with the previous chronic headache. Is this opening pressure high enough to warrant a diagnosis of idiopathic intracranial hypertension? If not, how high must the opening pressure be to warrant that diagnosis? How would you manage this patient?

**Dr. Digre:**

This patient has no symptoms of high ICP, no signs of high ICP, and no relief when her pressure is lowered. She does not have IIH.

What is normal opening pressure? Although the normal range is often said to be between 100 and 180–200 mm H₂O, studies (28,29) show that there is an even wider variation of “normal.” Continuous pressure measurements show that normal individuals may have pressures that fluctuate up to 250 mm H₂O (30,31). In a series of 242 adults (55% women) undergoing lumbar pressure, Whiteley et al (32) demonstrated a mean opening pressure of 170 mm H₂O with a range from 80 to 280 mm H₂O. They calculated the 95% range to be 100 to 250 mm H₂O. Although the opening pressure increased with BMI, the increase was not clinically significant. They cautioned that the diagnosis of increased ICP or IIH would have to be made cautiously if the opening pressure were not elevated well above these values. On the other hand, opening pressures between 200 and 250 mm H₂O have been found in patients with IIH and papilledema (7, 30).

I have diagnosed IIH in patients without papilledema and published the results in 20 such cases, comparing them with 20 patients with IIH and papilledema (26). We found that the symptoms and signs were similar in the 2 groups except that papilledema and sixth cranial nerve palsy were more frequent in the patients with IIH. IIH without papilledema constitutes about 5% of our patients with IIH. Others (20,33) have found that IIH without papilledema constitutes up to 20% of patients with chronic daily headache and that such patients benefit from treatment with acetazolamide and an antimigraine drug (4). Even modest weight loss can be helpful (34,35).
This patient has a new daily headache, which could be of the chronic tension or “new daily persistent headache” type (36). Treatment of either of these headache types is challenging. New daily persistent headache is often associated with a previous viral infection. Treatment has been difficult and often resistant to all efforts (37).

I suggest that the patient keep a diary of exacerbating factors, and I would treat with a tricyclic antidepressant (amitriptyline or nortriptyline), a calcium channel blocker (verapamil), or an anticonvulsant (topiramate and valproate are Food and Drug Administration–approved for headache therapy; levetiracetam, gabapentin, and pregabalin would be off-label uses). Tizanidine and botulinum toxin therapy are also considerations for treatment of her headaches (38,39).

I would also look for (and possibly treat) a sleep disturbance, depression, or anxiety. Weight loss would also be helpful (39). I would continue to follow her for other findings.

Dr. Friedman:
The opening pressure in this patient falls into the “gray zone,” not clearly meeting the criteria for IIH but above the level that is considered unequivocally normal (30). Although the response to lumbar puncture is not diagnostic of IIH, improvement in her headache after the lumbar puncture might lend some credence to that diagnosis. The development of a postlumbar puncture headache might cloud the clinical picture but should resolve within a week.

At this point, I am still not convinced that the patient has IIH and would proceed with a sleep study to make sure that she does not have obstructive sleep apnea. A higher dose of topiramate may be required or she may respond to a different prophylactic medication. Repeating the lumbar puncture is also an option.

Acetazolamide or furosemide treatment may benefit this patient. The experiences of Mathew et al (20) and Digre et al (26) have indicated that some patients without papilledema improve after shunting, but I try to avoid shunting whenever possible because of the high failure rate and the “downward spiral” that repeated shunting creates for patient and physician.

Editor's Comments

This patient is meant to represent an overweight young woman with new chronic headache, a normal ophthalmic examination showing no papilledema, and a normal brain MRI, in whom the consideration of “idiopathic intracranial hypertension without papilledema” (IIHWOP) would come up.

It did come up for our 2 experts, board-certified neurologists with considerable experience in the care of patients with headache and IIH. They both consider IIHWOP a real but rare entity on the basis of several publications (4,19–24,26), including one co-authored by Dr. Digre (26). Those reports have described obese patients with chronic headache—often described as “transformed migraine”—who have undergone lumbar puncture that has shown an opening pressure greater than 200 mm H2O (usually greater than 250 mm H2O). In some of those patients, headache has improved after the lumbar puncture, in others after treatment with carbonic anhydrase inhibitors or other diuretics, and in a small minority after cerebrospinal diversion procedures.

In this Point Counter Point, both debaters dismissed the diagnosis of IIHWOP because the opening pressure of 240 mm H2O was too low and there were no other corroborative features (pulsatile tinnitus and empty sella). Yet in the publication coauthored by Dr. Digre (26), the cutoff pressure between control subjects and those labeled as having IIH with or without papilledema was an opening pressure of 260 mm H2O, not so much higher than the 240 mm H2O of our patient! Would an opening pressure of 260 have changed their minds?

Although Drs. Digre and Friedman agree that IIHWOP is rare, other authors have asserted that IIHWOP could account for 10% (21) or 15% (20) of patients with chronic daily headache.

No one doubts that ICP can be chronically elevated without causing papilledema. But in the absence of papilledema, there are no reliable indicators to mark IIH. Basing a diagnosis of IIHWOP on sustained relief of headache after a trial of an ICP-lowering agent is risky. Headache is much too subjective a complaint and can arise from too many other causes. Besides, many patients with chronically elevated ICP do not report headache, probably because intracranial nociceptive receptors rapidly adapt under those circumstances.

As the debaters both admit, there are many technical errors in doing a lumbar puncture that can lead to a falsely elevated opening pressure. Thus, I am uneasy about making the diagnosis of IIHWOP unless the opening pressure is greater than 300 mm H2O on at least 2 lumbar punctures done with optimal technique or on ICP monitoring.

Even if those conditions are met, I would hesitate to prescribe ICP-lowering agents such as acetazolamide, which can cause kidney stones and induce life-threatening allergic reactions. Nor would I expose the patient to the complications of a CSF shunt. After all, visual function is not at risk in IIHWOP, and relief of headache is the only objective of treatment.

I have yet to make a diagnosis of IIHWOP. Am I missing something?
REFERENCES


A “First Cut” at Interpreting Brain MRI Signal Intensities: What’s White, What’s Black, and What’s Gray

Hemant Parmar, MD, Jonathan D. Trobe, MD

Abstract: We propose that a simple but reasonable initial interpretation of brain and spinal cord MRI can be made by considering whether signal intensity is white or black or gray on precontrast T1-weighted and T2-weighted pulse sequences. We have formulated this task as a $2 \times 2$ table.

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MRI interpretation depends chiefly on locating and characterizing signal abnormalities and deciding what alterations in tissue are causing these abnormalities. Much of this interpretation depends on MRI signal intensities, which range from very high (“bright” or “white”) to very low (“dark” or “black”). The changes in signal intensity are based on tissue features and technical parameters used to image these tissues. Many pulse sequences are used to generate MRI signals, but conventional T1 and T2 weighted images (abbreviated here as T1 and T2) remain the most used. So MRI interpretation really comes down to what causes tissues and their lesions to look white or black or gray.

We propose that a “first cut” at MRI interpretation can be formulated as a $2 \times 2$ table (Fig. 1) that compares the precontrast (noncontrast) T1 and the T2 signal intensities in relation to gray matter. Tissues that appear in this table have either white or black signal intensities.

### BLACK ON PRECONTRAST T1, WHITE ON T2

Most pathologic conditions of brain and spinal cord parenchyma produce this combination of signal intensities, including cyst fluid, abscess, edema, encephalomalacia, demyelination, and necrosis. Normal cerebrospinal fluid (CSF) will also have this combination of signal intensities, which helps orient you to whether the pulse sequence is T1 or T2.

These tissues or lesions show black T1 and white T2 signal because they contain more water than normal gray matter. The fluid attenuation inversion recovery (FLAIR) pulse sequence is a modification of T2 designed to attenuate the high signal of free-flowing fluid, allowing the T2 signal of stationary tissues to stand out. Free-flowing fluid is found in CSF, cysts, and large areas of encephalomalacia. Thus FLAIR differs from standard T2 in that the FLAIR signal intensity of these tissues will be black. The FLAIR signal intensity will remain white in the presence of excessive interstitial or intracellular water, which does not have free flow.

### BLACK ON PRECONTRAST T1, BLACK ON T2

This appearance is caused by air, dense calcium, cortical bone, rapidly flowing blood, dense fibrous tissue, iron, and hemosiderin (from parenchymal hemorrhage of more than one week’s duration).

Air, dense calcium, cortical bone, and dense fibrous tissue generate a “pitch black” signal on T1 and T2 because they have a complete absence of mobile protons. Rapidly flowing blood generates a pitch black signal because its protons are flowing out of the scanned slice and so produce a “signal void.”

Hemosiderin and iron are strongly paramagnetic and will therefore be pitch black on T2 and less so on T1.
WHITE ON PRECONTRAST T1, BLACK ON T2

<table>
<thead>
<tr>
<th>BLACK on T1***</th>
<th>WHITE on T1***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrospinal fluid</td>
<td>Extracellular methemoglobin</td>
</tr>
<tr>
<td>Cyst</td>
<td>Slowly flowing blood^</td>
</tr>
<tr>
<td>Abscess</td>
<td>Fat**</td>
</tr>
<tr>
<td>Edema</td>
<td>Melanin</td>
</tr>
<tr>
<td>Encephalomalacia</td>
<td>Intracellular methemoglobin</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Fat**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHITE on T2</th>
<th>BLACK on T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air*</td>
<td>Dense calcium*</td>
</tr>
<tr>
<td>Cortical bone*</td>
<td>Rapidly flowing blood**^</td>
</tr>
<tr>
<td>Iron</td>
<td>Hemosiderin</td>
</tr>
</tbody>
</table>

**Fat appears white on T2 on modern turbo/fast spin echo sequences and black on T2 on older spin echo sequences.***T1 signal without contrast (“precontrast” or “noncontrast”). Intravenous injection of contrast material is used with T1 pulse sequences (“postcontrast” T1). It will generate a whiter signal than that on precontrast T1 in tissues that have an especially dense arterial blood flow (“high vascularity”) or in which the dye has escaped across an absent or deficient blood-brain barrier (“staining”). ^Rapidly flowing blood causes a black T1 and T2 signal because the protons have escaped the scanned slice. Slowly flowing blood, usually venous, gives rise to a white T1 and T2 signal because the protons are moving too slowly to escape from the scanned slice.

Regarding the gray area, the MRI signal intensities of some tissues and lesions defy simple classification because they depend on concentration, cellularity (nuclear to cytoplasmic ratio), flow rate, or hemoglobin degradation state.

High protein content in body fluids will reduce its “water purity” and shift the white T2 signal toward gray and the black T1 signal toward gray. Among tumors, the higher the fibrous content, cellular density, or nuclear-cytoplasmic ratio (round blue cell tumors like lymphomas or primitive neuroectodermal tumors) are, the lower the proportion of water purity will be, and therefore the grayer the signal on T1 and T2.

Dense calcium has no mobile protons and behaves like cortical bone: black on T1 and T2. Lower densities of calcium show variable and unpredictable signals.

Slowly flowing blood can give rise to a variably intense signal on T1 and T2. As the protons within the blood vessels are moving at variable rates out of the scanned slice. In such cases, evaluation by magnetic resonance angiography or venography may be required.

Gradient echo (T2*) images improve detection of calcification and hemosiderin, which often appear larger and blacker (“blooming”) on this pulse sequence than on T1 or T2 as a result of dephasing of water protons created by differences in magnetic susceptibility. Because the gradient echo images lack a refocusing radiofrequency...
pulse, this intravoxel dephasing accumulates, making these tissues appear especially dark.

The MRI signal in fungal infections is related to the amount of proteinaceous secretions and the presence of paramagnetic or ferromagnetic material within the infected material. Fungal sinusitis may result in black T1 and T2 signal, but chronic densely concentrated mucosal secretions, which may contain no mobile protons, may also produce black T1 and T2 signals. The finding of bone erosion on CT suggests aggressive fungal disease.

The MRI signal from parenchymal hematoma is difficult to interpret but evolves in a predictable manner as the clot is degraded (Fig. 2). Among the complex factors responsible for signal intensity are protein concentration, red blood cell hydration status, red blood cell size and shape, hematocrit, clot formation, clot retraction, inflammatory response, and extrinsic factors such as MRI magnetic field strength and pulse sequences. The pattern of MRI signals seen in parenchymal hematoma evolution cannot be extrapolated to extraparenchymal or extracranial hematoma.

### Table: MRI Signal Evolution of Parenchymal Hematoma

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time from Bleed</th>
<th>Stage of Hemoglobin</th>
<th>T1***</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>&lt;6 hours</td>
<td>Oxyhemoglobin</td>
<td>Gray</td>
<td>White</td>
</tr>
<tr>
<td>Acute</td>
<td>6-72 hours</td>
<td>Deoxyhemoglobin</td>
<td>Gray</td>
<td>Black</td>
</tr>
<tr>
<td>Early subacute</td>
<td>3-7 days</td>
<td>Intracellular methemoglobin</td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>Late subacute</td>
<td>1-4 weeks</td>
<td>Extracellular methemoglobin</td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td>Early chronic</td>
<td>&gt; 4 weeks</td>
<td>Extracellular methemoglobin with hemosiderin rim</td>
<td>White</td>
<td>White with black rim</td>
</tr>
<tr>
<td>Late chronic</td>
<td>Months to years</td>
<td>Hemosiderin</td>
<td>Black</td>
<td>Black</td>
</tr>
</tbody>
</table>

**FIG. 2.** MRI signal in parenchymal hematoma. T1 refers to precontrast T1.
Another Case of Bisphosphonate-Induced Orbital Inflammation

Bisphosphonates are used to inhibit bone absorption as a treatment for hypercalcemia associated with osteolytic bone cancer, bony metastasis, Paget disease, and osteoporosis. There have been 7 reported cases of bisphosphonate-induced orbital inflammation (1–7). We describe another case and document MRI abnormalities.

An 89-year-old woman was well until 20 minutes after receiving her first dose of 4 mg zoledronic acid intravenously when she developed acute, severe lower extremity arthralgias, followed by ascending arthralgias and a left-sided headache. Three days later she developed bilateral periocular pain associated with intense sharp pain provoked by eye movement, blurred vision in the left eye, and binocular horizontal diplopia with image separation greater in lateral gaze.

Best-corrected visual acuity was 20/40 in the right eye and 20/50 in the left eye without a relative afferent pupil defect. In primary gaze position, she had 10 prism-diopters (PD) of esotropia which increased to 25 PD in right and left gaze (Fig. 1). Confrontation visual fields were full. Slit-lamp examination showed diffuse conjunctival injection and bullous chemosis with no sign of anterior uveitis. Ophthalmoscopy disclosed no abnormalities.

MRI showed diffuse fat stranding, optic nerve sheath enhancement, posterior scleral enhancement, and slight enlargement of extraocular muscles bilaterally (Fig. 2).

Bisphosphonate-induced orbital inflammation was diagnosed and treated with 1 g methylprednisolone intravenously per day for 3 days followed by prednisone on a tapered dose regimen. Over the next 3 days, headache, double vision, chemosis, and orbital pain dramatically improved. One month later, ophthalmic abnormalities had largely resolved (Fig. 3).

This is the first reported case of orbital inflammation caused by bisphosphonate treatment for osteoporosis. In all reported cases of bisphosphonate-induced orbital inflammation, the onset of ocular symptoms has varied from 1 to 6 days after drug administration. The symptoms have included orbital pain, diplopia, and lid swelling. The common signs have been periocular edema, chemosis, conjunctival injection, proptosis, reduced ocular ductions, and minimal anterior chamber inflammation.

The treatment of this adverse event has been discontinuation of the offending drug and use of high-dose systemic corticosteroids. All reported patients have had rapid and complete resolution. Although discontinuation of bisphosphonate alone may be sufficient (1,2,3,4,5), corticosteroids may hasten the recovery process.

The mechanism of orbital inflammation in this setting is unsettled. Inflammatory factors have been implicated, given that augmented levels of tumor necrosis factor- (TNF-),

FIG. 1. At initial presentation, the patient displays esotropia, bilateral abduction deficits, and a small upgaze deficit, as well as conjunctival hyperemia and chemosis.
interleukin (IL)-1 and IL-6 have been detected in patients after zoledronic acid infusion (8).

**Addendum:** After this letter was accepted for publication, a paper on this subject was published. Procianoy F, Procianoy E. Orbital inflammatory disease secondary to a single-dose administration of zoledronic acid for treatment of postmenopausal osteoporosis. *Osteoporos Int* October 27, 2009 [e pub ahead of print].

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**FIG. 2.** Postcontrast fat-suppressed T1 axial (A) and coronal (B) MRI studies show enhancement of the sclera, extraocular muscles, and optic nerve sheaths bilaterally.

**FIG. 3.** Four months after corticosteroid treatment, the esotropia and abduction deficits have resolved and the conjunctival hyperemia and chemosis have dissipated.
Visual Loss Without Papilledema in Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (IIH) is classically associated with papilledema, which can produce progressive irreversible visual field constriction and blindness if untreated (1,2). It has long been suggested that papilledema is required for visual loss to occur in IIH (3), implying that patients without papilledema are not at risk for visual loss. We report a patient with IIH who developed visual loss due to papilledema in one eye and a progressive optic neuropathy without papilledema in the other.

A 32-year-old obese African-American man presented with intermittent headache and transient visual obscurations (TVOs) in the right eye. He had no history of hypertension, sleep apnea, or any other obesity-related illnesses, and he was taking no medications. Before referral, he had been evaluated by a neurologist and an ophthalmologist, both of whom had documented optic disc edema in the right eye and a normal optic disc in the left eye. Because his TVOs were thought to be vascular in origin, retinal fluorescein angiography had been performed, and results for the left eye were normal; there was no leakage to suggest subtle optic disc edema. Results of catheter cerebral angiography were normal.

On our examination, his height was 6 feet 2 inches (188 cm) and weight was 266 lb (121 kg), giving a body mass index of 34 kg/m². Blood pressure was within normal limits. Visual acuity was 20/20 in both eyes. There was chronic optic disc edema in the right eye and a normal optic disc, without signs to suggest resolved optic disc edema, in the left eye. Visual field testing showed a superior arcuate and ceco-central scotoma (Fig. 1A), and results for the left eye were normal; there was no leakage to suggest subtle optic disc edema. Results of catheter cerebral angiography were normal.

MRI of the brain and orbits was unremarkable. Lumbar puncture showed an opening pressure of 55 cm H₂O with normal cerebrospinal fluid (CSF) composition. His headache and TVOs transiently improved after the lumbar puncture. IIH was diagnosed and treatment with acetazolamide was started.

Over the following months, he developed a progressive optic neuropathy in the left eye, with visual acuity decreasing to finger counting, a ceco-central scotoma (Fig. 1A), and a left relative afferent pupillary defect. Progressive left optic disc pallor was noted (Fig. 1B–D), but optic disc edema was never observed. Despite a thorough workup for compressive, inflammatory, toxic, and hereditary disorders, no cause for the optic neuropathy was identified.

Repeat MRI of the brain and orbits was normal, except for posterior scleral flattening and optic nerve sheath dilatation, both greater on the right. He did not return for scheduled lumbar punctures.

Despite treatment with acetazolamide, the visual field defect and papilledema in the right eye persisted, as did his headache and TVOs. Therefore, a right optic nerve sheath fenestration (ONSF) was performed. At surgery, there was a gush of CSF upon fenestration. The visual field defect and optic disc edema in the right eye subsequently improved (Fig. 1C). In the left eye, however, the visual acuity deficit and ceco-central scotoma persisted, the optic disc became paler (Fig. 1C), and a dense left relative afferent pupillary defect was noted.

Accordingly, a left ONSF was performed 1 month after the right ONSF. At surgery, the optic nerve sheath did not appear distended and no CSF drained upon fenestration. Results of histopathologic examination of a biopsy specimen from the optic nerve sheath were unremarkable. Postoperatively, visual acuity in the left eye did not improve, but the ceco-central scotoma decreased in size (Fig. 1D).

Although optic atrophy is a classic complication of papilledema in IIH (2,4), our patient developed a left optic neuropathy and subsequent optic atrophy without ever having had papilledema, as far as we could tell. Given that we were unable to identify an alternative cause for this optic neuropathy, we presume that it resulted from raised intracranial pressure (ICP). Although there was no formal documentation of raised ICP after the initial lumbar puncture, our patient reported ongoing headache and TVOs, and there was persistent papilledema in the right eye, suggesting that ICP was elevated.

Although papilledema can be asymmetric, unilateral, or absent in patients with IIH (5–7), it is unclear how visual loss would develop in the absence of papilledema. Others have suggested that the visual loss in such cases is non-organic (7). However, it is possible that raised ICP could produce intracranial or retrobulbar optic nerve compression if there is anatomic compartmentation of the subarachnoid space around the optic nerve. Such compartmentation has been proposed on the basis of histologic, radiologic, and biologic data (8–10). Although functional compartmentation could potentially contribute to the development of papilledema in patients with IIH (10), anatomic compartmentation of the subarachnoid space around the optic nerve could stop the CSF pressure gradient from reaching the retrolaminar portion of the

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nerve, thereby producing retrobulbar optic nerve compression without optic disc swelling. In our patient, the operative finding of a nondistended retrolaminar optic nerve sheath, without CSF drainage upon fenestration, supports this hypothesis.

A second explanation is that sequestration of CSF containing a toxic metabolite could have produced a unilateral toxic optic neuropathy (10). Because many patients with IIH have cerebral venous hypertension (11), a third explanation is that the optic neuropathy could have resulted from posterior optic nerve ischemia due to impaired venous drainage, as has been proposed for optic neuropathy occurring with carotid-cavernous fistulas (12).

Despite this unusual case, we advise extreme caution before attributing visual loss in IIH to raised ICP when there is no papilledema.

**FIG. 1.** A. Several months after our initial examination, the right optic disc shows chronic optic disc edema and the left optic disc appears normal. The Humphrey 24-2 visual field of the right eye shows superior arcuate and nasal defects; the Goldmann visual field of the left eye (II4e isopter) shows a ceco-central scotoma. B. Six weeks later, the right optic disc has not changed, but the left optic disc has developed mild pallor. The visual field defect in the right eye has not changed, but the visual field defect in the left eye has enlarged, despite a lumbar puncture and treatment with acetazolamide. C. One week after right optic nerve sheath fenestration, the optic disc edema in the right eye has improved, but the left optic disc has become paler. The visual field defect in the right eye has improved, but the ceco-central scotoma in the left eye persists. D. Two years after left optic nerve sheath fenestration, the right optic disc edema has resolved, but the left optic disc has become paler. The ceco-central scotoma in the left eye has decreased in size.
Letters to the Editor

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Monocular Embolic Retinal Arteriolar Occlusions After Ipsilateral Intraoral Triamcinolone Injection

We describe multiple branch retinal artery occlusions, mydriasis, and iritis after triamcinolone injection into an intraoral fibrous scar.

A 36-year-old year old woman underwent multiple oral maxillofacial procedures to correct jaw asymmetry. At the time of a subsequent irrigation and drainage procedure, 1 mL of triamcinolone was injected submucosally intraorally into a fibrous scar in the left mandibular retromolar pad. After the procedure, the patient complained of blurred vision in her left eye. The following morning an oral surgeon reported a fixed and dilated left pupil.

Three hours later, ophthalmologic examination revealed the patient’s visual acuity to be 20/25 in the right eye and counting fingers at 3 feet in the left eye. Ocular motility and alignment were normal in both eyes. There was no ptosis. The right pupil measured 2.5 mm in dim illumination and the left measured 5.5 mm; the right pupil constricted normally to direct light and the left pupil did not constrict. There was a left afferent pupillary defect. The left pupil did not demonstrate light-near dissociation. Slit lamp examination revealed 2+ white blood cells and flare in the anterior chamber in the left eye. Intraocular pressure was 17 mm Hg in the right eye and 12 mm Hg in the left eye. Humphrey visual field protocol (30-2 SITA) were normal in the right eye and demonstrated a dense paracentral scotoma in the left eye. Dilated ophthalmoscopy demonstrated multiple white emboli within the retinal vasculature of the left eye; fluorescein angiography confirmed blockage of multiple retinal arterioles (Fig. 1).

The patient declined therapeutic paracentesis, but digital massage was performed. After other embolic sources were ruled out, the occlusion was attributed to the triamcinolone injection.

One month later the patient’s visual acuity was unchanged. The pupils measured 4 mm in dim illumination and reacted adequately to light, but a mild relative afferent
pupillary defect persisted in the left eye. The anterior chamber of the left eye was free of cells and flare and the retinal emboli had disappeared.

There are reports of various ophthalmic complications after intraoral anesthetic injection of common dental anesthetics such as lidocaine, mepivacaine, and procaine (1). In our patient, intraoral injection of triamcinolone resulted in an ocular ischemic syndrome manifested by branch retinal artery occlusions, mydriasis, and iritis. We are unaware of previous reports documenting these ocular complications in this setting. Retinal artery occlusions have occurred after intralesional injection of corticosteroids for eyelid hemangiomas and after retrobulbar injections and other procedures near the orbit (2–4). Corticosteroid particles can reach the ophthalmic system through retrograde flow and through anastomotic connections between the external carotid and ophthalmic arteries (2–4).

We believe that corticosteroid particle embolization also caused temporary loss of pupillary sphincter function and iritis in our patient’s left eye. Anterior segment inflammation as a result of ciliary ischemia has been demonstrated in other cases of ocular ischemic syndrome and frequently after muscle surgery (5); however, there are no reported cases of orbital vascular occlusion by corticosteroid emboli. Mydriasis and iritis may have occurred in other cases of corticosteroid orbital vascular occlusion but were overlooked or underreported in the face of retinal pathologic lesions.

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REFERENCES

**Protracted Cortical Visual Loss in a Child With Ornithine Transcarbamylase Deficiency**

We describe a 5-year-old girl with ornithine transcarbamylase deficiency (OTCD) who presented with headache and cortical visual loss in the absence of other neurologic signs. Serum ammonia levels were found to be elevated and vision recovered slowly over several weeks with protein restriction. To our knowledge, isolated cortical visual loss has not been reported as a presenting feature of this condition, although visual loss has been described as a complication of hyperammonemic encephalopathy.
Two weeks prior to her presentation to us, OCTD had been diagnosed in a 5-year-old girl after she presented to the hospital with acute lethargy and ataxia. She had started a school program that included meals containing a greater protein load than she had eaten at home. Her parents had noted that she generally avoided high-protein foods such as meat. On her initial admission to the hospital at that time, her serum ammonia level had been elevated to 226 mmol/L (normal range 29–57 mmol/L). She was started on a restricted protein diet and treated with phenylbutyrate and citrulline, which produced normalization of mental status and of serum ammonia levels over a period of 2 days. DNA analysis, performed at the time of admission and 2 days after onset of symptoms, showed a frameshift mutation in the OTC gene at position 287 in exon 8, because of insertion of 2 nucleotides (ACA–ACACA). Results of genetic testing for mutations in the CACNA1A and ATP1A2 genes for familial hemiplegic migraine were negative.

Two weeks after her initial admission, while still taking phenylbutyrate and citrulline, she presented to us with a 3-day history of blindness, headaches, and ataxia. On our examination, she was unable to detect the presence of bright light shined into either eye. Both pupils reacted briskly to light without afferent pupillary defect. Extraocular movements were full, and there was no nystagmus or strabismus. Slit lamp biomicroscopy and retinal examination showed no abnormalities. Blood pressure, measured throughout her hospitalization, was repeatedly normal.

Lumbar pressure measurement, performed on the first day of admission, showed a normal opening pressure with no neurochemical abnormalities (glutamine levels were not measured). Results of electroencephalography were normal. Serum ammonia levels had normalized to 22 mmol/L. Brain MRI, performed on day 5 of her visual loss, showed no abnormalities on precontrast studies (Fig. 1A), even on diffusion imaging. Postcontrast studies showed mild bilateral enhancement confined to the occipital lobes (Fig. 1B). Results of magnetic resonance angiography and venography were normal.

Over a 2-week period, she was treated with verapamil (for migraine) and oral corticosteroids (for an inflammatory component). Ataxia improved during the first 3 days of treatment, but severe headache and visual loss persisted. Several neuro-ophthalmologic examinations over the following 2 weeks showed no papilledema.

Over a 6-week period, the patient experienced a gradual visual recovery to 20/25 in both eyes, with normal color vision and normal visual fields to confrontation. Her parents reported a milder episode of reduced vision 2 months later, which lasted for 2 days and was not associated with hyperammonemia. No examination occurred during that event, so the visual loss could not be medically confirmed. A brain MRI performed 6 weeks after this reported episode of visual loss was entirely normal, showing no residual enhancement.

With an incidence of 1 case per 14,000 births, OTCD is the most common inborn error of metabolism of the urea cycle (1,2). OTCD is an X-linked disorder characterized by the accumulation of precursors of urea, principally ammonia and glutamine (1). The presenting signs of OTCD are largely due to cerebral edema caused by elevated levels of ammonia (1). The most severe clinical form of OTCD occurs in full-term infants who appear healthy for
24–48 hours and then exhibit signs of progressive lethargy, hypothermia, and apnea (2). Milder forms of OTCD, which include vomiting, abnormal mental status, ataxia, seizures, or developmental delay, may become evident at any age from infancy to adulthood (2).

Late-onset OTCD occurs commonly in women who have a mutation at the OTC locus on one of the X chromosomes (2). Hyperammonemic attacks can be triggered by a high-protein diet, infections, valproic acid and other medications, and the postpartum state (3). In heterozygous females, the clinical phenotype can range from complete absence of symptoms to severe hyperammonemnic episodes (4). This striking phenotypic variability may reflect genetic heterogeneity as well as the random pattern of X inactivation that occurs within hepatocytes (5). Treatment with medications that activate new pathways of nitrogen waste excretion can reduce the number of hyperammonemnic episodes and the long-term risk of cognitive decline in young girls with symptomatic OTCD (6).

In some young women, OTCD causes recurrent stroke-like episodes (4,5). Reports of late-onset OTCD described neuroimaging findings that resemble those of ischemic stroke (7–10). The basis of hyperammonemnic encephalopathy in OTCD has not been established (1,2). One theory attributes the manifestations to the intracerebral accumulation of glutamine due to high levels of ammonia in astrocytes, which promotes the conversion of glutamate to glutamine via glutamine synthetase (1,2). According to this proposed mechanism, the accumulation of glutamine produces changes in intracellular osmolality, leading to swelling of astrocytes, cerebral edema, intracranial hypertension, and cerebral hypoperfusion. In support of this mechanism is the fact that the cerebral edema associated with hyperammonenemia can be prevented by reducing glutamine accumulation in the brain, suggesting that hyperammonenemia alone does not produce cerebral edema (1,2). In patients with OTCD, cerebrospinal glutamine concentrations are extremely elevated during hyperammonemnic encephalopathy (11,12). Proton magnetic resonance spectroscopy has also demonstrated high glutamine concentrations in patients with hyperammonemnic encephalopathy (11,12).

Brain MRI generally demonstrates injury to the cingulate gyrus and insular cortex, with sparing of the perirolandic and occipital cortex (2). These perisulcal white matter lesions may reflect diminished cerebral perfusion in the face of elevated intracranial pressure (13,14). It has been suggested that the occipital cortex is particularly resistant to hyperammonemnic-hyperglutaminergic encephalopathy (2,15).

Our patient had newly diagnosed OTCD associated with isolated protracted cortical blindness. This episode began shortly after treatment of her hyperammonenemia and persisted over a 6-week period. Typically, neurologic manifestations of hyperammonenemia occur quite rapidly—within 24 hours of elevated ammonia levels. Usually these manifestations resolve as the ammonia level falls. Because our patient’s serum ammonia levels were normal at the time of visual loss, its cause remains unclear. The differential diagnosis includes migraine, stroke, seizure, or inflammatory infectious or a metabolic disorder (16). Although we treated her presumptively for migraine and epilepsy, the protracted nature of the event is inconsistent with these causes, and it is doubtful that our treatment influenced her recovery. This unusual clinical history demonstrates that OTCD can relatively selectively injure the occipital cortex to produce protracted blindness.

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Third Cranial Nerve Palsy as the Presenting Neuro-Ophthalmic Feature of Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma, the most common carcinoma to involve the skull base, may present with neuro-ophthalmic features. Most patients have multiple cranial nerve dysfunction, the fifth and sixth cranial nerves being most often affected (1–3). We report a case that presented with third cranial nerve palsy as the only neuro-ophthalmic feature.

A 48-year-old man with no significant past medical history presented to our clinic with a complaint of diplopia and ipsilateral periocular pain of 3 days’ duration. The patient also reported having noticed a mass in the left submandibular area 6 months earlier.

Neurologic examination revealed partial right ptosis and complete absence of adduction, supraduction, and infraduction of the right eye. The pupils in low illumination were equal at 4 mm and symmetrically reactive to light and near targets. Visual acuity, ophthalmoscopy, and cranial nerve and motor examination results were normal. Results of the remaining physical examination were within normal limits except for a painless mass over the left submandibular area.

All laboratory values were within the normal ranges. MRI of the brain and nasopharynx showed a large mass centered at the clivus region and spreading into the nasopharynx, invading the basis of the occipital bone, both sphenoid and posterior ethmoid sinuses, the medial part of the right cavernous sinus, and the petrous apex (Fig. 1A–B). The mass enhanced heterogeneously. The superior and inferior orbital fissures, optic nerves, and other intraorbital structures were spared. Significant bilateral lymphadenopathy of the neck was evident and some lymph nodes showed hypodense centers indicative of necrosis. A digital subtraction angiogram revealed no vascular abnormalities.

FIG. 1. A. T2 axial MRI shows a tumor with mixed signal intensity that is invading the sphenoid and posterior ethmoid sinuses. B. Postcontrast coronal MRI shows an enhancing tumor centered at the clivus with partial right cavernous sinus invasion (arrow).

FIG. 2. Histopathology of a nasopharyngeal punch biopsy shows fibrous connective tissue with infiltrating cords of anaplastic cells (hematoxylin and eosin, ×40).
Biopsy of the nasopharyngeal mass revealed a nonkeratinizing differentiated carcinoma (Fig. 2). The patient was referred to the oncology department for radiotherapy and chemotherapy.

The third cranial nerve paralysis remained stable without improvement, and no other neurologic symptoms had occurred after 3 months.

A retrospective study of 79 patients with nasopharyngeal carcinomas (4) disclosed that one quarter of these patients have neuro-ophthalmic manifestations. In a group of 564 patients with nasopharyngeal carcinomas (1), cranial nerve dysfunction was present in 12%. In 92% of the patients, neurologic deficits were confined exclusively to cranial nerves. Another study (5) showed that the most frequently affected cranial nerves were the fifth and sixth.

Our patient is unusual in that the third cranial nerve was the only one involved. The extent of the tumor on MRI fails to indicate why the third cranial nerve was the only affected cranial nerve.

REFERENCES

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In a recent publication in this journal, Sobaci et al (1) concluded that patients with multiple sclerosis (MS) without optic neuritis had considerable abnormalities in stereopsis and that the Randot stereoacuity (RSA) test might be a useful marker of subclinical disease activity in MS.

Several conditions can lead to impaired performance on the RSA test. In addition, it is not clear whether optic nerve or retinal diseases are likely to have a big impact on stereoacuity performance (2). The clinical usefulness of the RSA still needs further validation (2,3). Although the sensitivity and specificity of the test are acceptable for screening of strabismus (4), it has never been proved for optic neuritis.

REFERENCES

Dr. Viroj Wiwanitkit has made meaningful comments on our article.

In this study, we showed that patients with multiple sclerosis (MS) without optic neuritis (ON) had significantly worse Randot stereoacuity (RSA) levels compared with age- and sex-matched healthy control subjects. This finding, as indicated in the Discussion, may indicate some structural and/or functional abnormalities or dysfunctional processing in the visual pathways of patients with MS who had no ON attacks. We agree that the diagnostic value of RSA in ON has never been proven.

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**Neuro-Ophthalmology Illustrated**
Valerie Biousse, MD and Nancy J. Newman, MD.

**Scope**: This is a 600-page soft cover training manual that covers every important topic in neuro-ophthalmology. There are no references. As the authors declare in the preface, it is intended as an introduction to neuro-ophthalmology for medical students and physicians in training in ophthalmology, neurology, and neurosurgery.

The material is organized in a fashion that has become standard for books of this nature. Techniques of examination come first, followed by chapters on persistent and transient visual loss, retinal and optic nerve diseases, retrogeniculate disorders, pupils, diplopia, eyelid, orbital, and cavernous sinus diseases, ocular oscillations, headache and facial pain, and nonorganic manifestations. The text is amplified with flowcharts, boxes that succinctly highlight "take-home" points (called "pearls"), decision trees, lists of differential diagnoses, and hundreds of illustrations, including anatomic drawings from Thieme atlases, external ocular photographs, fundus photographs, CT scans, magnetic resonance scans, and cerebral angiograms.

**Strengths**: The text is tightly and cogently written. The illustrations are simple enough so that a newcomer can quickly catch on, yet ample enough for an experienced reader to capture a deeper understanding of how these things work and how to teach them.

**Weaknesses**: There aren’t any. One could object that there are no references to back up the material, but training manuals do not need them. Besides, the authors adhere to accepted wisdom in the field without making controversial points. I wonder if the soft binding will hold up with repeated use, which this book will certainly get.

**Recommended Audience**: This book will work best as a training manual, as the authors suggest. But it would also suit practitioners of all clinical neurologic specialties who are looking for an elegant rendition of the subject matter supported by beautiful illustrations.

**Critical Appraisal**: This is the best soft cover training manual in neuro-ophthalmology that I have read. Its excellence is no surprise, for the authors are renowned for their clinical wizardry. The amalgamation of so much good information with such good pictures under one cover is a triumph. Novices will learn pleasurably from the succinct text and apt illustrations. The cognoscenti will marvel at how masterfully this book has been put together.

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**Manual of Neuro-Ophthalmology**
Amar Agarwal, MD and Athiya Agarwal, MD.
ISBN: 978-0-07-163231-7, $64.95.

**Scope**: This is a 257-page multi-authored book that covers the fundamentals of neuro-ophthalmology. Bearing in mind that neuro-ophthalmology is a complex subspecialty that is not easily understood by many, this book has been written to address the subject in a simple and concise manner. With contributions from several authors, Amar Agarwal and Athiya Agarwal have accomplished the task of providing a fairly comprehensive overview of neuro-ophthalmology. They have taken enormous effort to make the subject accessible to the reader.

The book is divided into 19 chapters, each dealing with a specific topic in neuro-ophthalmology. Each chapter has plenty of colorful schematic diagrams and tables. A few clinical photographs have been added. Salient features of relevant neuro-ophthalmology diseases and pathways have been covered in each chapter. The first 2 chapters deal with supranuclear pathways and supranuclear eye movement disorders. These chapters highlight the fundamentals of the complex supranuclear pathways. The subsequent chapters deal with common topics in neuro-ophthalmology such as nystagmus, congenital optic nerve anomalies, and ocular myopathies.

An entire chapter is dedicated to imaging in neuro-ophthalmology. This chapter covers the basics of neuroradiology in a concise manner. As cited in the foreword the book can serve as a quick reference guide for a wide spectrum of readers such as medical students, ophthalmology and neurology residents, and practicing ophthalmologists.

**Strengths**: The authors have taken great care in presenting the topics in a simple and easily understood style; yet complicated pathways and diseases have also been well covered. This presentation allows medical students and residents to do self-directed learning of neuro-ophthalmology. The book has only 257 pages, and most of the chapters are short, thus allowing one to read the book in a fairly short period of time.

**Weakness**: The organization of the chapters is bizarre. They are not arranged in the order of the afferent or efferent system. In addition, there are glaring typographical errors that could have been avoided with careful review of the text. The style of presentation adopted by each author seems to be different. Hence, there is lack of uniformity in the book. Although the illustrations and figures appear simplified, in reality they are complex and often do not clearly convey the message. The references are also very limited in most chapters. The authors have mainly used their own textbook of ophthalmology as a reference and have omitted some important topics such as nonarteritic ischemic optic neuropathy.
Recommended Audience: This book would serve as a good introductory text for medical students as well as ophthalmology and neurology residents. Post-residency physicians preparing for recertification courses could use this book for quick review. Practicing ophthalmologists and neurologists who do not see neuro-ophthalmology patients on an everyday basis may also find this book useful.

Critical Appraisal: The authors have been successful in accomplishing their goal of simplifying the subject matter. Because the book is short and focused, it will attract many student readers. It may also serve as a valuable adjunct to a comprehensive textbook of neuro-ophthalmology.

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Neuro-Ophthalmology Problem Solving: A Practical and User-Friendly Guide
Jesse Halpern, MD, Steven B. Flynn, MD, PhD, and Scott Forman, MD.
ISBN: 978-1-59756-085-6, $98.00.

Scope: This manual is one in a series of small volumes that attempt to simplify the approach to the neuro-ophthalmology patient. It is divided into 11 chapters and 8 appendices tailored toward an approach to common and less common neuro-ophthalmic problems.

Afferent system dysfunction is included in 3 chapters (visual field interpretation, optic nerve disease, and unexplained visual loss) and there is a chapter on optic disc edema. Ocular motility is addressed in 4 chapters (ocular motility basic concepts, neurologic motility patterns, performing the ocular motility examination, and case studies). There are also chapters on nystagmus, saccadic intrusions, ocular bobbing, and pupillary problems and appendices on covert retinal diseases and optic disc anomalies.

Strengths: The text is strong in that it has bypassed the rare and less important conditions more appropriate for a comprehensive text. There are many good videos.

Weaknesses: In some cases, the video quality is suboptimal.

Recommended Audience: Although the authors have directed this text mainly toward ophthalmologists and neurologist in training, it should serve well even for experienced clinicians.

Critical Appraisal: This is a useful pocket-sized volume with helpful videos. It will be even better when the videos are brought to a uniformly high quality in future editions.

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Using Eye Movements as an Experimental Probe of Brain Function. A Symposium in Honor of Jean Büttner-Ennever (Volume 171, Progress in Brain Research)
Christopher Kennard PhD, FRCP, FMedSci and R. John Leigh MD, Editors.

Scope: This multiauthored compendium was collected from an international symposium held in December 2007 to honor Dr. Jean Büttner-Ennever, a revered figure in the science of eye movement. It contains 87 chapters written by who’s who of ocular motility research. The investigations that are covered here reflect an interesting blend of experimental animal work with normal and abnormal human studies. The text is organized into 6 sections with an average of about 15 entries per section.

Section 1 covers work on eye muscle physiology, touching particularly on the role of afferent proprioceptive signals and mechanisms of adaptation to cranial nerve palsy. There is a very accessible overview of the anatomy of the brainstem ocular motor network by the honoree, Dr. Büttner-Ennever. Sections 2 and 3 discuss ocular motor control within the brainstem and cerebellum. Topics include modeling of saccadic oscillations and oculopalatal tremor and new insights into abnormal eye movements in patients with cerebellar dysfunction. Section 4 is concerned with the physiology of eye movement systems as they relate to balance and gait. Section 5 addresses the fascinating insights gleaned from investigations into attention, intention, and memory as they relate to ocular motor control. Finally, and of perhaps the greatest interest to neuro-ophthalmologists, Section 6 covers a range of topics on abnormal eye movements. There are entries on clinical application of head-impulse vestibular testing (Halmagyi et al), experimental control of motion sickness with baclofen (Cohen et al) and treatment of vertical nystagmus with aminopyridines (Glasauer and Rössert, Strupp et al).

Strengths: The volume offers a variety of basic science work on animal (mainly primate) physiology and anatomy and studies of normal and disordered eye movements in humans. Each chapter is succinct and well-written by authorities in the field. The depth and breadth of topic coverage is well chosen to reflect recent research activity in the field.

Weaknesses: This is not intended to be a comprehensive clinical text such as Leigh and Zee’s venerable tome, The Neurology of Eye Movements, 4th edition (Oxford, 2006) and the content is heavier on cutting edge science than on information regarding the diagnosis and treatment of eye movement conditions.

Recommended Audience: This volume is indispensable for ocular motor enthusiasts, but there is much to entertain the curious clinician whether one’s primary training is in neurology, ophthalmology, or otolaryngology.
**Critical Appraisal:** This book is a must read for anyone interested in the state of the art in eye movement research and for those who would like a peek at the direction of treatments for some of the most vexing clinical problems.

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**Recommended Audience:** This book will most useful to non-ophthalmic physicians and trainees but would not be out of place on an ophthalmologist’s shelf.

**Critical Appraisal:** This edition is an improvement over the previous one, containing better pictures, more topics, and updated management and treatment strategies. Its simplicity makes it less than ideal for an ophthalmologist who may, however, find it useful as a companion to the *Wills Eye Manual.*

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**The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 3rd Edition**

Neil J. Friedman, MD, Peter K. Kaiser, MD, and Roberto Pineda II, MD.

**Scope:** A pocket atlas with treatment guidelines, this volume is aimed to emergency physicians, family physicians, and internists. It is also suitable for medical students and ophthalmology residents. Using a standard template for all disorders, including definition, signs, symptoms, differential diagnosis, epidemiology, and management, the authors manages to cover nearly all significant diseases with adequate detail.

**Strengths:** The book is laid out in a visually pleasing manner, with emergencies outlined in red and management strategies outlined in the color that corresponds to that chapter. Each subtopic header is color-coded, making topics easy to find. There are excellent color photographs, many with helpful highlighting arrows. Basic diagnostic and treatment algorithms are easy to follow.

This edition has been updated with additional photographs, and all previous black and white photos were converted to color. The authors have added essential information about new technologies, including optical coherence tomography (OCT). There is an excellent appendix, which includes basic examination techniques and guidance on how to use fundamental equipment such as the Goldmann applanation tonometer, prisms, and crossover testing. The appendix includes common drug dosages, eponyms, and even basic differential diagnosis of common complaints, thereby combining the attributes of standard pocket manuals such as the *Wills Eye Manual* (Lippincott Williams & Wilkins, 2008) and *Basic Ophthalmology* (American Academy of Ophthalmology, 2004).

**Weaknesses:** The size of the photographs is limited by the size of the book; many are too small to make this a first-class atlas. Advanced topics are brushed over, for example, the section on exudative age-related macular short changes the size of the book; many are too small to make this a first-class pocket manuals such as the *Wills Eye Manual.*

**Recommended Audience:** This edition is out of place on an ophthalmologist’s shelf.

**Weaknesses:** However, some readers may view the lack of extensive literature review and discussions as deficiencies.

**Recommended Audience:** Without any doubt, this textbook and atlas will be of great value to all individuals involved in the field of ophthalmology, especially ophthalmic pathology. It is of particular value to those in ophthalmology residency and fellowship training.

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**Ocular Pathology, 6th Edition**

Myron Yanoff, MD and Joseph W. Sassani, MD.

**Scope:** This is a scholarly and comprehensive multi-authored ocular pathology textbook (and DVD-ROM) that has stood the test of time through 5 prior editions. It describes in detail, with great color illustrations, a wide variety of ocular pathology aspects ranging from basic eye pathology principles to rare congenital and neoplastic ocular and orbital processes. It is of great value to all personnel involved in the ophthalmic field.

**Strengths:** The beauty of the book is that it contains extensive information yet in a concise fashion. The bulleted structure of the text allows for easy reference. This, in addition to the detailed illustrations, makes the book not only a textbook but also an atlas. The text is very easy to read and straight to the point. Although the literature is not extensively reviewed for each topic, the critical references are listed. Moreover, the reference list of each chapter is organized into groupings of specific topic headings that also allows for efficient referencing.

**Weaknesses:** It is difficult to find weaknesses in this book because most of its shortcomings have favorable aspects. For example, the bulleted nature of the text makes it more of an atlas than a textbook; however, as noted above, this allows for easier reference and concise information. In most instances, especially in the hands of residents and fellows, this is desirable. The same applies for the nonextensive yet very organized and efficient nature of the reference lists. However, some readers may view the lack of extensive literature review and discussions as deficiencies.

**Recommended Audience:** Without any doubt, this textbook and atlas will be of great value to all individuals involved in the field of ophthalmology, especially ophthalmic pathology. It is of particular value to those in ophthalmology residency and fellowship training.
programs and medical students. The value of this book may even be greater than initially appreciated when one considers how few eye pathologists there are and how difficult it is to teach eye pathology in most academic institutions these days.

**Critical Appraisal:** Because this book (and DVD-ROM) addresses major aspects of eyelid, lacrimal, orbital, and ocular pathology, all ophthalmologists, ranging from general practitioners to subspecialists, and all those involved in ophthalmic education will be favorably affected by this book. Teaching eye pathology has never been more difficult times than this time. This book certainly helps alleviate this problem.

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John Nolte, PhD.  

**The Human Brain in Photographs and Diagrams, 3rd Edition**  
John Nolte, PhD and Jay B. Angevine Jr., PhD.  

**Elsevier’s Integrated Neuroscience**  
John Nolte, PhD.  
**Essentials of the Human Brain**  
John Nolte, PhD.  

**Scope:** Although each of these 4 books is a “stand-alone” text, they complement one another in making up a “teaching system” aimed at students of the health sciences, especially medical students. The system was developed by a single phenomenally talented and veteran teacher, John Nolte, PhD, professor of anatomy and cell biology at the University of Arizona. All 4 are oversized books in soft cover. *The Human Brain. An Introduction to Its Functional Anatomy,* now in its 6th edition, is the centerpiece, a 700-page text that melds anatomy and physiology. *The Human Brain in Photographs and Diagrams,* now in its 3rd edition, is a 250-page atlas that supports the centerpiece. *Elsevier’s Integrated Neuroscience* is a 250-page text of neurophysiology laden with schematic illustrations that is part of the giant medical publisher Elsevier’s series of books on basic science topics related to medicine. At 240 pages, *Essentials of the Human Brain* is the latest addition to the system, a distillate of the other 4 texts. CD-ROMs and online versions are now available.

**Strengths:** These books are brilliantly written and illustrated in the service of teaching. Concepts I never understood suddenly emerge as graspable. Nolte has had a lot of practice teaching this material—and it shows. The prose is succinct and clear. The schematic diagrams and stained anatomic specimens have been carefully selected to support the text and are always in the service of understanding normal and diseased function. In the latest editions, the author does not pad for the sake of producing a new product.

**Weaknesses:** Most physicians will not make the time commitment to read this material.

**Recommended Audience:** This system has had its greatest use in medical schools, but it should also serve as an excellent starting point for graduate students in neuroscience. *Essentials of the Human Brain* is the volume most approachable for ophthalmologists, neurologists, and neurosurgeons in their quest for understanding this subject matter. Each of the 4 books could also serve as a source of illustrations in teaching medical students, other physicians, and ancillary health care personnel.

**Critical Appraisal:** There are many textbooks on these topics, but none so exquisitely written and illustrated for learning and teaching. Nolte is the master. He excites you with that “aha moment” as you discover the secrets of nervous system function. Even though he is not a physician, he has somehow figured out what insights matter most to physicians. If you don’t have the fortitude to tackle the text, you could at least scrutinize the illustrations.

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**Atlas of Brain Function, 2nd ed.**  
William W. Orrison, Jr., MD, MBA.  

**Scope:** This is an atlas intended as a guide to the structural and functional relationships of the human brain. The goal is to provide detailed anatomic information using MRI combined with labeled schematic diagrams and correlate the anatomic location with current understanding regarding function. Although the title specifically mentions brain function, there is little to no information regarding functional MRI or pathology.

The book is divided into sections covering 2-dimensional sagittal, axial, and coronal views and 3-dimensional images. There is a final section dealing with diffusion tensor and fiber tract imaging. Each section (except the
Strengths: The use of MRI instead of gross pathology is much more practical to students at all levels of training, and the author has elegantly selected images that highlight certain structures. The correlation between MRI image and schematic diagram is usually very good. The resolution of detail for most images is outstanding. The discussions of functional correlates are good but necessarily limited.

Weaknesses: For some sections, there is a noticeable mismatch between the magnetic resonance images and the labeled diagrams. The discussion of function is superficial in many sections. The inclusion of diffusion tensor imaging seems somewhat arbitrary and may not be of much practical use to the clinician. The demonstrated pulse sequences are also somewhat arbitrary and without clear consistency or rationale.

Recommended Audience: Health care providers who order neuroimaging and review the studies will find this book useful. Neuro-ophthalmologists, neurosurgeons, and neurologists and particularly resident physicians would find this book a helpful adjunct to standard neuroradiology textbooks.

Critical Appraisal: This book is highly recommended as a reference source.

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Atlas of Interventional Neurology
Adnan I. Qureshi, MD, and Alexandros L. Georgiadis, MD.

Scope: This book provides a detailed, step-by-step approach to procedures performed in the practice of interventional neurology, neurosurgery, and neuroradiology. It contains 150 case illustrations.

Strengths: Explaining how interventional neurology is conducted is hard to do with words alone. But this atlas provides all the tools for those who want to understand what happens. Each of the 150 cases illustrates a specific procedure. As many as 10 black and white and color illustrations are provided for each condition to explain the details of the procedure.

Weaknesses: Because each case is condensed into 1 page and because this book is an atlas, there is very little room for details regarding the indications for each procedure. Moreover, it does not really deal with the issue of whether the procedure should be performed instead of surgery or observation alone. The numerous trials designed to answer that question are not covered.

Recommended Audience: This atlas is perfect for physicians who look after patients who undergo interventional neurologic procedures.

Critical Appraisal: This excellent atlas is published by one of the leaders in the field of interventional neurology. It is beautifully illustrated and the case-study format makes it easy to read cover-to-cover. The field of interventional neurology is changing very quickly, and this atlas will probably need many revisions over the next few years. It should help non-interventionists understand how most procedures are performed, thereby providing the background necessary to analyze the numerous studies published on this topic and to follow and educate patients.

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Dizziness: A Practical Approach to Diagnosis and Management
Adolfo M. Bronstein, MD and Thomas Lempert, MD, PhD.

Scope: This is a 221-page practical book on the assessment and treatment of the dizzy patient. There are 8 chapters written by 2 authors. The book is organized by patient presentation. There are 3 additional chapters covering anatomy, examination of the patient with vertigo, and the treatment of the dizzy patient. Each chapter begins with a table listing the differential diagnosis. At the end of each chapter is a section entitled “what to do if you don’t have a clue”? There are 54 tables and several figures. Included is a CD-ROM with 45 video clips of the most common eye movement disorders found in patients with dizziness and video clips from individuals with normal eye movements. There are videos of how to treat benign paroxysmal positional vertigo and vestibular hypofunction.

Strengths: The strength of this book is its organization around patient clinical manifestations. The table of
differential diagnoses at the beginning of each chapter make it very practical.

Weaknesses: The book is weighted toward inner ear disorders and vertigo. Imbalance is discussed to a limited degree. Fear of falling, perhaps the most common cause of imbalance seen in a dizzy clinic, is discussed in 1 paragraph. Some of the figures are not reproduced well or confusing, but these problems are minor.

Recommended Audience: This book should appeal to a wide variety of medical specialists and physicians-in-training who examine patients with dizziness. It will also be appropriate for physical therapists and audiologists.

Critical Appraisal: This is a very practical book that should be placed in the clinic or emergency room near where patients with dizziness are examined and treated. It will appeal most to physicians and allied health personnel who are relatively inexperienced in the field.

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Stroke in Children and Young Adults, 2nd Edition
Jose Biller, MD, Editor.

Scope: This is the 2nd edition of a multiauthored volume consisting of 17 chapters covering the diagnosis and management of stroke in children and young adults. The intended audience is clinicians caring for children and young adults with ischemic and hemorrhagic cerebrovascular disease. The book begins with an overview chapter on the epidemiology, risk factors, and prognosis of stroke in these patients. Chapter 2, written by the late Dr. William DeMyer, is a compendium of the vascular anatomy of the brain and the clinical and radiologic features of a wide variety of stroke syndromes. Chapter 3 is a brief overview of stroke in neonates and children.

The remaining 14 chapters cover the diagnosis and management of the major cerebrovascular disorders affecting infants and children, including chapters on cardiac disorders, migraine, coagulopathies, genetic disorders, pregnancy, and venous thrombosis, among others.

Strengths: The major strengths of the book are its state-of-the-art coverage of current diagnostic techniques, therapeutic recommendations, and current understanding of pathophysiology. References are current, and illustrations and tables are excellent. Most chapters contain a well-written, "stand-alone" review. References are quite current. Treatment of controversial areas is, in general, well-balanced. Illustrations are well-chosen and explanatory material is often presented in helpful tables.

Weaknesses: The major weakness of the book, from the point of view of a neuro-ophthalmologist caring for children, is the lack of detailed coverage of the visual aspects of cerebrovascular disease in children, especially neonates and premature infants. Cerebral visual impairment (CVI) is now the most common cause of bilateral visual loss in children in developed countries. This is due to the increased survival of premature infants with periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH) and secondarily to increased survival of full-term infants with various forms of ischemic encephalopathy. Clinicians caring for these children are often not aware of the serious visual consequences of PVL and other forms of neonatal cerebrovascular disease, including defects in visual acuity and more subtle defects of higher order visual cognitive function. These serious visual consequences should receive more detailed treatment in the text.

Recommended Audience: Clinicians in all specialties who deal with children and young adults with cerebrovascular disease will find that this book contains current and informative discussions. Neurologists, neurosurgeons, and neuro-ophthalmologists interested in a detailed exposition of the visual signs and symptoms of various cerebrovascular disorders will have to look elsewhere.

Critical Appraisal: This volume provides an updated review of current diagnostic and therapeutic concepts. However, the text does not provide detailed information about the visual signs and symptoms of these disorders. Clinicians interested in the visual consequences of cerebrovascular disease in children will need to look elsewhere for this information.

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Neurology of the Newborn, 5th Edition
Joseph J. Volpe, MD.

Scope: Few scholars have the time or aptitude to produce comprehensive medical textbooks by themselves. In the 5th edition of his seminal work, the author has enhanced his masterpiece, incorporating scientific and technologic breakthroughs into a unified hypothesis of brain development and pathology.

The book begins with 2 chapters on the anatomical and functional development of the brain, exquisitely incorporating the latest imaging techniques and developmental genetics. Enlightenment comes from the pathologic examples of developmental breakdown. The author interjects these examples into a unifying model of brain development but readily admits the level of confidence with
which certain diseases fit the model. Even with an imperfect model, the hypothetical framework is a great guide for clinical thinking.

Following 2 good chapters on examination and testing of the newborn, the book is broken into traditional sections dealing with categories of pathology (hypoxic-ischemic, metabolic, infectious, and iatrogenic). Each of these chapters harkens to the developmental model of the brain, emphasizing the timing and location of injury in determining clinical manifestations. A section on neuromuscular disorders appropriately begins with a separate chapter on motor anatomy and physiology to provide a comprehensive scaffold.

**Strengths:** As with any quality medical textbook, the reader can selectively find the description of important clinical manifestations and treatments for specific diseases. On the other hand, this book bids one to read on, or back, to get the full story. Where does this disease fit with others on the developmental timeline? Why does it manifest differently from another disease caused by a similar insult?

**Weaknesses:** The tables summarizing key points, found on nearly every page, sometimes seem superfluous. On the other hand, they are quick references for those who have read the section.

**Recommended Audience:** The principal users will be neurologists and neonatologists.

**Critical Appraisal:** With more than 1000 pages, this book is densely packed with current information. The bibliography is contemporary and comprehensive, making the book an excellent reference source.

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**Multimodal Imaging in Neurology: Special Focus on MRI Applications and MEG**
Hans-Peter Müller and Jan Kassubek, MD.

**Scope:** Noninvasive functional neuroimaging as provided by magnetoencephalography (MEG), MRI, functional MRI (fMRI), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS) is a rapidly evolving field. Resources are few to bridge the gaps in knowledge among the diverse professions involved in their creation and validation. Accordingly, engineers, software authors, neuroradiologists, neurologists, and neurosurgeons bring a wide range of non-overlapping experiences to this burgeoning field.

In this work, the authors provide a review of multimodal imaging and its applications to neurology. Their goal is to present the background and methods of 2 aspects of multimodal imaging to engineers and physicians: 1) intermodal multimodality, the co-registration of diverse neuroimaging and electrophysiologic techniques, and 2) intramodal multimodality, the co-registration within a neuroimaging technique to develop norms and profiling of disease states in comparison to norms.

**Strengths:** The book’s strengths are its concise presentation and its organized approach to the basic mathematical underpinnings of magnetic resonance and magnetoencephalography and the first steps in image post-processing. A section on coordinate transformation outlines the techniques of co-registration with the use of fiducial markers and statistical techniques. Application of intermodal co-registration is provided by the authors’ use of MEG, fMRI, and MRS in brain mapping. Intramodal co-registration is illustrated with the use of DTI in the evaluation of morphology of tracts within the corpus callosum. In these aspects, the review is a handy resource for the technical professions.

**Weaknesses:** The relative lack of graphics to illustrate mathematical concepts will hamper some clinicians. Images are shown in gray scale rather than in color, a disappointment because much multimodal neuroimaging information is based on the prudent use of color. The authors may have intended to use color, as several captions refer to “the red dot” or “yellow/red” mapping. The English is not always clear, perhaps because the text is translated from German.

**Recommended Audience:** This book will prove useful as a guide mostly to engineers.

**Critical Appraisal:** As fine a review of the theory and potential medical applications of multimodal neuroimaging as this book provides, it will probably not appeal to physicians because of its technical nature and limited clinical correlations.

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**Exploring the Thalamus and Its Role in Cortical Function, 2nd Edition**
S. Murray Sherman, PhD, and R. W. Guillery, PhD.

**Scope:** An excellent introduction and overview of thalamic anatomy, physiology, and function, this edition is a revision of a book that appeared in 2001. In addition to updating the scientific material, the authors have changed the emphasis from a corticocentric view to an acknowledgment that subcortical structures are not passive way stations, but that they play a significant role in brain function.

The authors are 2 leading figures in the study of the intrinsic characteristics and functional role of the thalamus.
Their emphasis has long been on the visual system, and the book reflects this bias. Even so, key points of thalamic function can be generalized from the visual system.

There are 11 chapters that cover the expanse of thalamic neurobiology from basic anatomy to higher level regional interactions, including the many different cell types. There is an excellent section on the intrinsic properties that are common to the physiology of many types of neurons throughout the brain as well as those properties that are unique to thalamic neurons. The book then steps up a functional level to examine how thalamic activity can be modulated from cortical as well as subcortical inputs. The authors then integrate the material to create a functional unit that includes the thalamus and the cortex.

**Strengths:** For many of us the thalamus has been an uninteresting and amorphous mass of gray matter interposed between the spinal cord and the cortex. The authors skillfully disabuse us of that notion. They demonstrate in clear fashion and in multiple ways that this collection of neurons has a far more important role in regulating the information that passes back and forth and that it is not just the cortex that matters.

**Weaknesses:** The book could have had more figures to illustrate key points more clearly.

**Recommended Audience:** This book provides an excellent and useful resource for those who wish to develop a good understanding of basic thalamic structure and function. It will also be an important reference for researchers who are active in a particular aspect of thalamic neurobiology but who wish to broaden their horizons. It provides enough background information for the beginning neuroscientist, while highlighting key points in the complexity of the system in a way that the jaded expert will also find useful.

**Critical Appraisal:** This is a relatively concise and approachable book. It will probably appeal mostly to neuroscientists, but clinicians with an interest in brain function will want to read it.

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Upcoming Meetings

April 10–April 17, 2010
American Academy of Neurology Annual Meeting
Toronto, ON
http://www.aan.com/go/am10
Contact: memberservices@aan.com

April 14–April 18, 2010
American Assn. of Pediatric Ophthalmology and Strabismus (AAPOS) 36th Annual Meeting
Orlando, FL
http://www.aapos.org/news/show/11
Contact: aapos@ao.org

May 1–May 5, 2010
American Association of Neurological Surgeons
Philadelphia, PA
http://www.aans.org/annual/default.asp
Contact: info@aans.org

May 2–May 6, 2010
Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Fort Lauderdale, FL
Contact: arvo@arvo.org

May 15–May 20, 2010
48th American Society of Neuroradiology (ASNR) Annual Meeting
Boston, MA
http://www.asnr.org/2010
Contact: meetings@asnr.org

May 25–May 28, 2010
XIX European Stroke Conference
Barcelona, Spain
http://www.eurostroke.org/
Contact: Hennerici@eurostroke.org

June 5–June 9, 2010
World Ophthalmology Congress
XXXII International Congress of Ophthalmology (ICO), 108th DOG Congress (German Society of Ophthalmology), AAD Congress 2010 (German Academy of Ophthalmology)
Berlin, Germany
http://www.woc2010.de/

June 8–June 11, 2010
Canadian Neurological Sciences Federation 45th Annual Congress
Quebec City, QC
http://www.cnsfederation.org/congress_program.html
Contact: info@cnsfederation.org

June 13–June 18, 2010
18th International Neuro-Ophthalmology Society (INOS) Meeting
Lyon, France
http://www.inos2010.org/
Contact: inos2010@carco.fr

June 19–June 22, 2010
Society of Neurological Surgeons Annual Meeting
New Haven, CT
http://www.societyns.org/meeting_info.html

June 19–June 23, 2010
20th Meeting of the European Neurological Society
Berlin, Germany
http://www.congres.ch/ens2010/
Contact: info@ensinfo.org

June 24–June 27, 2010
American Headache Society Scientific Meeting
Los Angeles, CA
http://www.americanheadachesociety.org/events/ahsevents.asp
Contact: ahsq@talley.com

June 26–June 29, 2010
Canadian Ophthalmological Society Annual Meeting
Quebec City, QC
http://www.eyesite.ca/english/amindex.htm
Contact: cos@eyesite.ca

July 3–July 7, 2010
Forum of European Neuroscience Societies (7th)
Amsterdam, The Netherlands
http://fens2010.neurosciences.asso.fr/
Contact: E-mail form on above website

July 9–July 16, 2010
International Society on Metabolic Eye Disease
Vancouver, BC (cruse to Alaska)
http://www.continuingeducation.net/
coursedetails.php?program_number=797
Contact: 070910MetEye@continuingeducation.net
July 17–July 22, 2010
XII International Congress on Neuromuscular Diseases
Naples, Italy
http://www.icnmd2010naples.org/
Contact: ICNMD201O@congrex.com

July 18–July 23, 2010
XIX Biennial Meeting of the International Society for Eye Research, International Congress on Eye Research (ICER)
Montreal, QC
http://www2.kenes.com/iser/pages/home.aspx
Contact: iser@kenes.com

Sept. 11–Sept. 15, 2010
XVIIth International Congress of Neuropathology
Salzburg, Austria
http://www.icn2010.org/
Contact: daniela.gaertner@meduniwien.ac.at

Sept. 12–Sept. 15, 2010
135th Annual Meeting of the American Neurological Association
San Francisco, CA
http://www.aneproa.org/index.php?src=gendocs&link= FutureMeetings
Contact: anameeting@llmsi.com

Sept. 25–Sept. 28, 2010
14th Congress of the European Federation of Neurological Societies (EFNS)
Geneva, Switzerland
http://www.efns.org/14th-efns-congress-geneva-2010.365.0. html
Contact: headoffice@efns.org

Oct. 6–Oct. 9, 2010
European Association for Vision Research (EVER)
Annual Congress
Crete, Greece
Contact: ever@ever.be

Oct. 16–Oct. 19, 2010
114th American Academy of Ophthalmology Annual Meeting
Chicago, IL
http://www.aao.org/meetings/annual_meeting/chicago.cfm
Contact: meetings@aao.org

Oct. 16–Oct. 21, 2010
60th Annual Meeting of the Congress of Neurological Surgeons
San Francisco, CA
Contact: info@1cns.org

Nov. 13–Nov. 17, 2010
40th Annual Meeting of the Society for Neuroscience
San Diego, CA
http://www.sfn.org/am2010/
Contact: info@sfn.org

American Society of Neuroimaging 34th Annual Meeting
Fort Myers, FL
http://www.asnweb.org
Contact: asn@llmsi.com

April 9–April 16, 2011
American Academy of Neurology Annual Meeting
Honolulu, HI
http://www.aan.com/go/am10
Contact: memberservices@aan.com

June 4–June 7, 2011
18th Congress of the European Society of Ophthalmology-Joint Meeting with the American Academy of Ophthalmology
Geneva, Switzerland
http://www.soe2011.org/
Contact: soe2011@congrex.com

July 14–July 19, 2011
8th IBRO World Congress of Neuroscience
Florence, Italy
http://www.ibro2011.org/site/home.asp
Contact: ibro2011@newtours.it

June 18–June 21, 2011
European Neuro-ophthalmology Society (EUNOS)
Barcelona, Spain
http://www.eunos2011barcelona.com/
Contact: congresos.barcelona@viajesiberia.com
Erratum

Reflections and Advice from an Aging Academic: Erratum

In my Jacobson Lecture article (1), I wrote that Arthur Asbury conducted the epidemiological study that disproved the link between the swine flu vaccinations of 1976 and Guillain Barre syndrome (GBS). The study was actually performed by Langmuir et al and published in the American Journal of Epidemiology in June 1984 (2). I initially learned of it in an article by Asbury in the October 1984 issue of the Annals of Neurology (3).

Moreover, Langmuir et al (2), and other studies, did show a slight increase in GBS up to 5 weeks after vaccinations, but probably not beyond.

REFERENCES